Therapeutic Class Overview
Immunomodulators

Therapeutic Class

- **Overview/Summary:** This review encompasses immunomodulators agents used in immune-mediated inflammatory diseases. These agents include interleukin (IL) receptor antagonists (anakinra, tocilizumab), tumor necrosis factor (TNF)-blocking agents (adalimumab, certolizumab, etanercept, golimumab, and infliximab) and T-cell activation inhibitors (abatacept). These agents interfere with inflammatory pathways through slightly different mechanisms and are used for rheumatoid arthritis, psoriatic arthritis, psoriasis, ankylosing spondylitis, ulcerative colitis, Crohn's disease and neonatal-onset multisystem inflammatory disease.[1-8,10-12]

  Generally, current consensus guidelines support the use of the TNF-blockers with respect to their Food and Drug Administration (FDA)-approved indications and no one agent is preferred over another.[13-29] As more recent guidelines are published, the recommendations for use TNF-blockers earlier in therapy is becoming a more common occurance.[20,21,25] Because the immunomodulators are biologic agents made from living organisms and are extremely difficult to duplicate, congress has struggled to create regulations to approve generic versions of these agents. Currently, none of the agents in this class are available generically; however, the recently upheld Patient Protection and Affordable Care provides a legal framework for regulatory approval of biosimilar drugs.[30]

Table 1. Current Medications Available in the Therapeutic Class[3-8, **10-12**]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Abatacept (Orencia®)	Monotherapy or concomitantly with disease modifying antirheumatic drugs other than tumor necrosis factor antagonists in moderately to severely active rheumatoid arthritis in adults; monotherapy or concomitantly with methotrexate for moderately to severely active polyarticular juvenile idiopathic arthritis in pediatric patients six years of age and older	Prefilled syringe: 125 mg/mL Single use vial: 250 mg	-
Adalimumab (Humira®)	Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis; reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis (in pediatric patients four years of age and older; reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis; reducing signs and symptoms in adult patients with active ankylosing spondylitis; reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy; reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab; inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to	Prefilled pen: 40 mg/0.8 mL Prefilled syringe: 20 mg/0.4 mL 40 mg/0.8 mL Single use vial: 40 mg/0.8 mL	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine; treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.		
Anakinra (Kineret®)	Reduction in signs and symptoms and slowing the progression of structural damage in moderately to severely active rheumatoid arthritis, in patients 18 years of age or older who have failed one or more disease modifying antirheumatic drugs; treatment of neonatal-onset multisystem inflammatory disease	Prefilled syringe: 100 mg/0.67 mL	-
Certolizumab (Cimzia®)	Reducing signs and symptoms of Crohn's disease and maintaining clinical response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy; treatment of adults with moderately to severely active rheumatoid arthritis	Prefilled syringe: 200 mg/mL Vial (powder for injection): 200 mg	-
Etanercept (Enbrel®)	Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis in combination with methotrexate or used alone; reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients ages two and older; reducing signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function in patients with psoriatic arthritis in combination with methotrexate in patients who do not respond adequately to methotrexate alone; reducing signs and symptoms in patients with active ankylosing spondylitis; treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy	Prefilled "SureClick" autoinjector: 50 mg/mL Prefilled syringes: 25 mg/0.5 mL 50 mg/mL Vial (powder for injection): 25 mg	-
Golimumab (Simponi®)	Treatment of adult patients with moderately to severely active rheumatoid arthritis in combination with methotrexate; treatment of adult patients with active psoriatic arthritis alone or in combination with methotrexate; treatment of adult patients with active ankylosing spondylitis; treatment of moderately to severely active ulcerative colitis who have demonstrated corticosteroid dependence or who have had an inadequate response to or failed to tolerate oral aminosalicylates, oral corticosteroids, azathioprine, or 6-mercaptopurine	Prefilled "SmartJect" autoinjector: 50 mg/0.5 mL Prefilled syringe: 50 mg/0.5 mL	-
Infliximab (Remicade®)	Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy	Single use vial: 100 mg	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	Reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. Reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy. Reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely ulcerative colitis who have had an inadequate response to conventional therapy. In combination with methotrexate to reduce signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis. Reducing signs and symptoms in patients with active ankylosing spondylitis. Reducing signs and symptoms of active psoriatic arthritis, inhibiting the progression of structural damage, and improving physical function. Treatment of adult patients with chronic severe plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.		
Tocilizumab (Actemra®)	Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more disease modifying anti-rheumatic drugs. Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis. Patients 2 years of age and older with active systemic juvenile idiopathic arthritis.	Single use vials: 80 mg/4 mL 200 mg/10 mL 400 mg/20 mL	-
Ustekinumab (Stelara®)	Treatment of adult patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy	Prefilled syringe: 45 mg/0.5 mL 90 mg/mL Single use vials:	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		45 mg/0.5 mL 90 mg/mL	

Evidence-based Medicine

- The immunomodulators have been shown to be effective in their respective Food and Drug Administration (FDA)-approved indications, particularly in conditions where patients were unresponsive or refractory to disease modifying antirheumatic drugs (DMARDs). Most research with these agents and FDA-approved indications (with the exception of ustekinumab) are for rheumatoid arthritis. In these trials, the immunomodulator were compared directly to placebo or older DMARD medications, either as monotherapy or in combination with a DMARD. Consistently, immunomodulators have shown greater improvement in symptoms over the comparator.[32-102]
- Recently anakinra was FDA-approved for neonatal-onset multisystem inflammatory disease (NOMID), the only agent FDA-approved for this indication. The approval was made following a single trial demonstrating sustained improvements in affected patients over 60 months.[102]
- To date, majority of trials conducted have been placebo-controlled, with very few trials directly comparing two immunomodulators head-to-head for any of the FDA-approved indications. Those that have been conducted, most have shown comparable results.[32-102] One trial in RA patients intolerant to methotrexate treatment found significantly greater improvements in patients with tocilizumab patients compared to adalimumab.[96] The few direct head-to-head trials available prevent clearly determining superiority of one agent over another.
- Generally, current consensus guidelines support the use of the TNF-blockers with respect to their FDA-approved indications and no one agent is preferred over another.[13-29] As more recent guidelines are published, the recommendations for use TNF-blockers earlier in therapy is becoming a more common occurance.[20,21,25] The adverse event profiles are similar across the class; however routes of administration and dose frequency may vary. Currently, adalimumab and infliximab have the most FDA-approved indications among the agents in the class.

Key Points within the Medication Class

- According to Current Clinical Guidelines:[56-61]
    - Support the use of the immunomodulators with respect to their Food and Drug Administration (FDA)-approved indications.
    - No one agent is preferred over another.
- Other Key Facts:
    - There are no generic biologic agents.
    - Dosing frequency and route of administration vary between products.
        - Currently none of the agents available may be administered via oral route.
        - Several agents require intravenously (IV) infusion administration (infliximab, tocilizumab) and are not conducive to self-administration. A loading- dose of abatacept is recommended to be administered IV, but can be given subcutaneously if the patient is not able to received IV infusion.
        - Anakinra is administered subcutaneously (SC), but requires more frequent daily administration.
    - Anakinra is the only FDA-approved agent for neonatal-onset multisystem inflammatory disease.

References

1. Overview of biologic agents in the rheumatic diseases. In: Furst DE, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2012 [cited 2012 Sept 3]. Available from: http://www.utdol.com/utd/index.do.
2. Tumor necrosis factor-alpha inhibitors: An overview of adverse effects. In: Furst DE, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2012 [cited 2012 Sept 3]. Available from: http://www.utdol.com/utd/index.do.
3. Humira® [package insert]. North Chicago (IL): Abbott Laboratories; 2013 May.
4. Cimzia® [package insert]. Smyrna (GA): UCB, Inc.; 2012 Apr.
5. Enbrel® [package insert]. Thousand Oaks (CA): Immunex Corporation; 2011 Dec.
6. Simponi® [package insert]. Horsham (PA): Janssen Biotech, Inc.; 2011 Sep.
7. Remicade® [package insert]. Horsham (PA): Janssen Biotech, Inc; 2011 Oct.

8. Kineret® [package insert]. Thousand Oaks (CA): Swedish Orphan Biovitrum AB; 2012 Dec.
9. Mertens M, Singh JA. Anakinra for rheumatoid arthritis. Cochrane Database of Systematic Reviews 2009, Issue 1. Art. No.: CD005121. DOI: 10.1002/14651858. CD005121.pub3.
10. Actemra® [package insert]. South San Francisco (CA): Genetech, Inc.; 2011 Apr.
11. Stelara® [package insert]. Horsham (PA): Janssen Biotech, Inc.; 2012 Jun.
12. Orencia® [package insert]. Princeton (NJ): Bristol-Myers Squibb; 2011 Dec.
13. Braun J, van den Berg R, Baraliakos X, Boehm H, Burgos-Vargas R, Collantes-Estevez E, et al. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. Ann Rheum Dis. 2011 Jun;70(6):896-904.
14. van der Heijde D, Sieper J, Maksymowych WP, Dougados M, Burgos-Vargas R, Landewé R, et al. Assessment of SpondyloArthritis international Society. 2010 Update of the international ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis. Ann Rheum Dis. 2011 Jun;70(6):905-8.
15. National Institute for Health and Clinical Excellence (NICE). Adalimumab, etanercept and infliximab for ankylosing spondylitis. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 May. 47 p. (Technology appraisal guidance; no. 143).
16. National Institute for Health and Clinical Excellence (NICE). Golimumab for the treatment of ankylosing spondylitis. London (UK): National Institute for Health and Clinical Excellence (NICE); 2011 Aug. Available at: http://www.nice.org.uk/guidance/TA233
17. Lichtenstein GR, Hanauer SB, Sandborn WJ; Practice Parameters Committee of the American College of Gastroenterology. Management of Crohn's disease in adults. Am J Gastroenterol. 2009;104:465-83.
18. National Institute for Health and Clinical Excellence (NICE). Crohn's disease Management in adults, children and young people. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Oct. Available at: http://www.nice.org.uk/guidance/TA225
19. Beukelman T, Patkar NM, Saag KG, Tolleson-Rinehart S, Cron RQ, DeWitt EM, et al. 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. Arthritis Care Res (Hoboken). 2011 Apr;63(4):465-82.
20. Gossec L, Smolen JS, Gaujoux-Viala C, Ash Z, Marzo-Ortega H, van der Heijde D, et al. European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies. Ann Rheum Dis. 2012 Jan;71(1):4-12.
21. Hsu S, Papp KA, Lebwohl MG, Bagel J, Blauvelt A, Duffin KC, et al. Consensus guidelines for the management of plaque psoriasis. Arch Dermatol. 2012 Jan;148(1):95-102.
22. Gottlieb A, Korman NJ, Gordon KB, Feldman SR, Lebwohl M, Koo JYM, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 2. Psoriatic arthritis: Overview and guidelines of care for treatment with an emphasis on the biologics. J Am Acad Dermatol. 2008;58(5):851-64.
23. Menter A, Korman NJ, Elmets CA, Feldman SR, Gelfand JM, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 3. Guidelines of care for the management and treatment of psoriasis with topical therapies. J Am Acad Dermatol. 2009;60:643-59.
24. Menter A, Korman NJ, Elmets CA, Feldman SR, Gelfand JM, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents [article in press]. J Am Acad Dermatol. 2009. May 30 [cited 2012 Sept 3]; Available from: http://www.aad.org/research/guidelines/documents/pso4tsys609.pdf.
25. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken). 2012 May;64(5):625-39.
26. National Institute for Health and Clinical Excellence (NICE). National Collaborating Centre for Chronic Conditions. Rheumatoid arthritis: national clinical guideline for management and treatment in adults. London: Royal College of Physicians, February 2009.
27. National Institute for Health and Clinical Excellence (NICE). Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor. August 2010 Available from http://guidance.nice.org.uk/CG79.
28. National Institute for Health and Clinical Excellence (NICE). Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs. London (UK): National Institute for Health and Clinical Excellence (NICE); 2011 Jun. Available at: http://www.nice.org.uk/guidance/TA225
29. Kornbluth A, Sachar DB; Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol. 2010 Mar;105(3):501-23.
30. H.R. 5894-112th Congress: Patient Protection and Affordable Care Act Education and Outreach Campaign Repeal Act of 2012. (2012). In GovTrack.us (database of federal legislation). Retrieved September 4, 2012, from http://www.govtrack.us/congress/bills/112/hr5894.
31. Micromedex® Healthcare Series [intranet database]. Version 5.1. Greenwood Village, (CO): Thomson Healthcare. Cited 2013 Jun]. Available from: http://www.thomsonhc.com/.
32. van der Heijde D, Kivitz A, Schiff MH, Sieper J, Dijkmans BAC, Braun J, et al. Efficacy and safety of adalimumab in patients with ankylosing spondylitis. Arthritis Rheum. 2006;54(7):2136-46.
33. Van Assche G, Vermeire S, Ballet V, Gabriels F, Noman M, D'Haens G, et al. Switch to adalimumab in patients with Crohn's disease controlled by maintenance infliximab: prospective randomised SWITCH trial. Gut. 2012 Feb;61(2):229-34.
34. Gorman JD, Sack KE, Davis JC. Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor α. N Engl J Med. 2002;346(18):1349-56.
35. Calin A, Dijkmans BAC, Emery P, Hakala M, Kalden J, Leirisalo-Repo M, et al. Outcomes of a multicentre randomized clinical trial of etanercept to treat ankylosing spondylitis. Ann Rheum Dis. 2004; 63:1594-600.
36. Davis JC, van der Heijde DM, Braun J, Dougados M, Clegg DO, Kivitz AJ, et al. Efficacy and safety of up to 192 weeks of etanercept therapy in patients with ankylosing spondylitis. Ann Rheum Dis. 2008;67:346-52.
37. Braun J, van der Horst-Bruinsma IE, Huang F, Burgos-Vargas R, Vlahos B, Koenig AS, et al. Clinical efficacy and safety of etanercept vs sulfasalazine in patients with ankylosing spondylitis: a randomized, double-blind trial. Arthritis Rheum. 2011 Jun;63(6):1543-51.

38. Inman RD, Davis JC Jr, van der Heijde D, Diekman L, Sieper J, Kim SI, et al. Efficacy and safety of golimumab in patients with ankylosing spondylitis: results of a randomized, double-blind, placebo-controlled, phase III trial. Arthritis Rheum. 2008 Nov;58(11):3402-12.
39. Braun J, Brandt J, Listing J, Zink A, Alten R, Golder W, et al. Treatment of active ankylosing spondylitis with infliximab: a randomized controlled multicentre trial. Lancet. 2002 Apr 6;359(9313):1187-93.
40. van der Heijde D, Dijkmans B, Geusens P, Sieper J, DeWoody K, Williamson P, Braun J; Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy Study Group. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). Arthritis Rheum. 2005 Feb;52(2):582-91.
41. Ma C, Panaccione R, Heitman SJ, Devlin SM, Ghosh S, Kaplan GG. Systematic review: the short-term and long-term efficacy of adalimumab following discontinuation of infliximab. Aliment Pharmacol Ther. 2009;30:977-86.
42. Löfberg R, Louis EV, Reinisch W, Robinson AM, Kron M, Camez A, Pollack PF. Adalimumab produces clinical remission and reduces extraintestinal manifestations in Crohn's disease: results from CARE. Inflamm Bowel Dis. 2012 Jan;18(1):1-9.
43. Watanabe M, Hibi T, Lomax KG, Paulson SK, Chao J, Alam MS, et al. Adalimumab for the induction and maintenance of clinical remission in Japanese patients with Crohn's disease. J Crohn's Colitis. 2012 Mar;6(2):160-73.
44. Shao L-M, Chen M-Y, Chen Q-Y, Cai J-T. Meta-analysis: the efficacy and safety of certolizumab pegol in Crohn's disease. Aliment Pharmacol Ther. 2009;29(6):605-14.
45. Targan SR, Hanauer SB, van Deventer SJ, Mayer L, Present DH, Braakman T, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. N Engl J Med. 1997 Oct 9;337(15):1029-35.
46. Present DH, Rutgeerts P, Targan S, Hanauer SB, Mayer L, van Hogezand RA, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med. 1999 May 6;340(18):1398-405.
47. Hyams J, Crandall W, Kugathasan S, Griffiths A, Olson A, Johanns J, et al; REACH Study Group. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. Gastroenterology. 2007 Mar;132(3):863-73;quiz 1165-6.
48. Behm BW, Bickston SJ. Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease. Cochrane Database of Systematic Reviews 2008, Issue 1. Art. No.: CD006893. DOI: 10.1002/14651858. CD006893.
49. Ruperto N, Lovell DJ, Quartier P, Paz E, Rubio-Pérez N, Silva CA, et al; Pediatric Rheumatology International Trials Organization; Pediatric Rheumatology Collaborative Study Group. Abatacept in children with juvenile idiopathic arthritis: a randomized, double-blind, placebo-controlled withdrawal trial. Lancet. 2008 Aug 2;372(9636):383-91.
50. Lovell D, Ruperto N, Goodman S, Reiff A, Jung L, Jarosova K, et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. N Engl J Med. 359;8:810-20.
51. Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. N Engl J Med. 2000;342:763-9.
52. Lovell DJ, Reiff A, Jones OY, Schneider R, Nocton J, Stein L, et al. Long-term safety and efficacy of etanercept in children with polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum. 2006;54:1987-94.
53. Horneff G, Schmeling H, Biedermann T, Foeldvari I, Ganser G, Girschick, et al. The German etanercept registry for treatment of juvenile idiopathic arthritis. Ann Rheum Dis. 2004 Dec; 63(12):1638-44.
54. De Benedetti, Brunner H, Ruperto N, Calvo I, Cuttica R, Schneider R, et al. Tocilizumab in patients with systemic juvenile idiopathic arthritis: efficacy data from the placebo-controlled 12-week part of the phase 3 TENDER trial [abstract]. Arthritis Rheum. 2010 Oct; 62(10 Suppl):596S. Abstract no. 1434.
55. Bagel J, Lynde C, Tyring S, Kricorian G, Shi Y, Klekotka P. Moderate to severe plaque psoriasis with scalp involvement: a randomized, double-blind, placebo-controlled study of etanercept. J Am Acad Dermatol. 2012 Jul;67(1):86-92.
56. Saurat JH, Stingl G, Dubertret L, Papp K, Langley RG, Ortonne JP, et al; CHAMPION Study Investigators. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs methotrexate vs placebo in patients with psoriasis (CHAMPION). Br J Dermatol. 2008 Mar;158(3):558-66.
57. Leonardi C, Kimball A, Papp K, Yeilding N, Guzzo C, Wang Y, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomized, double-blind, placebo-controlled trial (PHOENIX 1). Lancet. 2008;371:1665-74.
58. Papp K, Langley R, Lebwohl M, Krueger G, Szapary P, Yeilding N, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomized, double-blind, placebo-controlled trial (PHOENIX 2). Lancet. 2008;371:1675-84.
59. Griffiths CE, Strober BE, van de Kerkhof P, Ho V, Fidelus-Gort R, Yeilding N, Guzzo C, Xia Y, Zhou B, Li S, Dooley LT, Goldstein NH, Menter A; ACCEPT Study Group. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. N Engl J Med. 2010 Jan 14;362(2):118-28.
60. Schmitt J, Zhang Z, Wozel, G, Meurer M, Kirch W. Efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate-to-severe psoriasis: meta-analysis of randomized controlled trials. Br J Derm. 2008;159:513-26.
61. Genovese MC, Mease PJ, Thomson GTD, Kivitz AJ, Perdok RJ, Weinberg MA, et al. Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy. J Rheum. 2007;34:1040-50.
62. Mease PJ, Gladman DD, Ritchlin CT, Ruderman EM, Steinfeld SD, Choy EHS, et al. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis. Arthritis Rheum. 2005; 52(10):3279-89.
63. Mease PJ, Goffe BS, Metz J, VanderStoep A, Finck B, Burge DJ. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomized trial. The Lancet. 2000;356;385-90.
64. Mease PJ, Kivitz AJ, Burch FX, Siegel EL, Cohen SB, Ory P, et al. Etanercept treatment of psoriatic arthritis: safety, efficacy and effect on disease progression. Arthritis Rheum. 2004;50:2264-72.
65. Kavanaugh A, McInnes I, Mease P, Krueger GG, Gladman D, Gomez-Reino J, et al. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four week efficacy and safety results of a randomized, placebo-controlled study. Arthritis Rheum. 2009;60(4):976-86.

66. Antoni C, Krueger GG, de Vlam K, Birbara C, Beutler A, Guzzo C, et al; IMPACT 2 Trial Investigators. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. Ann Rheum Dis. 2005 Aug;64(8):1150-7.
67. Baranauskaite A, Raffayová H, Kungurov NV, Kubanova A, Venalis A, Helmle L, et al. Infliximab plus methotrexate is superior to methotrexate alone in the treatment of psoriatic arthritis in methotrexate-naive patients: the RESPOND study. Ann Rheum Dis. 2012 Apr;71(4):541-8.
68. Westhovens R, Robles M, Ximenes AC, Nayiager S, Wollenhaupt J, Durez P, et al. Clinical efficacy and safety of abatacept in methotrexate-naive patients with early rheumatoid arthritis and poor prognostic factors. Ann Rheum Dis. 2009 Dec;68(12):1870-7.
69. Genovese MC, Covarrubias A, Leon G, Mysler E, Keiserman M, Valente R, et al. Subcutaneous abatacept vs intravenous abatacept: A phase IIIb noninferiority study in patients with an inadequate response to methotrexate. Arthritis Rheum. 2011 Oct;63(10):2854-64.
70. Keystone EC, Kremer JM, Russell A, Box J, Abud-Mendoza C, Elizondo MG, et al. Abatacept in subjects who switch from intravenous to subcutaneous therapy: results from the phase IIIb ATTUNE study. Ann Rheum Dis. 2012 Jun;71(6):857-61.
71. Haraoui B, Cividino A, Stewart J, Guérette B, Keystone EC. Safety and effectiveness of adalimumab in a clinical setting that reflects Canadian standard of care for the treatment of rheumatoid arthritis (RA): results from the CanACT study. BMC Musculoskelet Disord. 2011 Nov 17;12:261.
72. van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, García Meijide JA, Wagner S, et al. Tofacitinib or adalimumab vs placebo in rheumatoid arthritis. N Engl J Med. 2012 Aug 9;367(6):508-19.
73. Keystone E, van der Heijde D, Mason D, Landewe R, van Vollenhoven R, Combe B, et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis. Arthritis Rheum. 2008;58(11):3319-29.
74. Smolen J, Landewe R, Mease P, Brzezicki J, Mason D, Luijtens K, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomized controlled trial. Ann Rheum Dis. 2009;68:797-804.
75. Fleishmann R, Vencovsky J, van Vollenhoven RF, Borenstein D, Box J, Coteur G, et al. Efficacy and safety of certolizumab pegol monotherapy every four weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. Ann Rheum Dis. 2009; 68:805-11.
76. Weinblatt ME, Fleischmann R, Huizinga TW, Emery P, Pope J, Massarotti EM, et al. Efficacy and safety of certolizumab pegol in a broad population of patients with active rheumatoid arthritis: results from the REALISTIC phase IIIb study. Rheumatology. 2012 Dec; 51(12):2204-14.
77. Tanaka Y, Harigai M, Takeuchi T, Yamanaka H, Ishiguro N, GO-FORTH Study Group, et al. Golimumab in combination with methotrexate in Japanese patients with active rheumatoid arthritis: results of the GO-FORTH study. Ann Rheum Dis. 2012 Jun;71(6):817-24.
78. Emery P, Fleischmann RM, Moreland LW, Hsia EC, Strusberg I, Durez P, et al. Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. Arthritis Rheum. 2009 Aug;60(8):2272-83.
79. Keystone EC, Genovese MC, Klareskog L, Hsia EC, Hall ST, Miranda PC, et al. Golimumab, a human antibody to tumor necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. Ann Rheum Dis. 2009 Jun;68(6):789-96.
80. Smolen JS, Kay J, Doyle MK, Landewé R, Matteson EL, Wollenhaupt J, et al; GO-AFTER study investigators. Golimumab in patients with active rheumatoid arthritis after treatment with tumor necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomized, double-blind, placebo-controlled, phase III trial. Lancet. 2009 Jul 18;374(9685):210-21.
81. Smolen JS, Kay J, Landewé RB, Matteson EL, Gaylis N, Wollenhaupt J,et al. Golimumab in patients with active rheumatoid arthritis who have previous experience with tumour necrosis factor inhibitors: results of a long-term extension of the randomised, double-blind, placebo-controlled GO-AFTER study through week 160. Ann Rheum Dis. 2012 Oct;71(10):1671-9.
82. Weinblatt ME, Bingham CO 3rd, Mendelsohn AM, Kim L, Mack M, Lu J, et al. Intravenous golimumab is effective in patients with active rheumatoid arthritis despite methotrexate therapy with responses asearly as week 2: results of the phase 3, randomised, multicentre, double-blind, placebo-controlled GO-FURTHER trial. Ann Rheum Dis. 2013 Mar; 72(3):381-9.
83. Jones G, Sebba A, Gu J, Lowenstein MB, Calvo A, Gomez-Reino JJ, et al. Comparison of tocilizumab monotherapy vs methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: The AMBITION study. Ann Rheum Dis. 2010 Jan;69(1):88-96.
84. Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, Aleckck E, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomized trial. Lancet. 2008 Mar;371(9617):987-97.
85. Genovese M, McKay J, Nasonov E, Mysler EF, da Silva NA, Alecock E, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs. Arthritis and Rheumatism. 2008 Oct;58(10):2968-80.
86. Kremer JM, Blanco R, Brzosko M, Burgos-Vargas R, Halland AM, Vernon E, et al. cilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structural joint damage at one year. Arthritis Rheum. 2011 Mar;63(3):609-21.
87. Yazici Y, Curtis JR, Ince A, Baraf H, Malamet RL, Teng LL, Kavanaugh A. Efficacy of tocilizumab in patients with moderate to severe active rheumatoid arthritis and a previous inadequate response to disease-modifying antirheumatic drugs: the ROSE study. Ann Rheum Dis. 2012 Feb;71(2):198-205.
88. Emery P, Keystone E, Tony H, Cantagrel A, R van Vollenhoven, Sanchez A, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumor necrosis factor biological: results from a 24-week multicenter randomized placebo-controlled trial. Ann Rheum Dis. 2008 July;67:1516-23.

89. Dougados M, Kissel K, Sheeran T, Tak PP, Conaghan PG, Mola EM, et al. Adding tocilizumab or switching to tocilizumab monotherapy in methotrexate inadequate responders: 24-week symptomatic and structural results of a 2-year randomised controlled strategy trial in rheumatoid arthritis (ACT-RAY). Ann Rheum Dis. 2013 Jan;72(1):43-50.
90. Maxwell L, Singh JA. Abatacept for rheumatoid arthritis. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD007277.
91. Navarro-Sarabia F, Ariza-Ariza R, Hernandez-Cruz B, Villanueva I. Adalimumab for treating rheumatoid arthritis. Cochrane Database of Systematic Review 2005, Issue 3. Art. No.: CD005113. DOI: 10.1002/14651858.CD005113.pub2.
92. Blumenauer BTB, Cranney A, Burls A, Coyle D, Hochberg MC, Tugwell P, et al. Etanercept for the treatment of rheumatoid arthritis. Cochrane Database of Systematic Reviews 2003, Issue 3. Art. No.: CD004525. DOI: 10.1002/14651858.CD004525.
93. van Vollenhoven RF, Geborek P, Forslind K, Albertsson K, Ernestam S, Swefot study group et al. Conventional combination treatment vs biological treatment in methotrexate-refractory early rheumatoid arthritis: two year follow-up of the randomised, non-blinded, parallel-group Swefot trial. Lancet. 2012 May 5;379(9827):1712-20.
94. Wiens A, Correr CJ, Venson R, Grochocki MC, Otuki MF, Pontarolo R. A meta-analysis of the efficacy and safety of using infliximab for the treatment of rheumatoid arthritis. Clin Rheumatol. 2009 Dec;28(12):1365-73.
95. Nixon R, Bansback N, Brennan A. The efficacy of inhibiting tumor necrosis factor α and interleukin 1 in patients with rheumatoid arthritis: a meta-analysis and adjusted indirect comparisons. Rheumatology. 2007;46:1140-7.
96. Gabay C, Emery P, van Vollenhoven R, Dikranian A, Alten R, Pavelka K, et al. ADACTA Study Investigators. Tocilizumab monotherapy vs adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. Lancet. 2013 May 4; 381(9877):1541-50.
97. Weinblatt ME, Schiff M, Valente R, van der Heijde D, Citera G, Zhao C, et al. Head-to-head comparison of subcutaneous abatacept vs adalimumab for rheumatoid arthritis: findings of a phase IIIb, multinational, prospective, randomized study. Arthritis Rheum. 2013 Jan; 65(1):28-38.
98. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005 Dec 8;353(23):2462-76.
99. Hyams JS, Damaraju L, Blank M, Johanss J, Guzzo C, Winter H, et al. A randomized multicenter, open-label phase 3 study to evaluate the safety and efficacy of infliximab in pediatric patients with moderate to severe ulcerative colitis [abstract]. Gastroenterology. 2011 May;140(5 Suppl. 1):124S-5S. Abstract no. 747.
100. Reinisch W, Sandborn WJ, Hommes DW, D'Haens G, Hanauer S, Schreiber S, et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. Gut. 2011 Jun;60(6):780-7.
101. Sandborn WJ, van Assche G, Reinisch W, Colombel JF, D'Haens G, Wolf DC,et al.Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2012 Feb;142(2):257-65.
102. Sibley CH, Plass N, Snow J, Wiggs EA, Brewer CC, King KA, et al. Sustained response and prevention of damage progression in patients with neonatal-onset multisystem inflammatory disease treated with anakinra: a cohort study to determine three- and five-year outcomes. Arthritis Rheum. 2012 Jul;64 (7):2375-86.

Therapeutic Class Review
Immunomodulators

Overview/Summary

Tumor necrosis factor (TNF) is a pro-inflammatory mediator, which is released by lymphocytes. Several conditions have been associated with elevated TNF levels including rheumatoid arthritis, psoriatic arthritis, psoriasis, ankylosing spondylitis, ulcerative colitis and Crohn's disease. TNF-blocking agents including adalimumab, certolizumab, etanercept, golimumab, and infliximab interfere with this inflammatory pathway through slightly different mechanisms. Adalimumab, golimumab, and infliximab are monoclonal antibodies that bind to TNF-α, etanercept is a fusion protein that binds to both TNF-α and TNF-β, certolizumab pegol is a pegylated antibody-binding fragment TNF-α blocker.[1, 2]

Golimumab is the newest TNF-blocker to be approved by the Food and Drug Administration (FDA) for rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. In addition to these three indications, etanercept is also indicated for juvenile idiopathic arthritis and plaque psoriasis. Adalimumab is approved for all the aforementioned conditions and has an additional indication for Crohn's disease and ulcerative colitis. With the exception of juvenile idiopathic arthritis, infliximab is approved for the same indications as adalimumab. Furthermore, infliximab is approved for use in both pediatric Crohn's disease and pediatric ulcerative colitis. Currently, certolizumab is only indicated for rheumatoid arthritis and Crohn's disease. Each of the TNF-blockers approved for a particular indication have been shown to be efficacious compared to placebo. These agents have been found to be similar with respect to adverse events and interacting medications.[3-7]

Anakinra is an interleukin (IL)-1 receptor antagonist that competitively inhibits the binding of IL-1 to its affiliated receptor. IL-1 is a pro-inflammatory mediator associated with cartilage breakdown as well as stimulation of bone resorption. Anakinra disrupts this inflammatory process and is FDA-approved for rheumatoid arthritis. This agent may be used alone or in combination with other disease modifying antirheumatic agents such as hydroxychloroquine, methotrexate or sulfasalazine.[8] For rheumatoid arthritis, anakinra demonstrates modest efficacy compared to TNF-blocking agents.[9] Anakira has also been approved for the treatment of children and adults with neonatal-onset multisystem inflammatory disease (NOMID). NOMID is a form of cryopyrin-associated periodic syndromes (CAPS), a group of rare, inherited, autoinflammatory diseases. Anakinra is the first and only FDA-approved treatment for NOMID.[8]

Another IL antagonist, tocilizumab, binds specifically to both soluble and membrane-bound IL-6 receptors and inhibits IL-6 mediated signaling through these receptors. IL-6 is a chemical messenger that has been associated with the ongoing inflammatory process. Tocilizumab is indicated for the treatment of adult patients with rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies and for the treatment of pediatric patients with active systemic juvenile idiopathic arthritis.[10] A third IL antagonist, ustekinumab, is a fully-humanized monoclonal antibody that binds with high affinity to both IL-12 and IL-23 cytokines, which are involved in inflammatory and immune responses. Ustekinumab is indicated for the treatment of adult patients with plaque psoriasis who are candidates for phototherapy or systemic therapy.[11]

Abatacept is the only T-cell activation inhibitor in the immunomodulator class of drugs. Abatacept binds to CD80 and CD86 preventing CD28 activation, which is required for the costimulatory signal necessary for full activation of the T-cell. Abatacept is indicated for rheumatoid arthritis and juvenile idiopathic arthritis.[12]

Generally, current consensus guidelines support the use of the TNF-blockers with respect to their FDA-approved indications and no one agent is preferred over another.[13-29] As more recent guidelines are published, the recommendations for use TNF-blockers earlier in therapy is becoming a more common occurance.[20,21,25] Because the immunomodulators are biologic agents made from living organisms and are extremely difficult to duplicate, congress has struggled to create regulations to approve generic versions of these agents. Currently, none of the agents in this class are available generically; however,

the recently upheld Patient Protection and Affordable Care provides a legal framework for regulatory approval of biosimilar drugs.[30]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Abatacept (Orencia®)	T-cell activation inhibitor	-
Adalimumab (Humira®)	Tumor necrosis factor-inhibitor	-
Anakinra (Kineret®)	Interleukin-1 inhibitor	-
Certolizumab (Cimzia®)	Tumor necrosis factor-inhibitor	-
Etanercept (Enbrel®)	Tumor necrosis factor-inhibitor	-
Golimumab (Simponi®)	Tumor necrosis factor-inhibitor	-
Infliximab (Remicade®)	Tumor necrosis factor-inhibitor	-
Tocilizumab (Actemra®)	Interleukin-6 inhibitor	-
Ustekinumab (Stelara®)	Interleukin-12 and Interleukin-23 inhibitor	-

Indications

Table 2. Food and Drug Administration Approved Indications[3-8,10-12]

Generic Name	Ankylo-sing Spondy-litis	Crohn's Disease	Juvenile Idio-pathic Arthritis	NO-MID	Plaque Psoriasis	Psoriatic Arthritis	Rheum-atoid Arthritis	Ulcer-ative Colitis
Abatacept			✔ *				✔ *	
Adalimumab	✔	✔ †	✔		✔ ‡	✔ *	✔ *	✔ §§
Anakinra				✔			✔ §*	
Certolizumab		✔ ‖					✔	
Etanercept	✔		✔		✔ ¶	✔ #	✔ ‡‡	
Golimumab	✔					✔ ‡‡	✔ **	
Infliximab	✔	✔ ‖			✔ ¶	✔	✔ **	✔ ‖
Tocilizumab			✔				✔ ††	
Ustekinumab					✔ ¶			

NOMID=Neonatal-onset multisystem inflammatory disease
*Alone or in combination with disease modifying antirheumatic drugs (DMARDs) other than tumor necrosis factor inhibitors.
†In patients who have had an inadequate response to conventional therapy and if they have also lost response to or are intolerant of infliximab.
‡In patients who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.
§In patients who have failed one or more DMARDs.
‖ In patients who have had an inadequate response to conventional therapy.
¶ In patients who are candidates for systemic therapy or phototherapy.
#May be used in combination with methotrexate in patients who do not respond adequately to methotrexate alone.
**In combination with methotrexate.
††In patients who had an inadequate response to one or more tumor necrosis factor inhibitors.
‡‡ May be used alone or in combination with methotrexate.
§§ in patients who had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine.

As a class, the immunomodulators are used off-label for a wide-variety of autoimmune diseases. Etanercept is under investigation for the treatment of Wegener's granulomatosis and is designated as an orphan drug by the Food and Drug Administration for this indication. Infliximab is under investigation for the treatment of juvenile idiopathic arthritis, rheumatoid arthritis, Uveitis and Behcet's syndrome. [31]

Pharmacokinetics

Table 3. Pharmacokinetics[3-8,10-12,31]

Generic Name	Bioavailability (%)	Time to Peak Concentration	Elimination Half-Life
Abatacept	100 (intravenous); 78.6 (subcutaneous)	Not reported	13.0 to 14.3 days
Adalimumab	64	131±56 hours	10 to 18days
Anakinra	95	3 to 7 hours	4 to 6 hours
Certolizumab	80	54 to 171 hours	14 days
Etanercept	58	69±34 hours	102±30 hours
Golimumab	53	48 to 144 hours	14 days
Infliximab	100	Not reported	8 to 10 days
Tocilizumab	100	Not reported	11 to 23 days
Ustekinumab	Not reported	7.0 to 13.5 days	14.9 to 45.6 days

Clinical Trials

Clinical studies evaluating the safety and efficacy of the immunomodulators in their respective Food and Drug Administration (FDA)-approved indications are described in Table 4.[32-93]

The approval of adalimumab for the treatment of ankylosing spondylitis (AS) was based on one randomized, double-blind, placebo-controlled study (N=315) in which a significantly greater proportion of patients achieved an improvement in Assessment in Spondyloarthritis International Society (ASAS) response ≥20% (primary endpoint) with adalimumab compared to placebo (58 vs 21%; *P*<0.001). A >50% improvement in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score, a measure of fatigue severity, spinal and peripheral joint pain, localized tenderness, and morning stiffness which is considered clinically meaningful, was detected in 45% of adalimumab-treated patients compared to 16% of placebo-treated patients at week 12 (*P*<0.001). This response was sustained through week 24, with 42% of patients in the adalimumab group achieving a ≥50% improvement in BASDAI score compared to 15% in the placebo group (*P*<0.001).[32]

The efficacy of etanercept in patients with AS was established in two double-blind, randomized, placebo-controlled trials. Patients treated with etanercept experienced a significantly greater response to treatment compared to placebo (*P*<0.001).[34] More patients achieved an ASAS 20 response compared to placebo (*P*<0.001).[35] In an open-label extension study evaluating the long-term safety and efficacy of etanercept in patients with AS, the most common adverse events were injection site reactions, headache and diarrhea after 192 weeks of treatment. A total of 71% of patients were ASAS 20 responders at week 96 and 81% of patients were responders at week 192. The ASAS 5/6 response rates were 61% at week 96 and 60% at week 144 and partial remission response rates were 41% at week 96 and 44% at week 192. Placebo patients who switched to etanercept in the open-label extension trial showed similar patterns of efficacy maintenance.[33] Etanercept and sulfasalazine were compared in a multicenter, randomized, double-blind trial in adult patients with active AS who had failed treatment with nonsteroidal antiinflammatory drugs (NSAIDs). A significantly greater proportion of patients treated with etanercept achieved the primary outcome of ASAS 20 at week 16 compared to patients treated with sulfasalazine (*P*<0.0001). There was also significantly more patients that achieved ASAS 40 and ASAS 5/6 in the etanercept group compared to the sulfasalazine group (*P*<0.0001 for both).[37]

The FDA-approval of golimumab for AS was based on a multicenter, randomized, double-blind, placebo-controlled trial in adult patients with active disease for at least three months (N=356). Golimumab with or without a disease modifying antirheumatic drug (DMARD) was compared to placebo with or without a DMARD and was found to significantly improve the signs and symptoms of AS as demonstrated by the percentage of patients achieving an ASAS 20 response at week 14.[38] The efficacy of infliximab in the treatment of AS was demonstrated in 12- and 24-week double-blind placebo-controlled trials. Significantly more patients that achieved a 50% BASDAI score in the infliximab group compared to the placebo group

at 12 weeks (*P*<0.0001).[39] At 24 weeks, significantly more patients in the infliximab group achieved ASAS 20 compared to the patients randomized to receive placebo (*P*<0.001).[40]

In a systematic review of patients with Crohn's disease who had failed a trial with infliximab, the administration of adalimumab was associated with remission rates of 19 to 68% at one year. Serious cases of sepsis, cellulitis, and fungal pneumonia occurred in 0 to 19% of patients in up to four years of treatment.[41] Shao et al performed a meta-analysis evaluating certolizumab use over 12 to 26 weeks for the treatment of Crohn's disease. The results demonstrated that certolizumab was associated with an increased rate of induction of clinical response (relative risk [RR], 1.36; *P*=0.004) and remission (RR, 1.95; *P*<0.0001) compared to placebo; however, risk of infection was higher with certolizumab use.[42] In a trial evaluating infliximab for induction of remission, significantly more patients achieved remission at four weeks with infliximab compared to placebo (*P*<0.005).[45] In a trial by Present et al, significantly more patients treated with infliximab 5 mg/kg and 10 mg/kg experienced a reduction of ≥50% in the number of fistulas compared to patients treated with placebo (*P*=0.002 and *P*=0.02, respectively).[46] In an open-label trial evaluating the use of infliximab in pediatric Crohn's patients, 88.4% responded to the initial induction regimen and 58.6% were in clinical remission at week 10.[47] Adalimumab, certolizumab and infliximab demonstrated the ability to achieve clinical response (RR, 2.69; *P*<0.00001; RR, 1.74; *P*<0.0001 and RR, 1.66; *P*=0.0046, respectively) and maintain clinical remission (RR, 1.68; *P*=0.000072 with certolizumab and RR, 2.50; *P*=0.000019 with infliximab; adalimumab, data not reported) over placebo in patients with Crohn's disease. Adalimumab and infliximab also had a steroid-sparing effect.[48]

In a trial by Ruperto et al in pediatric patients (six to 17 years of age) with juvenile idiopathic arthritis, patients treated with placebo experienced significantly more disease flares compared to patients treated with abatacept (*P*=0.0003). The time to flare was significantly different favoring abatacept (*P*=0.0002).[46] Adalimumab was studied in a group of patients (four to 17 years of age) with active juvenile rheumatoid arthritis who had previously received treatment with NSAIDs. Patients were stratified according to methotrexate (MTX) use and received 24 mg/m^2 (maximum of 40 mg) of adalimumab every other week for 16 weeks. The patients with an American College of Rheumatology Pediatric 30 (ACR Pedi 30) response at week 16 were randomly assigned to receive adalimumab or placebo in a double-blind fashion every other week for up to 32 weeks. The authors found that 74% of patients not receiving MTX and 94% of those receiving MTX had an ACR Pedi 30 at week 16. Among those not receiving MTX, flares occurred in 43% receiving adalimumab and 71% receiving placebo (*P*=0.03). In the patients receiving MTX, flares occurred in 37 and 65% in the adalimumab and placebo groups respectively (*P*=0.02). ACR Pedi scores were significantly greater with adalimumab than placebo and were sustained after 104 weeks of treatment.[50] In a trial involving 69 pediatric patients with active polyarticular juvenile rheumatoid arthritis despite treatment with NSAIDs and MTX, etanercept was associated with a significant reduction in flares compared to placebo (28 vs 81%; *P*=0.003).[51] Ninety-four percent of patients who remained in an open-label four-year extension met juvenile rheumatoid arthritis 30% definition of improvement; while C-reactive protein levels, articular severity scores, and patient pain assessment scores all decreased. There were five cases of serious adverse events related to etanercept therapy after four years.[52] The approval of tocilizumab for its newest indication of systemic juvenile idiopathic rheumatoid arthritis was based on a randomized, placebo-controlled trial (N=112). Children age two to 17 years of age with active systemic juvenile idiopathic rheumatoid arthritis and inadequate response to NSAIDs and corticosteroids were included in the study. The primary endpoint was ACR 30 and absence of fever at week 12. At week 12, the proportion of patients achieving ACR 30 and absence of fever was significantly greater in the tocilizumab-treated patients compared to the placebo treated patients (85 vs 24%; *P*<0.0001).[54]

In a randomized, double-blind, double-dummy trial, adalimumab was compared to MTX and placebo in patients with moderate to severe psoriasis despite treatment with topical agents. The primary outcome, the proportion of patients that achieved Psoriasis Area and Severity Index (PASI) 75 at 16 weeks, was achieved by significantly more patients in the adalimumab group compared to patients in the MTX (*P*<0.001) and placebo (*P*<0.001) groups.[56] In the PHOENIX 1 and PHOENIX 2 studies, more than 2,200 patients with moderate to severe psoriasis were randomized to receive ustekinumab 45 mg, 90 mg or placebo at weeks zero, four and every 12 weeks thereafter.[57,58] In PHOENIX 1, patients who were initially randomized to ustekinumab at week zero and achieved long-term response (≥75% improvement in

psoriasis area and severity at weeks 28 and 40) were re-randomized at week 40 to maintenance ustekinumab or withdrawal from treatment. Patients in the 45 mg ustekinumab and 90 mg ustekinumab groups had higher proportion of patients achieving PASI 75 compared to patients in the placebo group at week 12 (*P*<0.0001 for both). PASI 75 response was better maintained to at least one year in those receiving maintenance ustekinumab than in those withdrawn from treatment at week 40 (*P*<0.0001).[54] In PHOENIX 2, the primary endpoint (the proportion of patients achieving a PASI 75 response at week 12) was achieved in significantly more patients receiving ustekinumab 45 and 90 mg compare to patients receiving placebo (*P*<0.0001). Partial responders were re-randomized at week 28 to continue dosing every 12 weeks or escalate to dosing every eight weeks. More partial responders at week 28 who received 90 mg every eight weeks achieved PASI 75 at week 52 than did those who continued to receive the same dose every 12 weeks. There was no response to changes in dosing intensity in partial responders treated with 45 mg. Adverse events were similar between groups.[55] In a study comparing etanercept and ustekinumab, a greater proportion of psoriasis patients achieved the primary outcome (PASI 75 at week 12) with ustekinumab 45 (67.5%) and 90 mg (73.8%) compared to etanercept 50 mg (56.8%; *P*=0.01 vs ustekinumab 45 mg; *P*<0.001 vs ustekinumab 90 mg). In this trial, etanercept therapy was associated with a greater risk of injection site erythema (14.7 vs 0.7% of all ustekinumab patients).[56] In a meta-analysis evaluating the efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate to severe psoriasis, adalimumab use was associated with a risk difference of 64% compared to placebo in achieving a PASI 75 response (*P*<0.00001) while etanercept 25 and 50 mg twice weekly were associated with a risk difference of 30 and 44% compared to placebo (*P*<0.00001 for both strengths vs placebo). The infliximab group had the greatest response with a risk difference of 77% compared to the placebo group (*P*<0.0001). The withdrawal rate was 0.5% with adalimumab, 0.4 to 0.5% with etanercept and 1.3% with infliximab.[60]

In two trials, psoriatic arthritis patients receiving adalimumab 40 mg every other week achieved an ACR 20 at a higher rate compared to placebo. Thirty-nine percent of patients in the active treatment group compared to 16% in the placebo group achieved this endpoint by week 12 (*P*=0.012) in a trial by Genovese et al (N=100), while 58 and 14% of patients, respectively, achieved this endpoint in a second trial (*P*<0.001).[61,62] Adalimumab use was associated with an improvement in structural damage, as measured by the Modified Total Sharp Score (mTSS), compared to those receiving placebo (-0.2 vs 1.0; *P*<0.001).[62] In a 12-week trial in adult patients with psoriatic arthritis despite NSAID therapy, 87% of etanercept treated patients met psoriatic arthritis response criteria, compared to 23% of those on placebo (*P*<0.0001). A PASI 75 improvement and ACR 20 response was detected in 26 and 73% of etanercept-treated patients compared to 0 (*P*=0.0154) and 13% (*P*<0.0001) of placebo-treated patients.[63] In a second trial, the mean annualized rate of change in the mTSS with etanercept was -0.03 unit, compared to 1.00 unit with placebo (*P*<0.0001). At 24 weeks, 23% of etanercept patients eligible for psoriasis evaluation achieved at least a PASI 75, compared to 3% of placebo patients (*P*=0.001). Furthermore, health assessment questionnaire scores were significantly improved with etanercept (54%) over placebo (6%; *P*<0.0001). Injection site reaction occurred at a greater rate with etanercept than placebo (36 vs 9%; *P*<0.001).[64] The FDA-approval of golimumab for psoriatic arthritis was based on a multicenter, randomized, double-blind, placebo-controlled trial in adult patients with moderate to severely active psoriatic arthritis despite NSAID or DMARD therapy (N=405). Golimumab with or without MTX compared to placebo with or without MTX, resulted in significant improvement in signs and symptoms as demonstrated by the percentage of patients achieving a ACR 20 response at week 14. The ACR responses observed in the golimumab-treated groups were similar in patients receiving and not receiving concomitant MTX therapy.[62] In a trial by Antoni et al, more infliximab treated patients achieved ACR 20 at weeks 12 and 24 compared to placebo treated patients (*P*<0.001).[66]

The approval of the subcutaneous formulation of abatacept was based on a double-blind, double-dummy, randomized trial demonstrating noninferiority to the intravenous formulation. The trial enrolled patients with rheumatoid arthritis that had an inadequate response to MTX. The proportion of patients achieving ACR 20 was not significantly different between the groups.[69] The RAPID-1 and RAPID-2 studies compared certolizumab in combination with MTX to placebo plus MTX in adults with active rheumatoid arthritis despite MTX therapy.[73,74] A significantly greater proportion of patients on certolizumab 400 mg plus MTX at weeks zero, two, and four then 200 mg or 400 mg every two weeks attained ACR 20, ACR

50 and ACR 70 responses after 24 weeks compared to patients treated with placebo and MTX (*P*≤0.01). The response rates were sustained with active treatment over 52 weeks.[73] The mTSS' were significantly lower with certolizumab in combination with MTX compared to MTX in combination with placebo.[73,74] Fleischmann et al evaluated certolizumab monotherapy compared to placebo in patients with active disease who had failed at least one prior DMARD trial. After 24 weeks, ACR 20 response rates were significantly greater with active treatment (45.5%) compared to placebo (9.3%; *P*<0.001). Significant improvements in secondary endpoints (ACR 50, ACR 70, individual ACR component scores, and patient reported outcomes) were also associated with certolizumab therapy.[75,76]

The FDA-approval of golimumab for rheumatoid arthritis was based on three multicenter, double-blind, randomized, controlled trials in 1,542 with moderate to severe active disease. A greater percentage of patients from all three trials treated with the combination of golimumab and MTX achieved ACR responses at week 14 and week 24 compared to patients treated with MTX alone.[78-80] Moreover, the golimumab 50 mg groups demonstrated a greater improvement compared to the control groups in the change in mean Health Assessment Questionnaire Disability Index (HAQ-DI).[79,80]

The efficacy and safety of tocilizumab was assessed in five randomized, double-blind, multicenter studies in patients ages 18 years and older with active rheumatoid arthritis. Patients had rheumatoid arthritis diagnosed according to ACR criteria, with at least eight tender and six swollen joints at baseline. Tocilizumab was administered every four weeks as monotherapy (AMBITION), in combination with MTX (LITHE and OPTION) or other DMARDs (TOWARD) or in combination with MTX in patients with an inadequate response to tumor necrosis factor (TNF) antagonists (RADIATE). In all studies, mild to moderate adverse events were reported, occurring in similar frequencies in all study groups. The most common adverse events in all studies were infections and gastrointestinal symptoms.[83-88] AMBITION evaluated the safety and efficacy of tocilizumab monotherapy compared to MTX in patients with active rheumatoid arthritis for whom previous treatment with MTX or biological agents had not failed. A total of 673 patients were randomized to one of three treatment arms, tocilizumab 8 mg/kg every four weeks, MTX 7.5 mg/week and titrated to 20 mg/week within eight weeks, or placebo for eight weeks followed by tocilizumab 8 mg/kg. The primary endpoint was the proportion of patients achieving ACR 20 response at week 24. The results showed that tocilizumab monotherapy compared to MTX monotherapy produced greater improvements in rheumatoid arthritis signs and symptoms, and a favorable benefit-risk ratio in patients who had not previously failed treatment with MTX or biological agents. In addition, more patients treated with tocilizumab achieved remission at week 24 compared to patients treated with MTX.[83] The24-week ADACTA trial in RA patients intolerant to methotrexate treatment found significantly greater improvements in DAS 28 scores and ACR core set measures in patients taking with tocilizumab patients compared to adalimumab.[96]

In the LITHE study, 1,196 patients with moderate to severe rheumatoid arthritis who had an inadequate response to MTX were randomized to receive 4 mg/kg of tocilizumab, 8 mg/kg of tocilizumab or placebo every four weeks in addition to background MTX. At 52 weeks, more patients treated with tocilizumab 8 mg/kg achieved remission (47.2 vs 7.9%; P<0.0001) according to the Disease Activity Score using 28 joint counts (DAS28 score <2.6) or had low disease activity (DAS28 ≤3.2) compared to placebo (63.6 vs 45.3%; *P*<0.0001).[86] OPTION evaluated tocilizumab in 623 patients with moderate to severely active rheumatoid arthritis. Patients received tocilizumab 8 mg/kg, 4 mg/kg, or placebo intravenously every four weeks, with MTX at stable pre-study doses (10 to 25 mg/week). Rescue therapy with tocilizumab 8 mg/kg was offered at week 16 to patients with <20% improvement in swollen and tender joint counts. The primary endpoint was ACR 20 at week 24. An ACR 20 was seen in significantly more patients receiving tocilizumab compared to those receiving placebo at week 24 (*P*<0.001). Moreover, a significantly higher proportion of patients treated with tocilizumab achieved ACR 50 and ACR 70 responses at week 24 (*P*<0.001). Greater improvements in physical function, as measured by the HAQ-DI, were seen with tocilizumab when compared to MTX (-0.52 vs -0.55 vs -0.34; *P*<0.0296 for 4 mg/kg and *P*<0.0082 for 8 mg/kg).[84] In the TOWARD study, investigators examined the efficacy and safety of tocilizumab combined with conventional DMARDs in 1,220 patients with active rheumatoid arthritis. Patients remained on stable doses of DMARDs and received tocilizumab 8 mg/kg or placebo every four weeks for 24 weeks. At week 24, significantly more patients taking tocilizumab with DMARDs achieved an ACR 20 response compared

to patients in the control group. The authors concluded that tocilizumab, combined with any of the DMARDs evaluated (MTX, chloroquine, hydroxychloroquine, parenteral gold, sulfasalazine, azathioprine, and leflunomide), was safe and effective in reducing articular and systemic symptoms in patients with an inadequate response to these agents. A greater percentage of patients treated with tocilizumab also had clinically meaningful improvements in physical function when compared to placebo (60 vs 30%; *P* value not reported).[85] In the RADIATE trial, investigators evaluated the safety and efficacy of tocilizumab in patients with rheumatoid arthritis refractory to TNF antagonist therapy. A total of 499 patients with inadequate response to one or more TNF antagonists were randomly assigned to 8 or 4 mg/kg tocilizumab or placebo every four weeks with stable MTX doses (10 to 25 mg weekly) for 24 weeks. ACR 20 responses and safety endpoints were assessed. The results demonstrated that tocilizumab plus MTX is effective in achieving rapid and sustained improvements in signs and symptoms of rheumatoid arthritis in patients with inadequate response to TNF antagonists and has a manageable safety profile. The ACR 20 response in both tocilizumab groups was also found to be comparable to those seen in patients treated with adalimumab and infliximab, irrespective of the type or number of failed TNF antagonists.[88]

A Cochrane review examined abatacept for the treatment of rheumatoid arthritis. ACR 50 response was not significantly different at three months, but was significantly higher in the abatacept group at six and 12 months compared to placebo (RR, 2.47; 95% confidence interval [CI], 2.00 to 3.07 and RR, 2.21; 95% CI, 1.73 to 2.82). Similar results were seen in ACR 20 and ACR 70.[61] The safety and efficacy of adalimumab for the treatment of rheumatoid arthritis was assessed in a Cochrane systematic review. Treatment with adalimumab in combination with MTX was associated with a RR of 1.52 to 4.63, 4.63 (95% CI, 3.04 to 7.05) and 5.14 (95% CI, 3.14 to 8.41) for ACR 20, ACR 50, and ACR 70 responses at six months when compared to placebo in combination with MTX. Adalimumab monotherapy was also proven efficacious.[91] A Cochrane review was performed to compare anakinra to placebo in adult patients with rheumatoid arthritis. Significant improvement in both primary (ACR 20, 38 vs 23%; RR, 1.61; 95% CI, 1.32 to 1.98) and secondary (ACR 50 and ACR 70) outcomes were detected. The only significant difference in adverse events noted with anakinra use was the rate of injection site reactions (71 vs 28% for placebo).[9] In another Cochrane review, etanercept was compared to MTX or placebo in adult patients with rheumatoid arthritis and 64% of individuals on etanercept 25 mg twice-weekly attained an ACR 20 vs 15% of patients on either MTX alone or placebo after six months of treatment (RR, 3.8; number needed to treat [NNT], 2). An ACR 50 and ACR 70 were achieved by 39 and 15% in the etanercept group compared to 4% (RR, 8.89; NNT, 3) and 1% (RR, 11.31; NNT, 7) in the control groups. Etanercept 10 mg twice-weekly was only associated with significant ACR 20 (51 vs 11% of controls; RR, 4.6; 95% CI, 2.4 to 8.8; NNT, 3) and ACR 50 responses (24 vs 5% of controls; RR, 4.74; 95% CI, 1.68 to 13.36; NNT, 5). Seventy-two percent of patients receiving etanercept had no increase in Sharp erosion score compared to 60% of MTX patients. Etanercept 25 mg was associated with a significantly reduced total Sharp score (weighted mean difference, -10.50; 95% CI, -13.33 to -7.67). The Sharp erosion scores and joint space narrowing were not significantly reduced by either etanercept dose.[92] A meta-analysis by Wiens et al evaluated the efficacy of infliximab in combination with MTX compared to placebo plus MTX. There was a higher proportion of patients in the infliximab group that achieved an ACR 20 at 30 weeks compared to patients in the placebo group (RR, 1.87; 95% CI, 1.43 to 2.45). These effects were similar in the proportion of patients achieving ACR 50 and ACR 70 (RR, 2.68; 95% CI, 1.79 to 3.99 and RR, 2.68; 95% CI, 1.78 to 4.03).[94] Nixon et al performed a meta-analysis of randomized controlled trials including adalimumab, anakinra, etanercept, and infliximab with or without MTX. The odds ratio (OR) for an ACR 20 was 3.19 (95% CI, 1.97 to 5.48) with adalimumab, 1.70 (95% CI, 0.90 to 3.29) with anakinra, 3.58 (95% CI, 2.09 to 6.91) with etanercept and 3.47 (95% CI, 1.66 to 7.14) with infliximab compared to placebo. The OR to achieve an ACR 50 with adalimumab was 3.97 (95% CI, 2.73 to 6.07), 2.13 (95% CI, 1.27 to 4.22) with anakinra, 4.21 (95% CI, 2.74 to 7.43) with etanercept and 4.14 (95% CI, 2.42 to 7.46) compared to placebo. Further analysis of each agent against another was performed and no significant difference was determined between individual agents in obtaining an ACR 20 and ACR 50. However, the TNF-blockers as a class showed a greater ACR 20 and ACR 50 response compared to anakinra (OR, 1.96; 95% CI, 1.03 to 4.01 and OR, 1.93; 95% CI,1.05 to 3.50; $P<0.05$).[95]

Infliximab demonstrated effectiveness in ulcerative colitis in two trials. Studies ACT 1 and ACT 2 evaluated infliximab compared to placebo for this indication. In both trials, clinical response at week eight

was significantly higher in patients treated with infliximab 5 mg/kg or 10 mg/kg compared to placebo (all *P*<0.001). A significantly higher clinical response rate in both infliximab groups was maintained throughout the duration of the studies.[66] A randomized, open-label trail evaluated infliximab as different dosing intervals for the treatment of pediatric ulcerative colitis. At week eight, 73.3% of patients met the primary endpoint of clinical response (95% CI, 62.1 to 84.5%).[99]

Recently adalimumab gained FDA-approval for the inducing and sustaining clinical remission of patients with active ulcerative colitis. The approval was the result of adalimumab showing effectiveness in 2 studies evaluating adalimumab compared to placebo. In both studies adalimumab initially dosed at 160 mg, then 80 mg at week 2 and 40 mg every other week thereafter showed significant improvements in proportion of patients that were in remission after 8 weeks of treatment (*P*<0.05 in each study).[100,101] Patients also demonstrated significant decreases compared to placebo (*P*<0.05 in each study) in rectal bleeding, stool frequency and physician global assessment scores. In the study by Sandborn et al, remission observed by week 8 was sustained out to 52 weeks in 8.5% of the patients as did mucosal healing in 18.5% of patients (*P*<0.05 for all). In this study, it was noted that larger proportion of patients were also able to discontinue corticosteroid use at week 52 (13.3%) vs placebo (5.7%) and achieve remission (*P*=0.035).[101] It was noted that a treatment arm in the Reinisch et al trial that utilized a lower dose of adalimumab (initial dose 80 mg, then 40 mg every other week thereafter) did not show significant improvements in remission rates, clinical response or symptom improvement when compared to placebo.[100]

Neonatal-onset multisystem inflammatory disease (NOMID) is an rare autoinflammatory disorder that presents around birth with systemic inflammation and rash and may develop with severe organ manifestations involving the eyes, ears, bones and central nervous system. Progressive cognitive impairment and physical disability is a consequence of the organ damage with mortality rates estimated at up to 20% before adulthood. Anakinra recently became to first and only FDA-approved treatment for patients with neonatal-onset multisystem inflammatory disease NOMID. The approval was the result of a single trial in 43 NOMID patients over 60 months that demonstrated sustained improvements in patients' diary scores, physician global scores of disease activity, patient/parent pain scores, and inflammatory markers (all *P*<0.001 at 36 and 60 months). In addition, most patients showed stable or improved hearing as well as stable visual acuity and peripheral vision.[102]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ankylosing Spondylitis				
van der Heijde et al[32] Adalimumab 40 mg every other week vs placebo Patients were allowed to continue MTX, NSAIDs, prednisone or prednisone equivalent and SSZ.	DB, MC, RCT Patients ≥18 years of age with a diagnosis of AS based on the modified New York criteria with active disease BASDAI score ≥4, a total back pain score ≥4 by VAS (VAS, 0 to 10 cm) or a duration of morning stiffness ≥1 hour	N=315 24 weeks	Primary: ASAS 20 response at week 12 Secondary: ASAS 20 response at week 24, measures of disease activity, spinal mobility and function, ASAS partial remission	Primary: An ASAS 20 response was attained in 58% of participants taking adalimumab vs 21% of participants taking placebo at week 12 (*P*<0.001). Secondary: A significantly greater ASAS 20 response was also noted at week 24 with adalimumab vs placebo (52 vs 18%; *P*<0.001). Adalimumab, compared to placebo, resulted in a significant improvement in other measures of disease activity such as a 50% improvement in BASDAI at week 12 (45 vs 16%; *P*<0.001) which was sustained through week 24 (42 vs 15%; *P*<0.001). ASAS 5/6 and ASAS 40 responses were attained in 49 vs 13% and 40 vs 13% of adalimumab vs placebo patients at week 12 (*P*<0.001) and 45 vs 12% and 39 vs 13% at week 24 (*P*<0.001), respectively. Partial remission was achieved in 21 vs 4% at week 12 and 22 vs 6% at week 24 in the adalimumab and placebo groups, respectively (*P*<0.001).
Van Assche et al[33] (SWITCH) Adalimumab 80 mg at week zero and 40 mg every other week Patients not randomized to adalimumab continued prior infliximab at 5 mg/kg at their regularly scheduled interval. Patients with a disease flare were able to intensify	OL, PRO, RCT Patients ≥18 years with luminal CD treated with infliximab maintenance therapy started for ≥6 months with a complete clinical response (PGA assessment of signs and symptoms, but the CDAI at baseline <200) with stable	N=73 54 weeks	Primary: Proportion of patients in the adalimumab group preferring adalimumab over infliximab and proportion of patients who needed rescue therapy with short courses of steroids or intensified anti-TNF dosing or	Primary: There was a statistically significant increase in the preference of adalimumab over infliximab for patients who changed from infliximab to adalimumab therapy at all evaluation points (*P*<0.05), except week 56 (*P*=0.08). Dose intensification or early treatment termination occurred significantly more frequently over 54 weeks in patients switched to adalimumab (47%) compared to those who continued infliximab (16%; *P*=0.003). Significantly more patients initiating adalimumab therapy discontinued therapy due to loss of response or intolerance compared those who continued infliximab therapy (28 vs 2%; *P*<0.01). Of note, the patient who discontinued infliximab was successfully treated with adalimumab and eight of the 10 patients who stopped adalimumab treatment returned to infliximab

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
treatment as follows: adalimumab 40 mg every week and in the infliximab group, a decrease of the dosing interval with two-week decrements.	infliximab dosing intervals of ≥6 weeks		who had to stop the assigned anti-TNF agent Secondary: Proportion of patients with an injection- or infusion-related reaction and proportion of patients with an increase in the CDAI of >100 above baseline and IBDQ	therapy. The reasons for early discontinuation of treatment were loss of tolerance in six of 10 patients on adalimumab and in the one patient receiving infliximab. Four other patients in the adalimumab group stopped for loss of efficacy. Refractory eczema with fatigue or arthralgias (n=2), general malaise and diarrhea following injections (n=2) and fatigue plus inability to comply with injections (n=2) led to adalimumab intolerance and an infusion reaction to infliximab intolerance. Secondary: There was no difference in the change from baseline in CDAI at time of early termination in the adalimumab group (184 vs 78; *P*=0.10). Dose intensification occurred in 27.7% of patients in the adalimumab group, three of which later stopped adalimumab for loss of response, and in and 13.5% of patients in the infliximab group (*P*=0.20). The median time to dose intensification was not significantly different between the adalimumab and infliximab treatment arms (24 vs 32 weeks; *P*=0.64). An increase in CDAI ≥100 points was observed in 18.9% of patients in the infliximab group and in 27.7% of patients in the adalimumab group while on the initially assigned treatment. Median IBDQ values at baseline and at week 56 were comparable in both groups and the medians stayed well in the range compatible with disease remission throughout the trial.
Gorman et al[34] Etanercept 25 mg twice a week vs placebo Patients were allowed to continue stable doses of	DB, RCT Patients ≥18 years of age with active inflammatory AS based on the modified New York criteria, despite accepted treatments	N=40 4 months	Primary: Measures of morning stiffness, spinal pain, functioning, patient's global assessment of disease activity, joint swelling Secondary:	Primary: A response to treatment was detected in 80% of individuals receiving etanercept as opposed to 30% of individuals receiving placebo (*P*=0.004). Primary endpoints were reported as follows for the etanercept and placebo groups, respectively: duration of morning stiffness, 25.0±78.9 vs 60.0±65.0 minutes (*P*<0.001); scores for nocturnal spinal pain (0=none to 100=most severe), 15.0±24.3 vs 38.0±27.8 (*P*<0.001); mean swollen joint scores (0=none to 3=severe), 1.6±3.8 vs 3.7±7.6 (*P*=0.17); patient's global assessment of disease activity (0=none to 5=very severe), 2.0±0.6 vs 3.0±0.9 (*P*<0.001); and the BASFI scores (0=none to 10=severe

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
DMARDs, NSAIDs, and oral corticosteroids.			Physician's global assessment of disease activity, measures of spinal mobility, scores for enthesitis and peripheral-joint tenderness, ESR and CRP levels, adverse events	limitations), 2.2±2.1 vs 3.1±3.0 (*P*<0.001). Secondary: Differences in a number of secondary outcomes did reach statistical significance among those taking etanercept compared to those taking placebo including, physician's global assessment of disease activity (23.0±10.6; *P*<0.001), chest expansion (3.5±1.9 vs 2.9±1.7 cm; *P*=0.006), Modified Newcastle Enthesis Index, which is a measure of 17 enthesis on a 4 point pain scale (0.0±3.0 vs 1.5±8.0; *P*=0.001), ESR level (8.5±12.8 vs 16.5±18.7 mm/hour; *P*<0.001) and CRP level (0.7±1.1 vs 2.0±2.8 mg/dL; *P*=0.003). Injection site reactions and minor infections were the most commonly reported adverse events. The incidence in overall adverse events or specific events did not differ significantly.
Calin et al[35] Etanercept 25 mg twice a week vs placebo Patients were allowed to continue stable doses of DMARDs (HCQ, MTX, or SSZ) one NSAID, and oral corticosteroids (≤10 mg prednisone).	DB, MC, RCT Patients 18 to 70 years of age with active AS based on the modified New York criteria	N=84 12 weeks	Primary: ASAS 20 response Secondary: ASAS 50 response, ASAS 70 response, individual components of ASAS, BASDAI, acute phase reactants, spinal mobility tests, safety	Primary: ASAS 20 response was found in 60.0% of etanercept patients compared to 23.1% of placebo patients at 12 weeks (*P*<0.001). Secondary: The etanercept group was associated with higher rates of ASAS 50 and 70 responses (48.9 and 24.4%) compared to placebo (10.3 and 10.3%) at week 12. However, only the differences in ASAS 50 reached statistical significance at this assessment point (*P*<0.001). ASAS 70 was significantly different between groups up until week eight (28.9% with etanercept vs 7.7% with placebo; *P*<0.05). The changes in the individual ASAS components were reported as follows for etanercept and placebo: spinal inflammation, 43.3 vs 15.9% (*P*=0.003); nocturnal and total pain, 43.1 vs 6.2% (*P*=0.000); patient's global assessment, 37.0 vs 12.6% (*P*=0.11); functional impairment (BASFI), 35.4 vs 3.4% (*P*=0.000); BASDAI composite score, 43.6 vs 13.6% (*P*=0.001); and BASDAI fatigue score, 42.6 vs -4.9% (*P*=0.000). Injection site reactions occurred more frequently with etanercept compared to placebo (33 vs 15%; *P*<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Davis et al[36] Etanercept 25 mg twice weekly until week 72, then 50 mg once weekly Stable doses of corticosteroids and NSAIDs were required 2 weeks prior to enrollment; stable doses of HCQ, MTX, or SSZ were required if deemed necessary.	ES, OL Patients 18 to 70 years of age with active AS based on the modified New York criteria	N=257 Up to 192 weeks	Primary: Safety (adverse events, serious adverse events, infections, serious infections, death) and efficacy (ASAS 20 response, ASAS 5/6 response, partial remission rates) Secondary: Not reported	Primary: After up to 192 weeks of treatment, the most common adverse events were injection site reactions, headache and diarrhea; no deaths were reported. For etanercept treatment the exposure adjusted serious event rate/patient year was 0.08, the exposure adjusted infection rate/patient year was 1.10, and the exposure adjusted serious infection rate/patient year was 0.02. Injection site reactions were reported in 22.2% of patients, which lead to the withdrawal of 0.4% of patients. A total of 71% of patients were considered ASAS 20 responders at week 96 and 81% of patients were considered responders at week 192. ASAS 5/6 response rates were 61% at week 96 and 60% at week 144. Partial remission response rates were 41% at week 96 and 44% at week 192. Placebo patients who switched to etanercept in the OL extension showed similar rates of efficacy maintenance. Secondary: Not reported
Braun et al[37] ASCEND Etanercept 50 mg once weekly vs SSZ titrated to 3 g daily in divided doses	DB, MC, RCT Patients ≥18 years of age with active AS (diagnosed according to modified New York criteria) that failed treatment with ≥1 NSAID taken for ≥3 months at the maximum recommended dose	N=566 16 weeks	Primary: Proportion of patients achieving ASAS 20 at week 16 Secondary: Proportion of patients achieving ASAS 20 at weeks two, four, eight and 12; proportion of	Primary: At week 16, significantly more patients in the etanercept group achieved ASAS 20 compared to the SSZ group (75.9 vs 52.9%; *P*<0.0001). Secondary: The etanercept-treated patients had a significantly greater proportion achieving ASAS 20 at week two; this difference was maintained throughout the time points (*P*<0.0001 for all). Significantly more patients in the etanercept group achieved ASAS 40 and ASAS 5/6 compared to patients in the SSZ group at all time points (*P*<0.0001for all). At week 16, a greater proportion of patients achieved ASAS 40 and ASAS 5/6 in the etanercept group compared to the SSZ group (59.8 vs 32.6%; *P*<0.0001 and 45.5 vs 21.2%; *P*<0.0001, respectively).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	and were determined to be candidates for SSZ therapy by the investigators		patients achieving ASAS 40 and ASAS 5/6 at all time points	The rates of adverse events and serious adverse events were similar between the groups.
Inman et al[38] Golimumab 50 mg once every 4 weeks vs golimumab 100 mg once every 4 weeks vs placebo Patients who were on stable doses of HCQ, MTX, NSAID, oral corticosteroid and/or SSZ were permitted in the study.	DB, MC, PC, RCT Patients ≥18 years of age with a diagnosis of AS and no evidence of active TB and/or no evidence of latent TB on screening	N=356 24 weeks	Primary: ASAS 20 response at week 14 Secondary: Not reported	Primary: Golimumab with or without a DMARD, compared to placebo with or without a DMARD resulted in a significant improvement in signs and symptoms as demonstrated by ASAS 20 responses at week 14 (59 vs 22%; *P*≤0.001). All individual components of the ASAS response criteria were significantly improved in the golimumab 50 mg group vs the placebo group at week 14. Secondary: Not reported
Braun et al[39] Infliximab 5 mg/kg at weeks 0, 2 and 6 vs placebo Concurrent use of NSAIDs not to exceed the baseline	DB, MC, PC, RCT Adult patients (mean age of 40) with AS based on the modified New York criteria with BASDAI score ≥4 and spinal pain score ≥4	N=70 12 weeks	Primary: Improvement from baseline in BASDAI by 50% at week 12 Secondary: Improvement from baseline in spinal pain, BASFI, BASMI,	Primary: There were more patients that achieved a 50% improvement in BASDAI at week 12 in the infliximab group (53%; 95% CI, 37 to 69) compared to the placebo group (9%; 95% CI, 3 to 22). The difference between the groups was significant starting at week two and continuing through until 12 weeks (*P*<0.0001). Secondary: At week 12, the infliximab group had a significant mean improvement from baseline in spinal pain (*P*<0.0001), BASFI (*P*<0.0023), BASMI (*P*<0.0001), CRP (*P*<0.0001) and ESR (*P*<0.0001); while there was no significant

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
dose was allowed.			SF-36, CRP, ESR	difference in the placebo group. At 12 weeks, there were significant improvements from baseline in the physical component and mental component of the SF-36 in the infliximab group (*P*<0.0001); however, only the improvement in the physical component was significantly greater than the placebo group (*P*<0.0001). More patients reported infections in the infliximab group (51%) compared to the placebo group (35%; difference, 16%; 95% CI, -7 to 40; *P*=0.227). More patients in the infliximab group experienced serious adverse events and were withdrawn from the study compared to the placebo group (3 vs 0; *P*=0.239).
van der Heijde et al[40] (ASSERT) Infliximab 5 mg/kg at weeks 0, 2, 6, 12 and 18 vs placebo Concurrent NSAIDs, acetaminophen or tramadol were allowed during the study.	MC, PC, RCT Adult patients (median age of 40) with AS based on the modified New York criteria for at least three months with a BASDAI score ≥4, spinal pain assessment score ≥4 on a VAS and a normal chest radiograph within three months and negative TB screening	N=279 24 weeks	Primary: Proportion of patients with ASAS 20 at week 24 Secondary; ASAS 40 response, ASAS partial remission, ASAS 5/6, disease activity (BASDAI, night pain, patient's global assessment and CRP), physical function (BASFI), range of motion (BASMI), other musculoskeletal assessments (swollen joint count and degree of tenderness)	Primary: After 24 weeks, significantly more patients were ASAS 20 responders in the infliximab group (61.2%) compared to the placebo group (19.2%; *P*<0.001). The difference was significant at week two and continued to week 24. Secondary: Over the 24-week study period, there were significantly more ASAS 40 responders in the infliximab group compared to the placebo group (*P*<0.001). At 24 weeks 47% were ASAS 40 responders compared to 12% with placebo (*P*<0.001). There were significantly more infliximab treated patients with ASAS 5/6 (49%) compared to placebo treated patients (8%; *P*<0.001). There was a significantly greater proportion of patients that achieved a partial ASAS response in the infliximab group (22.4%) compared to the placebo group (1.3%; *P*<0.001). The median improvement in all measures of disease activity (BASDAI, night pain, patient's global assessment and CRP) was significantly greater in the infliximab treated patients compared to placebo treated patients (*P*<0.001). The patients in the infliximab group had a significantly greater median improvement in BASFI compared to patients in the placebo group (*P*<0.001). There was a significantly greater median improvement in BASMI in the infliximab group compared to the placebo group (*P*=0.019). The infliximab treated patients had a significantly greater median improvement in swollen joint count compared to the placebo treated patients (*P*=0.019). There was a significantly greater improvement in the physical component of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			and quality of life (SF-36)	the SF-36 in the infliximab group compared to the placebo group (*P*<0.001); there was no significant difference in the mental component (*P*=0.547). There were a higher proportion of patients experiencing at least one adverse event in the infliximab group compared to the placebo group (82.2 vs 72.0%). The number of patients reporting at least one infection was higher in the infliximab group compared to the placebo group (42.6 vs 36.0%) and the number of severe adverse reactions was higher in the in the infliximab group (3.5 vs 2.7%). Of the adverse event that occurred in at least 5% of patients in group, pharyngitis, rhinitis, and increased liver enzymes were greater in the infliximab group.
Crohn's Disease				
Ma et al[41] Adalimumab	SR OL and RCT cohort studies in patients with CD who had lost response and were intolerable or refractory to infliximab	N=1,810 (15 trials) 8 weeks to 4 years	Primary: Short-term and long-term efficacy Secondary: Adverse events	Primary: Short-term clinical response or remission was evaluated in nine trials. Forty-one to 83% of patients achieved a clinical response at four weeks, while 12 to 67% of participants attained clinical remission. Long-term remission rates ranged from 31 to 82% at six months and 19 to 68% at one year. Secondary: Serious adverse events were reported in 0 to 19% of patients and included sepsis, cellulitis, and fungal pneumonia.
Lofberg et al[42] (CARE) Adalimumab 160 mg at week zero followed by 80 mg at week two followed by 40 mg every other week At week 12 or later, patients who experienced a disease flare or did not respond to treatment could increase the adalimumab	MC, OL Patients 18 to 75 years of age with a radiologic or endoscopic diagnosis of CD for ≥4 months and a HBI >7 points at screening	N=945 20 weeks	Primary: Remission rates, proportion of patients free of EIM at week 20 Secondary: Fistula healing, remission rates based on concomitant therapies and adverse events	Primary: The percentage of patients in remission who received adalimumab was 43% at week four (95% CI, 40 to 46) and increased to 52% (95% CI, 49 to 55) at week 20. There was a significantly higher remission rate at week 20 among adalimumab-treated patients who were also infliximab naïve compared to patients exposed to infliximab (62 vs 42; *P*<0.001). A shorter disease duration (<2 years and 2 to <5 years) was associated with higher rates of clinical remission at week four compared to a disease duration >5 years (50, 52, and 38%, respectively; *P*<0.001); however the remission rates at 20 weeks were not significantly different (58, 56, and 50%, respectively; *P*=0.136). Overall, 53% of patients had at least one EIM at baseline, compared to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
dose to 40 mg weekly.				30% at week 20. Of these, 79% had resolution of at least one EIM and 51% were free of EIM signs and symptoms following 20 weeks of adalimumab treatment. The EIM resolution rates were similar across adalimumab-treated patients regardless of prior infliximab use (*P*=0.100) and prior infliximab response and those who discontinued treatment for other reasons (*P*=0.625). Secondary: Complete fistula healing occurred in 26% of patients at week 20. Fistula closure rates were numerically higher in the infliximab-naïve group at week 20 (33%) compared to the infliximab-experienced group (22%); however, the difference was not significant (*P*=0.275). Fistula healing rates were similar in nonresponders to infliximab compared to those who discontinued infliximab for other reasons (19 vs 23%; *P*=0.973). Of patients taking corticosteroids at baseline, 37% were able to discontinue them by week 20; Eleven percent and 14% of patients achieved a steroid-free remission at weeks 12 and 20, respectively. Seven percent of patients taking immunosuppressants at baseline were able to discontinue them at week 20. There were similar rates of clinical remission at week 20 between patients taking and not taking steroids at baseline (52% in both groups; *P*=0.976). By week 20 the rates of clinical remission were 55 and 49%, respectively in patients who were and were not taking immunosuppressants at baseline (*P*=0.052). Adverse events occurred in 80% of patients, and 11% of patients discontinued treatment due to adverse events. Serious events were reported in 19% of patients. The adverse events profiles were similar among patients who were exposed to infliximab previously and those who were naïve. The most common adverse event categories were “gastrointestinal disorders” and “CD’’ indicating a worsening the patient's underlying disease.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Watanabe et al[43] (Induction study) Adalimumab 160 mg at week zero followed by 80 mg at week two vs adalimumab 80 mg at week zero followed by 40 mg at week two vs placebo (Maintenance study) adalimumab 40 mg every other week vs placebo Patients achieving a Clinical Response 70 (decrease from baseline in CDAI ≥70 points at week four) entered the blinded maintenance trial.	2 DB, MC, PC, RCT Patients 15 to 75 years of age, with moderate to severely active CD, CDAI score 220 to 450 for >4 months and a diagnosis of ileal, colonic or ileocolonic CD confirmed by endoscopy or radiologic evaluation	N=90 (induction) N=83 (maintenance) 56 weeks (4 weeks induction study, 52 week maintenance study)	Primary: *Induction study* Proportion of patients in clinical remission (CDAI <150) at week four *Maintenance* Clinical remission (CDAI <150) at week 52 Secondary: *Induction study* Proportion of patients in clinical remission at week two and with CR-10 or CR-70 (CDAI decrease ≥100 or ≥70) at week four, changes from baseline in CDAI and IOIBD at week two and week four and changes in SF-36, MCS, and PCS, and IBDQ scores in each treatment group at week four *Maintenance*	Primary: *Induction* A higher proportion of patients treated with adalimumab 160/80 mg and 80/40 mg achieved a clinical remission by week four compared to placebo (33 and 18 vs 12%, respectively; *P* value not reported). *Maintenance* By week 52, a significantly higher proportion of patients treatment with adalimumab 40 mg achieved a clinical remission compared to placebo (*P*<0.05). Secondary: *Induction* At week two, clinical remission rates were higher with adalimumab 160/80 mg and 80/40 mg compared to placebo (18 and 15 vs 4%, respectively; *P* value not reported). At week four, significantly more patients receiving adalimumab 160/ 80 mg or 80/40 mg experienced a CR 100 (50 and 46 vs 17%, respectively; *P*<0.05 for both) compared to placebo. At week four, significantly more patients receiving adalimumab 160/80 mg experienced a CR 70 (70 vs 30%; *P*=0.0062); however, the improvement with the 80/40 mg adalimumab dose was not statistically significant. The changes in CDAI from baseline to week two and four, respectively, were, -75.9 and -101.3 in the adalimumab 160/80 mg group, -74.4 and -81.3 in the adalimumab 80/40 mg group, and -27.2 and -37.5 in the placebo group. The mean changes in IOIBD score from baseline to week two and week four, respectively, were -1.2 and -1.5 in the adalimumab 160/80 mg group, -0.7 and -0.8 in the adalimumab 80/40 mg group and -0.4 and -0.5 in the placebo group. Adalimumab 160/80 mg or 80 /40 mg significantly improved SF-36 MCS

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Proportion of patients in clinical remission, (CDAI decrease ≥100 or ≥70) every four weeks, changes from baseline of the induction to week 52 in CDAI, IOIBD, SF-36 MCS and PCS scores and IBDQ	from baseline to week four compared to placebo. (6.2 and 5.5 vs -1.6, respectively *P*<0.05 for both). There were no statistically significant differences in SF-36 PCS and IBDQ between patients receiving adalimumab 160/80 mg compared to patients receiving placebo. *Maintenance* Adalimumab therapy was more effective compared to placebo at each four-week evaluation throughout the 52-week trial compared to placebo with regard to CR-100 (*P*≤0.05), and CR-70 (*P*≤0.01). Adalimumab was more effective compared to placebo with regard to maintaining clinical remission at weeks eight, 36, 36, 40, 48 and 52 (*P*<0.05). The mean change in CDAI from baseline of the induction trial to week zero and week 52, respectively, were -147.7 and -83.7 in the adalimumab-treated patients and -139.0 and -9.1 in the placebo-treated patients. The mean changes in IOIBD from baseline to week zero and week 52, respectively, were -2.0 and -0.8 in adalimumab-treated patients and -1.2 and -0.2 in placebo-treated patients, respectively. Adalimumab 40 mg was associated with statistically significant improvements in SF-36 MCS and IBDQ compared to placebo at eight weeks (12.0 vs 2.0; *P*=0.03 and 34.8 vs 8.3; *P*=0.05, respectively); however, the differences were not significantly different at 52 weeks.
Shao et al[44] Certolizumab vs placebo	MA DB, RCTs in patients with moderate to severe CD	N=1,040 (3 trials) 12 to 26 weeks	Primary: Clinical response (a decrease ≥100 points from baseline in CDAI score) and clinical remission (CDAI score ≤150 points) at week four Secondary:	Primary: Certolizumab was associated with an increased rate of induction of clinical response (RR, 1.36; 95% CI, 1.10 to 1.68; *P*=0.004) and remission (RR, 1.95; 95% CI, 1.41 to 2.70; *P*<0.0001) over placebo. Secondary: Only infection was reported more frequently with certolizumab compared to placebo (60.6 vs 40.7%).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Safety	
Targan et al[45] Infliximab 5 mg/kg vs infliximab 10 mg/kg vs infliximab 20 mg/kg vs placebo	DB, MC, PC, RCT Adult patients with CD for six months with CDAI scores 220 to 400 and previously receiving mesalamine (for ≥8 weeks and a stable dose for four weeks), corticosteroids (maximum of 40 mg/day for ≥8 weeks and a stable dose for two weeks), mercaptopurine or azathioprine (for ≥6 months and stable dose for eight weeks)	N=108 12 weeks	Primary: Decrease from baseline in CDAI ≥70 points at four weeks without a change in concomitant medications Secondary: Not reported	Primary: At week four, the primary endpoint was reached in 81, 50, 64 and 17% in the 5 mg/kg, 10 mg/kg, 20 mg/kg and placebo groups, respectively. The overall response of the infliximab groups was significantly higher (65%) compared to the placebo group (*P*<0.001). At week two, 61% of the infliximab treated patients had a response compared to 17% of the placebo treated patients (*P*<0.001). More patients were in remission (CDAI score <150) in the infliximab group at two weeks (27%) compared to the placebo group (4%; *P*=0.06). At week four, 33% of the infliximab treated patients were in remission compared to 4% of the placebo treated patients (*P*<0.005). The response rate remained significantly higher in the infliximab treated patients through the 12 weeks of the study (41%) compared to placebo treated patients (12%; *P*=0.008); however, the remission rate was not significantly different at 12 weeks (24 vs 8%; *P*=0.31). Secondary: Not reported
Present et al[46] Infliximab 5 mg/kg at weeks 0, 2 and 6 vs infliximab 10 mg/kg at weeks 0, 2 and 6 vs placebo	DB, MC, PC, RCT Patients 18 to 65 years of age with ≥1 confirmed draining abdominal or perianal fistulas of ≥3 months as a complication of CD	N=94 18 weeks	Primary: Reduction ≥50% from baseline in number of draining fistulas at two or more consecutive study visits Secondary: Number of patients with a complete response	Primary: There were significantly greater response rates in the infliximab 5 (68%) and 10 mg/kg (56%) groups compared to the placebo group (26%; *P*=0.002 and *P*=0.02, respectively). The response rates were not significantly different between the two infliximab groups. Secondary: More patients in the infliximab 5 (55%) and 10 mg/kg (38%) groups had complete response compared to the placebo group (13%; *P*=0.001 and *P*=0.04, respectively). In the infliximab group, the median time to the onset of response was two weeks compared to six weeks in the placebo group. The duration of response was approximately three months in patients that reached the primary endpoint.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			(absence of any draining fistula at two consecutive visits), length of time to beginning of response and duration of response	The most frequently reported adverse events in the infliximab group were headache, abscess, upper respiratory tract infection and fatigue.
Hyams et al[47] (REACH) Infliximab 5 mg/kg at weeks 0, 2 and 6; those responding to therapy received continued therapy every 8 weeks at weeks 14, 22, 30, 38 and 36 or every 12 weeks at weeks 18, 30 and 42 vs infliximab 5 mg/kg at weeks 0, 2 and 6; those responding to therapy received continued therapy every 12 weeks at weeks 18, 30 and 42	MC, OL, RCT Patients 6 to 17 years of age with a PCDAI >30 at baseline and initiated immunomodulator therapy (azathioprine, mercaptopurine or MTX) ≥8 weeks before screening and at stable dose for two weeks	N=112 46 weeks	Primary: Clinical response at week 10 (decrease from baseline to week 10 in PCDAI ≥15 points and total PCDAI no more than 30) Secondary: Maintenance of clinical response and remission (PCDAI ≤10)	Primary: At week 10, 88.4% of patients responded to the induction regimen (95% CI, 82.5 to 58.9). Secondary: At week 10, 58.6% of patients were in clinical remission (95% CI, 49.8 to 68.0). At week 54, 63.4 and 55.8% of patients treated with infliximab every eight weeks were in clinical response and clinical remission, respectively compared to 33.3 and 23.5% of patients treated with infliximab every 12 weeks (P=0.002 and P<0.001, respectively). At week 10, there was a significant decrease in PCDAI score compared to baseline that continued at weeks 30 and 54 (all P<0.001). There was a significant decrease in corticosteroid use at week 10 compared to baseline that continued at weeks 30 to 54 (all P<0.001). Adverse events were similar between the two groups. Infection was the most common adverse event in both treatment groups.
Behm et al[48] Adalimumab, certolizumab, or infliximab vs placebo	SR RCTs including patients ≥18 years of age with CD who had a clinical response or clinical remission with a	N=3,586 (9 trials) Duration varied	Primary: Clinical remission, clinical response, steroid-sparing effects Secondary:	Primary: Adalimumab demonstrated the ability to maintain clinical remission and clinical response (RR, 2.69; 95% CI, 1.88 to 3.86; P<0.00001), while also having a steroid-sparing effect (data specific to clinical remission and steroid-sparing effect not reported). Certolizumab was shown to maintain both clinical remission (RR, 1.68; 95% CI, 1.30 to 2.16; P=0.000072) and clinical response (RR, 1.74; 95% CI,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	TNF-α blocker, or patients with CD in remission but unable to wean corticosteroids, who were then randomized to maintenance of remission with a TNF-α blocker or placebo		Not reported	1.41 to 2.13; *P*<0.00001) compared to placebo. Infliximab maintained fistula healing (RR, 1.87; 95% CI, 1.15 to 3.04; *P*=0.012), clinical remission (RR, 2.50; 95% CI, 1.64 to 3.80; *P*=0.000019), clinical response (RR, 1.66; 95% CI, 1.00 to 2.76; *P*=0.0046) and achieved a steroid sparing effect (RR, 3.13; 95% CI, 1.25 to 7.81; *P*=0.014) all compared to placebo. Secondary: Not reported
Juvenile Idiopathic/Rheumatoid Arthritis				
Ruperto et al[49] Abatacept 10 mg/kg every 28 days vs placebo	DB, MC, PC, RCT (OL lead in period) Patients 6 to 17 years of age with juvenile idiopathic arthritis with at least 5 active joints and active disease and who had inadequate response to or intolerance to ≥1 DMARD	N=122 (RCT); 190 (OL lead in period) 6 months (4-month OL lead in)	Primary: Time to flare Secondary: Proportion of patients with a disease flare, changes in baseline in each of six core response variables and assessment of safety and tolerability	Primary: In the placebo group the median time to flare was six months; however, insufficient events occurred in the abatacept group to assess median time to flare (*P*=0.0002). Secondary: There was a significantly greater proportion of patients that experienced a flare in the placebo group compared to the abatacept group (53 vs 12%; *P*=0.0003). The HR for patients in the abatacept to group experience a flare compared to the placebo group was 0.31 (95% CI, 0.16 to 0.59). After six months or at the time of first flare, 82% of the abatacept group and 69% of the placebo group improved by ≥30% as measured by ACR (*P*=0.1712), 77% of the abatacept group and 52% of the placebo group improved by ≥50% as measured by ACR (*P*=0.0071), 53% of the abatacept group and 31% of the placebo group improved by ≥70% as measured by ACR and 40% of the abatacept group and 16% of the placebo group improved by ≥90% as measured by ACR. In the abatacept group, 30% had inactive disease compared to 11% in the placebo group (*P*=0.0195). Adverse events were similar between the groups.
Lovell et al[50] Adalimumab 24 mg/m^2	DB, MC, OL, RCT Patients 4 to 17	N=171 48 weeks	Primary: Rate of disease flare in patients	Primary: Among those not receiving MTX, flares occurred in 43% receiving adalimumab and 71% receiving placebo (*P*=0.03). In the patients receiving

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(maximum of 40 mg) every other week with or without MTX vs placebo Patients were stratified according to MTX use and received OL adalimumab 24 mg/m^2 (maximum of 40 mg) every other week for 16 weeks. The patients with an ACR Pedi 30 response at week 16 were then randomly assigned to receive adalimumab or placebo.	years of age with active JRA who had previously received treatment with NSAIDs		not receiving MTX Secondary: ACR Pedi 30, 50, 70, and 90 responses at week 48, and safety	MTX, flares occurred in 37 and 65% of participants in the adalimumab and placebo groups, respectively (*P*=0.02). Secondary: In patients receiving MTX, ACR Pedi 30, 50, 70, and 90 responses were reported in 63 vs 38% (*P*=0.03), 63 vs 35% (*P*=0.03), 63 vs 27% (*P*=0.002) and 42 vs 27% (*P*=0.17), respectively. For those participants not taking MTX therapy, ACR Pedi 30, 50, 70, and 90 responses were detected in 57 vs 32% (*P*=0.06), 53 vs 32% (*P*=0.10), 47 vs 29% (*P*=0.16) and 30 vs 18% (*P*=0.28), respectively. The most frequently noted adverse events were mild to moderate in nature and included infections and injection site reactions. There were seven cases of serious infection reported with adalimumab use.
Lovell et al[51] Etanercept 0.4 mg/kg twice weekly vs placebo All patients received etanercept 0.4 mg/kg twice weekly for up to 3 months in the OL part of the study; the patients whose condition improved were then randomly	DB, MC, OL, RCT Patients 4 to 17 years of age with active polyarticular JRA despite treatment with NSAIDs and MTX ≥10 mg/m^2/week	N=69 7 months	Primary: Rate of disease flare Secondary: Median time to flare, safety	Primary: Seventy-four percent (51/69) of patients demonstrated improvement and were included in the DB part of the trial. The rate of disease flare was significantly higher in the placebo group compared to the etanercept group (81 vs 28%; *P*=0.003). Secondary: The median time to flare was reported as 116 days in the active treatment arm compared to 28 days with placebo (*P*<0.001). During the OL segment of the study the adverse events most often reported included injection-site reaction, upper respiratory tract infections, headache, rhinitis and gastrointestinal side effects. There were no differences noted between groups during the latter part of the study.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
assigned to either etanercept or placebo. Concurrent analgesics, NSAIDs, or oral corticosteroids (≤10 mg/day of prednisone or equivalent) were allowed.				
Lovell et al[52] Etanercept 0.4 mg/kg (maximum of 25 mg) twice weekly Intra-articular and soft-tissue injections of corticosteroids were permitted after 12 continuous weeks of etanercept. MTX could be added to treatment after one year. Concurrent analgesics, NSAIDs, or oral corticosteroids (≤10 mg/day of prednisone or equivalent) were allowed.	Ongoing ES, MC, OL by Lovell et al[22] (updated efficacy and safety results from the study)	N=58 Median of 4 years	Primary: JRA 30% DOI Secondary: JRA 50% DOI, JRA 70% DOI, an articular severity score (0 to 926), assessment of pain (Likert scale, 0 to 10), CRP levels, safety	Primary: Thirty-two patients were available for efficacy analysis after four years with 94% meeting the JRA 30% DOI. Secondary: Approximately 94 and 78% of participants met the JRA 50% DOI and JRA 70% DOI, respectively. At four years, the median CRP level was lowered to 0.1 mg/dL from 3.4 mg/dL at baseline, the median articular severity score was decreased to 18 from 88 at baseline and the median patient's assessment of pain score was lowered to 0.9 from 3.6 at baseline. Duration of morning stiffness was only assessed through one year and was reported as 5 minutes at month 12 (from 53 minutes at baseline). After four years, there were five reports of serious adverse events and 0.03 serious infections (requiring intravenous antibiotics or hospitalizations)/ patient year.
Horneff et al[53] Etanercept 0.4 mg/kg twice weekly Combination treatment with MTX or oral	MC, OL Patients 4 to 17 years of age with active idiopathic juvenile arthritis despite treatment	N=322 Up to 48 months, median of 12 months	Primary: Change in indices of disease activity, 30, 50 and 70% improvement in idiopathic	Primary: At 12 months, the mean number of tender joints, swollen joints and joints with limited range of movement were reduced to 1.7 (SD, 3.5), 2.6 (SD, 4.7) and 7.1 (SD, 8.9) from a baseline of 9.1 (SD, 9.5), 8.4 (SD, 9.0) and 11.8 (SD,11.8), respectively. The duration of morning stiffness was decreased to 7 (SD, 23) minutes from 45 (SD, 65) minutes and CHAQ scores (on a scale of 0=best to 3=worst) were decreased to 0.4 (SD, 0.6) from 1.0 (SD, 0.8).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
corticosteroids was permitted.	with MTX		juvenile arthritis Secondary: Safety	Patient's and PGA scores (on a scale of 0=best to 100=worst) were reduced to 16 (SD, 18) and 20 (SD, 23) from 56 (SD, 27) and 67 (SD, 25), respectively. At last report (30 months) a 30, 50 and 70% improvement was noted in approximately 60, 48 and 28% of patients remaining on etanercept, respectively. Significant improvements in all indices of disease activity were detected at all points of time (months one, three, six, 12, 18, 24 and 30; *P*<0.0001 with the exception of swollen joint count at 30 months; *P*<0.0005 and duration of morning stiffness; *P*<0.001). Secondary: There were 20 reports of infection or infection related events. Discontinuation of treatment was reported in 53 patients, 11 cases of which were secondary to adverse events.
De Benedetti et al TENDER (abstract)[54] Tocilizumab 8 mg/kg every 2 weeks for patients ≥30 kg or 12 mg/kg every 2 weeks for patients <30 kg vs placebo	RCT Patients 2 to 17 years of age with active systemic juvenile idiopathic arthritis for ≥6 months with an inadequate response to NSAIDs and corticosteroids	N=112 12 weeks	Primary: Proportion of patients with JRA ACR 30 plus absence of fever at week 12 Secondary: Not reported	Primary: At week 12, significantly more patients treated with tocilizumab achieved JRA 30 plus absence of fever (85%) compared to patients treated with placebo (24%; *P*<0.0001). Significantly more patients in the tocilizumab group achieved JRA ACR 50, JRA ACR 70 and JRA ACR 90 compared to patients in the placebo group (*P*<0.0001). Secondary: Not reported
Psoriasis				
Bagel et al[55] Etanercept 50 mg twice-weekly for 12 weeks followed by etanercept 50 mg weekly plus placebo weekly for 12 additional weeks (Group A) vs	DB, MC, PC, RCT Patients ≥18 years of age with stable moderate-to-severe plaque psoriasis covering ≥10% of BSA for ≥6 months and PASI scores ≥10 and ≥30% of	N=124 24 weeks	Primary: Percentage change in PSSI score at week 12 Secondary: Percentage change in the PSSI score at week 24 for	Primary: At week 12, Group A experienced a significantly greater mean improvement in PSSI score compared to Group B (86.8 vs 20.4%; *P*<0.001) with significant improvements as early as week four of treatment. Secondary: At week 24, both Group A and Group B experienced improvements in PSSI scores from baseline (90.6 vs 79.1%, respectively; *P* value not reported). A significantly greater proportion of patients in Group A compared to Group

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo twice-weekly for 12 weeks followed by etanercept 50 mg twice-weekly for 12 additional weeks (Group B) Patients discontinued the use of background therapies.	SSA affected, with PSSI scores ≥15		Group B patients, the proportion of patients achieving PSSI 75 improvement at week 12, patient satisfaction with treatment at week 12 and safety	B experienced a PSSI 75 at week 12 (86 vs 11%; *P*<0.0001). Significantly more etanercept-treated patients were either satisfied or very satisfied at week 12 compared to placebo (*P*<0.0001). At week 24, after etanercept treatment, Group B patients' satisfaction increased significantly over their first 12 weeks on placebo (*P*<0.0001). More than two thirds of Group A patients continued to be satisfied or very satisfied at week 24. The rates of adverse events were comparable between groups, both at week 12 (etanercept vs placebo) and week 24 (etanercept 50 mg twice-weekly vs once-weekly). No serious adverse events were reported at week 12; however, by week 24, three patients had reported serious events. The most commonly reported adverse events were upper respiratory tract infection, injection site reactions, headache, sinus congestion, cough and ear infection.
Saurat et al[56] (CHAMPION) Adalimumab 80 mg at week 0, then 40 mg every other week from week 1 through week 15 vs MTX 7.5 mg at week 0, then increased to 10 mg weekly at week 2, then increase to 15 mg weekly at week 4; at week 8, patients not achieving PASI 50 had the dose of MTX increased to 15 mg weekly; at week 12, patients not achieving PASI 50 at week 12 and 8	DB, DD, MC, RCT Patients ≥18 years of age with moderate to severe psoriasis (>10% of BSA and PASI ≥10), plaque psoriasis for >1 year, stable plaque psoriasis for >2 months, that are candidates for systemic therapy of phototherapy, with plaque psoriasis despite treatment with topical agents and treatment naïve to TNF-antagonists and MTX	N=271 16 weeks	Primary: Proportion of patients achieving PASI 75 at week 16 relative to baseline Secondary: Proportion of patients achieving PASI 50, PASI 90, PASI 100 and PGA	Primary: At 16 weeks, significantly more patients in the adalimumab group (79.6%) achieved PASI 75 compared to the MTX group (35.5%; RD, 43.7%; 95% CI, 30.8 to 56.7; *P*<0.001) and placebo group (18.9%; RD, 60.5%; 95% CI, 44.5 to 76.6; *P*<0.001). The difference in treatment groups was seen starting at two weeks for adalimumab vs MTX (*P*<0.05) and at four weeks for adalimumab vs placebo (*P*<0.001). Secondary: At week 16, PASI 100 was achieved in significantly more patients in the adalimumab group (16.7%) compared to the MTX group (7.3%; *P*<0.04) and the placebo group (1.9%; *P*<0.001).Significantly more patients achieved PASI 50, PASI 90 and a PGA of clear or minimal in the adalimumab group compared to the MTX and placebo groups (*P*<0.001 for all). Rates of reported infectious adverse events were not significantly different between the groups (*P* value not reported). Total adverse events and serious adverse events were similar.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
had the dose of MTX increased to 25 mg weekly vs placebo				
Leonardi et al[57] (PHOENIX-1) Ustekinumab 45 mg vs ustekinumab 90 mg vs placebo Each group received a subcutaneous injection at week 0, 4, and then every 12 weeks thereafter.	DB, MC, PC, PG, RCT Patients ≥18 years of age with a diagnosis of plaque psoriasis for ≥6 months, candidates for phototherapy or systemic therapy, had a baseline PASI score 12 or higher, and had ≥10% BSA involvement	N=766 ≤76 weeks	Primary: Proportion of patients achieving PASI 75 at week 12 Secondary: Not reported	Primary: Significantly more patients in both the 45 and 90 mg ustekinumab groups achieved the primary endpoint of PASI 75 at week 12 than did those in the placebo group (difference in response rate, 63.9%; 95% CI, 57.8 to 70.1; *P*<0.0001 and 63.3%; 95% CI, 57.1 to 69.4; *P*<0.0001 for 45 and 90 mg vs placebo, respectively. The onset of efficacy was rapid, with higher proportions of ustekinumab-treated patients achieving at least 50% improvement from baseline in PASI 50 by week two (*P*=0.0008 for 45 mg and *P*=0.0005 for 90 mg vs placebo) and PASI 75 by week four (*P*<0.0001 for each comparison vs placebo). Maximum efficacy was observed at week 24 in the 45 and 90 mg groups (PASI 75 response, 76.1% in 45 mg group and 85.0% in 90 mg group). Among patients re-randomized at week 40, maintenance of PASI 75 was better in patients receiving maintenance therapy than in patients withdrawn from therapy through at least one year (*P*<0.0001), The median percentage improvement in PASI remained stable to at least week 76. Secondary: Not reported
Papp et al[58] (PHOENIX-2) Ustekinumab 45 mg vs ustekinumab 90 mg	DB, MC, PC, RCT Patients ≥18 years of age, with a diagnosis of plaque psoriasis for ≥6 months, were candidates for	N=1,230 ≤52 weeks	Primary: Proportion of PASI 75 responders at week 12 Secondary: Proportion of	Primary: Significantly more patients in both ustekinumab groups achieved PASI 75 at week 12 than did patients in the placebo group (difference in response rate, 63.1%; 95% CI, 58.2 to 68.0; *P*<0.0001 and 72.0%; 95% CI, 67.5 to 76.5; *P*<0.0001 for 45 and 90 mg vs placebo, respectively). Secondary: A greater proportion of patients in each ustekinumab group achieved a

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo Each group received an injection at week 0, 4, and then every 12 weeks thereafter. Partial responders at week 28 were re-randomized to continue dosing every 12 weeks or escalate to dosing every 8 weeks.	phototherapy or systemic therapy, had a baseline PASI score 12 or higher, and had ≥10% BSA involvement		patients with a physician's global assessment score of cleared or minimal at week 12, change in dermatology life quality index, the number of visits with PASI 75 response between weeks 40 and 52	physician's global assessment of psoriasis of cleared or minimal at week 12 than did those in the placebo group (difference in response rate, 63.1%; 95% CI, 58.1 to 68.1; *P*<0.0001 for 45 mg vs placebo and 68.6%; 95% CI, 63.9 to 73.4; *P*<0.0001 for 90 mg vs placebo). Median changes in dermatology life quality index were greater in the ustekinumab groups than in the placebo group (mean of differences vs placebo, -8.0; 95% CI, -8.0 to -7.0; *P*<0.0001 for 45 mg and -9.0; 95% CI, -9.0 to -8.0; *P*<0.0001 for 90 mg vs placebo). A total of 22.7% of patients in the 45 mg group and 15.8% of patients in the 90 mg group were partial responders at week 28. Compared to patients responding to dosing every 12 weeks, partial responders tended to have higher bodyweight, more marked or severe disease as measured by physician's global assessment, and a higher incidence of PsA. Among the re-randomized partial responders, dosing intensification did not result in greater efficacy compared to continuing treatment every 12 weeks, as assessed by the number of visits between weeks 40 and 52 (four visits) at which patients achieved PASI 75 response (mean, 1.75 visits in the every eight week group and 1.56 in the every 12 week group; *P*=0.468). There was a lack of response to intensified dosing in the individuals receiving 45 mg, both in terms of number of visits at which patients achieved PASI 75 response (mean, 1.13 vs 1.54 visits; *P*=0.210), and in terms of PASI 75 rates over time. This is in contrast to patients receiving intensified 90 mg dosing, which resulted in a greater number of visits with PASI 75 response (mean, 2.63 vs 1.58 visits; *P*=0.014) and higher PASI 75 response rate (68.8% of patients with dosing every eight weeks vs 33.3% of patients with dosing every 12 weeks; difference in response rate, 35.4%; 95% CI, 12.7 to 58.1 at week 52 for dosing every eight weeks vs dosing every 12 weeks; *P*=0.004).
Griffiths et al[59] Etanercept 50 mg twice weekly	MC, PG, RCT Patients ≥18 years of age, with a	N=903 12 weeks	Primary: PASI 75 at week 12	Primary: A greater number of patients achieved PASI 75 in the ustekinumab 45 mg group (67.5%) and ustekinumab 90 mg group (73.8%) than in the etanercept group (56.8%; *P*=0.01 vs ustekinumab 45 mg; *P*<0.001 vs

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs ustekinumab 45 mg at weeks 0 and 4 vs ustekinumab 90 mg at weeks 0 and 4 Patients without a response to etanercept at week 12, received ustekinumab 90 mg at weeks 16 and 20; patients without a response to ustekinumab at week 12 received one additional study dose at week 16.	diagnosis of plaque psoriasis for ≥6 months, were candidates for phototherapy or systemic therapy, had a baseline PASI score ≥12, had a score ≥3 on physician's global assessment, had ≥10% BSA involvement, and had inadequate response, intolerance, or contraindication to ≥1 conventional systemic agent (i.e., MTX, cyclosporine, or psoralen plus ultraviolet A) and no previous treatment with etanercept or ustekinumab		Secondary: Physician's global assessment score of 0 or 1, PASI 90, difference between PASI at week 12 and 12 weeks after retreatment	ustekinumab 90 mg). Secondary: A larger proportion of ustekinumab patients met criteria for cleared or minimal on a physician's global assessment (score of 0 or 1) compared to etanercept patients (65.1% on ustekinumab 45 mg and 70.6% on ustekinumab 90 mg vs 49.0% on etanercept; *P*<0.001 for each comparison vs etanercept). PASI 90 was achieved by 36.4% of ustekinumab 45 mg patients, 44.7% of ustekinumab 90 mg patients and 23.1% of etanercept patients (*P*<0.001, for each comparison vs etanercept). Of the patients that crossed over to ustekinumab from etanercept, 48.9% achieved a PASI 75, 23.4% achieved PASI 90, 40.4% achieved cleared or minimal on the physician's global assessment. Of patients that received retreatment with ustekinumab, 84.4% had a physician's global assessment score of 0 to 2. The most commonly occurring adverse event in the etanercept group was injection site erythema (14.7%) and was reported more often than in the two ustekinumab groups combined (0.7%). At least one serious adverse effect was reported in 1.9, 1.2 and 1.2% of patients in the ustekinumab 45 mg, 90 mg and etanercept groups, respectively.
Schmitt et al[60] Adalimumab, cyclosporine, efalizumab*, etanercept, or infliximab vs placebo	MA RCTs in patients with moderate to severe psoriasis	16 trials Duration varied	Primary: PASI 75 Secondary: Tolerability	Primary: Compared to placebo a greater proportion of patients receiving adalimumab (RD, 64%; 95% CI, 61 to 68; *P*<0.00001), cyclosporine (RD, 33%; 95% CI, 13 to 52; *P*<0.0009), efalizumab (RD, 24%; 95% CI, 19 to 30; *P*<0.00001), etanercept 50 mg twice weekly (RD, 44%; 95% CI, 40 to 48; *P*<0.00001) and etanercept 25 mg twice weekly (RD, 30%; 95% CI, 25 to 35; *P*<0.00001) achieved PASI 75 response. The infliximab group had the greatest response (RD, 77%; 95% CI, 72 to 81; *P*<0.00001). Secondary: Average monthly rates of serious adverse events were 0.5% with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				adalimumab, 2.3% with cyclosporine, 1.2% with efalizumab, 0.6% with etanercept 50 mg twice weekly and 1.1% with infliximab. This outcome was not reported in with etanercept 25 mg twice weekly. Withdrawals due to adverse events occurred on average in 0.3% of adalimumab-treated patients, 16.1% of cyclosporine-treated patients, 1.2% of efalizumab-treated patients, 0.5% of patients on the lower dose of etanercept and 0.4% of patients on the higher dose of etanercept and 1.3% of infliximab-treated individuals/month.
Psoriatic Arthritis				
Genovese et al[61] Adalimumab 40 mg every other week vs placebo Patients who completed a 12 week blinded phase could elect to receive OL therapy.	DB, MC, RCT Patients with moderately to severely active PsA with an inadequate response to DMARD therapy	N=100 24 weeks	Primary: ACR 20 response at week 12 Secondary: ACR 50 response, ACR 70 response, PsARC scores, assessments of disability, psoriatic lesions, quality of life	Primary: At week 12, an ACR 20 response was achieved by 39% of adalimumab patients vs 16% of placebo patients (*P*=0.012). Secondary: ACR 50 and ACR 70 responses were also achieved by significantly more patients on adalimumab (25 and 14%, respectively) compared to patients on placebo at week 12 (2 and 0%, respectively; *P*=0.001 for ACR 50 and *P*=0.013 for ACR 70). A PsARC response was achieved by 51% of adalimumab patients vs 24% of placebo patients (*P*=0.007). At week 12, measures of skin lesions (-3.7 units with adalimumab vs -0.3 units with placebo; *P*≤0.001) and disability were statistically significantly improved with adalimumab. Adalimumab use was associated with significant mean improvements from baseline in components of quality of life assessments such as physical functioning (*P*=0.027), bodily pain (*P*=0.007), general health (*P*=0.017) and mental health (*P*=0.009). OL adalimumab provided continued improvement for adalimumab patients and initiated rapid improvement for placebo patients, with ACR 20 response rates of 65 and 57%, respectively, observed at week 24.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Serious adverse events occurred at a similar frequency during therapy with placebo (4.1%), blinded adalimumab (2.0%), and OL adalimumab (3.1%). Adalimumab use was not associated with serious infections.
Mease et al[62] Adalimumab 40 mg every other week vs placebo Stable doses of MTX were allowed and corticosteroid or DMARD rescue therapy was permitted in patients without at least a 20% reduction in swollen and tender joints by week 12.	DB, MC, PG, RCT Patients ≥18 years of age with moderately to severely active PsA with active psoriatic skin lesions or a documented history of psoriasis and a history of inadequate response to NSAIDs	N=315 24 weeks	Primary: ACR 20 response at 12 weeks, change in mTSS at week 24 Secondary: ACR 20 response at 24 weeks, ACR 50 and ACR 70 response at weeks 12 and 24, measures of joint disease, disability, quality of life, severity of skin disease in patients with psoriasis involving at least 3% of BSA	Primary: At week 12, 58% of the adalimumab treated patients achieved an ACR 20 response, compared to 14% of the placebo-treated patients (*P*<0.001). The mean change in the mTSS of radiographic structural damage was -0.2 in patients receiving adalimumab and 1.0 in those receiving placebo (*P*<0.001). Secondary: ACR 20 response at 24 weeks was 57% with adalimumab and 15% with placebo (*P*<0.001). An ACR 50 response was detected in 36% of adalimumab-treated individuals at 12 weeks and 39% of adalimumab-treated individuals at week 24 compared to 4 and 6% of those on placebo, respectively (*P*<0.001 for both outcomes). An ACR 70 response was found in 20% in the adalimumab arm and 1% in the placebo arm at 12 weeks and 23 and 1% at 24 weeks (*P*<0.001). PsARC response was achieved with adalimumab in 62% at 12 weeks and 60% at 24 weeks compared to 26 and 23% on placebo, respectively (*P* value not reported). Among the 69 adalimumab treated patients evaluated with the PASI, 59% achieved a PASI 75 improvement response at 24 weeks, compared to 1% of placebo-treated patients (*P*<0.001). Disability and quality of life measures were also significantly improved with adalimumab treatment compared to placebo treatment (*P*<0.001 for changes in both HAQ DI and SF-36 PCS scores at weeks 12 and 24). Changes in SF-36 MCS scores were not statistically significant between

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				groups at both week 12 (*P*=0.708) and week 24 (*P*=0.288). The rates of overall and serious adverse events were similar among groups.
Mease et al[63] Etanercept 25 mg twice weekly vs placebo Patients on stable doses of corticosteroids (equal to ≤10 mg/day of prednisone) or MTX were permitted to continue therapy.	DB, RCT Patients 18 to 70 years of age with active PsA despite NSAID therapy	N=60 12 weeks	Primary: PsARC, PASI 75 at 12 weeks Secondary: ACR 20 response, ACR 50 response, ACR 70 response, PASI 75, improvement in target psoriasis lesions	Primary: Eighty-seven percent of etanercept treated patients met the PsARC, compared to 23% of placebo-controlled patients (*P*<0.0001). PASI 75 improvement was detected in 26% of etanercept-treated patients vs none of placebo treated patients (*P*=0.0154). Secondary: The ACR 20 was achieved by 73% of etanercept-treated patients compared to 13% of placebo-treated patients (*P*<0.0001), while approximately 48 and 5% achieved an ACR 50 response and 12% and 0% achieved an ACR 70 response, respectively (*P*=0.0001 for ACR 50; *P* value not reported for ACR 70). Of the 19 patients in each treatment group who could be assessed for psoriasis, 26% of etanercept-treated patients achieved a 75% improvement in PASI, compared to none of the placebo-treated patients (*P*=0.0154). Median target lesion improvements were 50 and 0%, for etanercept and placebo, respectively (*P*=0.0004). There were no significant differences detected in the rate of adverse events between groups.
Mease et al[64] Etanercept 25 mg twice weekly vs placebo	DB, MC, RCT Patients 18 to 70 years of age with active PsA despite NSAID therapy	N=205 72 weeks	Primary: ACR 20 response Secondary: ACR 50 response, ACR 70 response, change in mTSS,	Primary: At 12 weeks, 59% of etanercept patients met the ACR 20 improvement criteria for joint response, compared to 15% of placebo patients (*P*<0.0001), and results were sustained at 24 and 48 weeks. Secondary: At 24 weeks, ACR 50 and ACR 70 responses were achieved in approximately 40 and 15% of etanercept patients and 5 and 1% of placebo patients, respectively (*P* values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Patients who completed a 24 week blinded phase could elect to receive OL therapy in a 48 week extension. Patients on stable doses of corticosteroids (equal to ≤10 mg/day of prednisone) or MTX were permitted to continue therapy.			PsARC, PASI 75, SF-36 Health Survey, HAQ, safety	The mean annualized rate of change in the mTSS with etanercept was -0.03 unit, compared to 1.00 unit with placebo (*P*<0.0001). A PsARC response was achieved by 72 and 70% of etanercept patients at weeks 12 and 24, respectively vs 31 and 23% of placebo patients (*P* values not reported). At 24 weeks, 23% of etanercept patients eligible for psoriasis evaluation achieved at least 75% improvement in the PASI, compared to 3% of placebo patients (*P*=0.001). SF-36 PCS scores improved more often with etanercept compared to placebo, but SF-36 MCS scores did not differ significantly between groups. HAQ scores at 24 weeks were significantly improved with etanercept (54%) over placebo (6%; *P*<0.0001). Injection site reactions occurred at a greater rate with etanercept than placebo (36 vs 9%; *P*<0.001).
Kavanaugh et al[65] Golimumab 50 mg once every 4 weeks vs golimumab 100 mg once every 4 weeks vs placebo Patients who had used or were currently using MTX,	MC, PC, RCT Patients ≥18 years of age with a diagnosis of PsA and active PsA despite current or previous DMARD or NSAID therapy and no evidence of active TB and/or no evidence of latent TB on screening	N=405 24 weeks	Primary: ACR 20 response at week 14 Secondary: Not reported	Primary: Golimumab 50 mg with or without MTX compared to placebo with or without MTX, resulted in a significant improvement in signs and symptoms as demonstrated by ACR 20 response at week 14 (51 vs 9%; *P*<0.001). Similar ACR 20 responses at week 14 were observed in patients with different PsA subtypes. ACR responses observed in the golimumab treated groups were similar in patients receiving and not receiving concomitant MTX. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
an NSAID, an oral corticosteroid, or a systemic or topical psoriasis treatment were enrolled.				
Antoni et al[66] Infliximab 5 mg/kg at weeks 0, 2, 6, 14 and 22 vs placebo	DB, MC, PC, PG, RCT Patients ≥18 year of age with active PsA for ≥6 months, inadequate response to current or previous DMARDs or NSAIDs, ≥1 qualifying lesion and negative serum RF	N=200 24 weeks	Primary: ACR 20 response at week 14 Secondary: PsARC, PASI 75, duration of morning stiffness, dactylitis in hands and feet, presence or absence of enthesopathy in the feet and SF-36	Primary: At week 14, there was significantly more patients in the infliximab group that achieved an ACR 20 response (58%) compared to the placebo group (11%; *P*<0.001). This difference continued through week 24 (54 vs 16%; *P*<0.001). Secondary: A significantly greater percentage of patients in the infliximab treated group had improvement in PsARC (77%) compared to the placebo group (27%; *P*<0.001) at week 14 and continued through week 24 (70 vs 32%; *P*<0.001). At weeks 14 and 24, fewer patients in the infliximab group had digits with dactylitis (18 and 12%) compared to the placebo group (30 and 34%; *P*=0.025 and *P*<0.001, respectively). Fewer patients in the infliximab group had enthesopathy compared to the placebo group at week 14 (22 vs 34%; *P*=0.016) and week 24 (20 vs 37%; *P*=0.002). A significantly higher proportion of patients achieved PASI 75 in the infliximab group compared to the placebo group at weeks 14 and 24 (64 vs 2%; *P*<0.001 and 60 vs 1%; *P*<0.001, respectively). At week 14, the physical and mental components of the SF-36 were significantly improved in the infliximab group compared to the placebo group (both *P*<0.001). There was also significant improvement at week 24 in the physical and mental components of the SF-36 in the infliximab group compared to the placebo group (*P*<0.001 and *P*=0.047, respectively). Adverse events were similar between the groups. There were a higher

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				proportion of patients who discontinued treatment due to adverse events in the infliximab group compared to the placebo group (4 vs 1%). There were a greater number of patients in the infliximab group that had increased ALT compared to the placebo group (1 vs 6%).
Baranauskaite et al[67] (RESPOND) Infliximab 5 mg/kg infusions at weeks 0, 2, 6 and 14 plus methotrexate 15 mg/week vs methotrexate 15 mg/week The use of NSAIDs and oral steroids (maximum dose 10 mg/day of prednisone or equivalent) was allowed if the dose was stable within four weeks before screening and kept stable throughout the study.	MC, OL, PC, PRO Patients ≥18 years of age who were treatment naïve and had active psoriasis in combination with peripheral articular disease with ≥1 of the following for three or more months before screening: distal interphalangeal joint involvement; polyarticular arthritis in the absence of rheumatoid nodules; arthritis mutilans; or asymmetric peripheral arthritis	N=115 16 weeks	Primary: Proportion of subjects achieving an ACR 20 response at week 16 Secondary: Proportions of patients with ACR 50 and ACR 70 responses, PASI 75 in subjects whose baseline PASI was 2.5 or greater, EULAR response, DAS28 scores, number of digits with dactylitis, Maastricht ankylosing spondylitis enthesitis score, fatigue scores, duration of morning stiffness and safety	Primary: In the ITT analysis, an ACR 20 response at week 16 was achieved by significantly more patients treated with infliximab plus MTX compared to patients treated with MTX alone (86.3 vs 66.7%; *P*=0.021). Secondary: The ACR 50 (72.5 vs 39.6%; *P*=0.0009) and ACR 70 (49.0 vs 18.8%; *P*=0.0015) response rates at week 16 were also significantly higher in the infliximab plus MTX group at 16 weeks compared to those receiving MTX alone. In patients with a PASI ≥2.5 or at baseline, a PASI 75 response at week 16 occurred in 97.1% of patients receiving infliximab plus MTX compared to 54.3% of patients receiving MTX alone (*P*<0.0001). By week 16, the mean reduction in PASI score was 93.3% for patients treated with infliximab plus MTX compared to 67.4% of patients treated with MTX alone (*P*=0.0029). The mean DAS28 at week 16 improved by 56.5% in the infliximab plus MTX patients compared to 29.7% of patients receiving MTX alone (*P*<0.0001). The EULAR response at week 16 was achieved in 98% of patients receiving infliximab plus MTX compared to 72.9% of those receiving MTX alone (*P*<0.0001). A median reduction of two digits with dactylitis was observed at week 16 in the patients treated with infliximab plus MTX, while no reduction was observed in the MTX monotherapy group (*P*=0.0006). Patients treated with infliximab plus MTX experienced a median reduction

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				of two sites with enthesitis at week 16 compared to a reduction of one site in the MTX alone group (*P*=0.082). A significantly greater reduction from baseline in fatigue scores occurred in the infliximab plus MTX group compared to the MTX monotherapy group at week 16 (70.8 vs 44.0%, respectively; *P*=0.0003). At week 16, the median change in the duration of morning stiffness was -0.92 hour with combination treatment vs –0.50 hour with methotrexate alone (*P*=0.0015). The incidence of adverse events was higher in patients receiving infliximab plus MTX compared to MTX alone. Most adverse events were mild or moderate in severity. One adverse event in each group was considered severe: increased transaminases in the infliximab plus MTX group and renal colic in the MTX-alone group. Treatment related adverse events were reported in 45.6% of the infliximab plus MTX group and 24.1% in the MTX alone group. The most frequent treatment-related adverse event involved hepatic enzyme increases.
Rheumatoid Arthritis				
Westhovens et al[68] Abatacept intravenous ~10 mg/kg on days 1, 15 and 29 then every four weeks plus MTX 15 mg/weekly vs placebo plus MTX 15 mg/weekly	DB, MC, PC, RCT Patients ≥18 years of age with RA for ≤2 years and ≥12 tender and 10 swollen joints, CRP ≥0.45 mg/dL, RF and/or anti-CCP2 seropositivity and radiographic evidence of bone erosion of the hands/wrists/feet; patients were either methotrexate-	N=509 24 months	Primary: Remission rates (DAS28 <2.6) and structural damage at year one (Genant-modified Sharp scoring system maximum score of 290) Secondary: ACR 50 responses, MCR (ACR 70 maintained for >6	Primary; A significantly higher proportion of patients in the abatacept group achieved DAS28-defined remission compared to the placebo group after one year of treatment (41.4 vs 23.3%, respectively; *P*<0.001). The mean change in structural damage at year one, measured using the Genant-modified Sharp scoring system total scores, was significantly lower in patients treated with abatacept compared to patients treated with placebo (0.63 vs 1.06, respectively; *P*=0.040). Secondary: A higher proportion of patients treated with abatacept achieved an ACR 50 (57.4 vs 42.3%; P<0.001), ACR 70 (42.6 vs 27.3%; *P*<0.001) and ACR 90 (16.4 vs 6.7%; *P*=0.001) compared to patients treated with placebo after one year of treatment.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	naive or had previous exposure of 10 mg/week or less for three weeks or less, with none administered		consecutive months); DAS28 scores, erosion score (maximum possible 145) and joint-space narrowing score (JSN; maximum possible 145), physical function (improvement of >0.3 units from baseline in the; HAQ-DI), SF-36 scores, proportion of patients achieving ACR 70 and ACR 90 responses and the proportion of patients without radiographic progression and safety	After one year of abatacept therapy, 27.3% of patients achieved an MCR (ACR 70 maintained for more than six consecutive months) compared to 11.9% of patients receiving placebo alone (*P*<0.001). Following one year of abatacept treatment, disease activity was significantly reduced compared to patients receiving placebo (-3.22 vs -2.49; *P*<0.001). Patients treated with abatacept achieved significantly greater improvements from baseline in total score and erosion score compared to patients randomized to the placebo group (*P*=0.040 and *P*=0.033, respectively). The changes from baseline in JSN scores were similar between the abatacept and placebo groups (*P*=0.246). The proportion of patients with no radiographic progression in the abatacept group at one year was 61.2% (95% CI, 55.0 to 67.3) compared to the group receiving placebo 52.9% (95% CI, 46.6 to 59.2), with an estimated difference of 8.3% (95% CI, 21.0 to 17.5). A significantly greater proportion of patients in the abatacept group compared to the placebo group experienced a change from baseline in HAQ-DI score ≥0.3 units following one year of therapy (71.9 vs 62.1%; *P*=0.024). Abatacept treatment was associated with statistically significant improvements in the mental and physical components of the SF-36 questionnaire compared to the placebo group (*P*<0.05 for both). The most frequently reported adverse events in the abatacept group were nausea, upper respiratory tract infection and headache. Six deaths were reported; two (0.8%) in the abatacept group and four (1.6%) in the placebo Of the two deaths in the abatacept group, one patient had pneumonia and severe gastrointestinal bleeding and the other had an acute myocardial infarction.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The most frequent infections in patients treated with abatacept and placebo respectively, were upper respiratory tract infection in 26 (10.2%) and 26 (10.3%) patients, nasopharyngitis in 21 (8.2%) and 26 (10.3%) patients and influenza in 19 (7.4%) and 23 (9.1%) patients. Serious infections occurred in five (2.0%) abatacept-treated patients (pneumonia, gastroenteritis, cellulitis, pseudomonal lung infection and postoperative wound infection, one patient each) and five (2.0%) patients receiving placebo (pneumonia, three patients; gastroenteritis, one patient; and breast cellulitis and staphylococcal infection, both in the same patient). No patients in the abatacept group discontinued due to an infection. In the abatacept treatment group, autoimmune disorders were reported in six patients compared to five patients in the placebo group. Sixteen patients in the abatacept treatment group experienced infusion related reaction compared to five patients receiving placebo.
Genovese et al[69] Abatacept subcutaneous 125 mg days 1 and 8 then weekly (intravenous loading dose of ~10 mg/kg was also administered on day 1) vs abatacept intravenous ~10 mg/kg on days 1, 15 and 29 then every 4 weeks	DB, DD, MC, RCT Patients with RA (defined by ACR 1987 criteria) and functional class I, II and III (defined by ACR 1991 revised criteria) that had an inadequate response to ≥3 months of MTX therapy (≥15 mg/week), with ≥10 swollen joints, ≥12 tender joints and CRP ≥0.8 mg/dL	N=1,457 6 months	Primary: Proportion of patients achieving ACR 20 at six months Secondary: Proportion of patients achieving ACR 50 and ACR 70	Primary: The proportion of patients achieving ACR 20 with abatacept subcutaneous (76.0%; 95% CI, 72.9 to 79.2) and abatacept intravenous (75.8%; 95% CI, 72.6 to 79.0) was not significantly different (estimated between group difference, 0.3%; 95% CI, -4.2 to 4.8). Secondary: The proportion of patients achieving ACR 50 with abatacept subcutaneous and abatacept intravenous (51.5 vs 50.3%) was not significantly different. The proportion of patients achieving ACR 70 with abatacept subcutaneous and abatacept intravenous (26.4 vs 25.1%) was not significantly different. Adverse events were also similar between the groups.
Keystone et al[70] (ATTUNE) Abatacept subcutaneous	OL Patients ≥18 years of age with active	N=128 12 months	Primary: Safety at three months	Primary: Up to month three, adverse events occurred in 39.8% of patients; no individual adverse events were reported in ≥5% of patients. One adverse event (musculoskeletal pain) led to discontinuation. Overall, 75.6% of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
125 mg	RA previously refractory to either MTX or anti-TNFs who had received ≥4 years of intravenous abatacept in either of two previous RCTs		Secondary: Immunogenicity at three months, efficacy at 12 months	patients experienced an adverse event during the cumulative period. After month three, 12 further adverse events were reported, of which three led to discontinuation (breast cancer, sarcoidosis and brain neoplasm). No deaths were reported in the study or during follow-up. Infections reported up to month three (more than one patient) included nasopharyngitis (n=4), urinary tract infection (n=3), bronchitis (n=2), gastroenteritis (n=2), sinusitis (n=2) and upper respiratory tract infection (n=2). No serious infections, malignancies or autoimmune events were reported during the first three months. Serious infections, malignancies or autoimmune events occurring after month three were as follows: one serious infection (pneumonia)), two malignancies (breast and uterine cancer) and two autoimmune events occurred (sarcoidosis and erythema nodosum). Secondary: Eight patients were seropositive based on ELISA through month three. Of these eight, six were already positive prior to enrolment. All seropositive patients continued treatment. Adverse events experienced by the seropositive patients were not consistent with immune-mediated toxicities, except for one patient who developed sarcoidosis and discontinued treatment. None of these patients had an abatacept-induced seropositive result based on the ECL assay. At baseline, mean DAS28 and HAQ-DI scores in the overall population were 3.39 and 0.94, respectively. Improvements in disease activity and physical function achieved during intravenous treatment were maintained through month 12 of subcutaneous treatment.
Haraoui et al[71] (CanACT) Adalimumab 40 mg subcutaneous injection every other week	MC, OL, PRO Patients ≥18 years of age with RA diagnosed according to the 1987 revised ACR	N=879 12 weeks	Primary: Mean change in DAS28 Secondary: Proportion of patients	Primary: Patients treated with adalimumab achieved significantly lower DAS28 scores at week 12 compared to baseline (4.2 vs 6.1; *P*<0.001). Secondary: Following 12 weeks of treatment with adalimumab, 15.3 and 28.9% of patients achieved clinical remission (DAS28 value <2.6) and low-disease

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	criteria with active disease, (≥5 swollen joints (of 66 joints evaluated) and one of the following: positive RF, ≥1 joint erosions present on x-ray, or a HAQ-DI score ≥1 and an unsatisfactory responses or intolerance to prior antirheumatic therapies		achieving clinical remission (DAS28 <2.6) and low-disease activity (DAS28 <3.2) at week 12, proportion achieving EULAR-moderate and good response, ACR 20, ACR 50, and ACR 70) responses at weeks four, eight, and 12, mean changes in ACR core components [tender joint count, swollen joint count, ESR, physician and patient assessments and HAQ-DI	activity (DAS28 value <3.2), respectively (*P* values not reported). At week 12, 25.9% of patients treated with adalimumab were considered EULAR responders to treatment. The proportion of patients who experienced an ACR 20, ACR 50 and ACR 70 response at 12 weeks was 58.4, 30.6 and 12.7%, respectively (*P* values not reported). At week eight, the proportion of patients who experienced an ACR 20, ACR 50 and ACR 70 response was 52.2, 21.7 and 7.2%, respectively (*P* values not reported). At week four, the proportion of patients who experienced an ACR 20, ACR 50 and ACR 70 response, was 37.6, 10.6 and 2.4%, respectively (*P* values not reported). Patients treated with adalimumab experienced a decrease in the number of tender joints at week 12 compared to baseline (6.8 vs 19.9; *P* value not reported) and the number of swollen joints was reduced from 13.2 at baseline to 6.4 after 12 weeks (*P* value not reported). As measured on a VAS, patient's assessment of pain decreased from a 66.2 at baseline to 37.3 following adalimumab therapy. Patients' assessment of disease activity decreased from 65.1 at baseline to 37.4 at follow up. Similarly physician assessment of disease activity decreased from 63.6 at baseline to 29.0 (*P* values not reported). The mean HAQ-DI score improved by an average of 0.5 units from 1.5 at baseline to 1.0 after 12 weeks of adalimumab treatment. In addition, the ESR decreased from a mean of 30.3 mm/h at baseline to 20.0 mm/h at 12 weeks (*P*<0.001). Adverse events were reported in 43.4% of patients treated with adalimumab. Most adverse events were mild to moderate in intensity. The most commonly reported adverse events were injection site reactions

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(9.9%), headache (5.2%), injection site erythema (3.5%), nausea (3%) and rash (2.8%). Of the treatment-emergent adverse events considered by the investigator to be related to study drug, injection site reaction and headache were the most frequently reported (≥5% of patients).
van Vollenhoven et al[72] (ORAL Standard) Adalimumab 40 mg subcutaneous injection every other week vs tofacitinib 5 mg orally twice-daily vs placebo for three months or six months followed by tofacitinib 5 mg twice-daily vs placebo for three months or six months followed by tofacitinib 10 mg twice-daily Patients in the placebo group who did not have a ≥20% reduction in the number of swollen and tender joints after three months were randomly assigned to either 5 mg or	AC, DB, MC, PC, RCT Patients ≥18 years of age with RA (defined by ACR 1987 criteria) and active disease was and either an ESR ≥28 mm/hour or a CRP >7 mg/L while receiving 7.5 to 25 mg of MTX weekly and experiencing an incomplete response	N=717 12 months	Primary: Proportion of patients at month six who achieved an ACR 20, mean change from baseline in HAQ-DI, and the percentage of patients who had a DAS28 <2.6 at month six Secondary: Proportion of tofacitinib patients achieved an ACR 20, ACR 50, and ACR 70 and safety	Primary: Significantly more patients receiving active treatment achieved an ACR 20 response at six months (51.5% in the 5 mg tofacitinib group, 52.6% in the 10 mg tofacitinib group and 47.2% in the 40 mg adalimumab group) compared to the placebo group (28.3%; *P*<0.001 for all comparisons). The mean change from baseline in the HAQ-DI score at three months was significantly lower with all active treatments compared to the placebo group (-0.55, -0.61 and -0.49 vs -0.24 for tofacitinib 5 mg, 10 mg and adalimumab 40 mg compared to placebo; *P*<0.001 for all). The percentage of patients with a DAS28 below 2.6 at six months was significantly greater with all active treatments compared to placebo (6.2, 13.1 and 7.3% vs 1.1% for tofacitinib 5 mg, 10 mg and adalimumab 40 mg compared to placebo; *P*≤0.005 for all). Significantly more patients treated with tofacitinib 5 mg or 10 mg experienced an ACR 20, ACR 50 and ACR 70 compared to placebo (*P*≤0.001 for all comparisons). Secondary: After an initial decrease in neutrophil counts at month three with all active treatments, neutrophil counts remained relatively stable through month 12. The incidence of mild neutropenia (1,500 to 1,999 neutrophils per cubic millimeter) and moderate-to-severe neutropenia (500 to 1,499 neutrophils per cubic millimeter) was low across all treatment groups. A total of 3.9% of patients in the 5 mg tofacitinib group, 6.5% in the 10 mg tofacitinib group, 0.1% in the adalimumab group and 0.93% in the placebo group had LDL cholesterol levels that were below 100 mg/dL at baseline that increased to 130 mg/dL higher after three months.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
10 mg of tofacitinib. After six months, all patients assigned to placebo were switched in a blinded fashion to either 5 mg or 10 mg of tofacitinib.				Most instances of decreased hemoglobin were mild to moderate in severity; decreased hemoglobin was potentially life threatening in one patient in the 10 mg tofacitinib group, one patient in the 5 mg tofacitinib group and one patient in the adalimumab group at month 12. More patients in the 5 mg and 10 mg tofacitinib groups than in the adalimumab or placebo group had AST levels ≥1 times the upper limit of the normal range at month three. ALT levels that were ≥1 times the upper limit of the normal range occurred most frequently in the 10 mg tofacitinib group. Less than 5% of patients in the active-treatment groups had AST or ALT levels ≥3 or more times the upper limit of the normal range. The most frequently reported adverse events were infections and infestations. After three months infections occurred in 18% if the 5 mg tofacitinib group, 17% in the 10 mg tofacitinib group, 16% in the adalimumab group and 9% in the placebo group. Discontinuation of treatment due to adverse events in the first three months occurred more frequently in the 5 mg tofacitinib group (6.9%) compared to 5.0% of the patients in the 10 mg tofacitinib group, 4.9% of patients in the adalimumab group and 2.8% of the patients in the placebo group. Two deaths were reported in the study; one patient receiving 5 mg tofacitinib, and one in the adalimumab group. There were two cases of pulmonary tuberculosis (both in the 10 mg tofacitinib group) and no cases of extrapulmonary tuberculosis or other major opportunistic infections.
Keystone et al[73] (RAPID 1) Certolizumab 400 mg at weeks 0, 2, and 4 then 200 mg every 2 weeks plus MTX (CZP 200 mg) vs certolizumab 400 mg at weeks 0, 2, and 4 then	DB, MC, PG, RCT Patients ≥18 years of age with a diagnosis of RA (defined by ACR 1987 criteria), for ≥6 months and up to 15 years with active disease despite treatment with MTX	N=982 52 weeks	Primary: ACR 20 at 24 weeks, mean change from baseline in mTSS at 52 weeks Secondary: Mean change from baseline in mTSS at 24 weeks, HAQ-DI,	Primary: A significantly greater number of ACR 20 responders at 24 weeks were found in the CZP 200 mg group (58.8%) and CZP 400 mg group (60.8%) compared to the placebo group (13.6%; *P*<0.001). There was no significant difference detected between the two CZP regimens. mTSS were significantly lower with CZP 200 mg (0.4 Sharp units) and 400 mg (0.2 Sharp units) vs placebo (2.8 Sharp units; *P*<0.001). Secondary: Active treatment was associated with reduced mTSS at 24 weeks compared to placebo (0.2 Sharp units for 200 and 400 mg vs 1.3 Sharp

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
400 mg every 2 weeks plus MTX (CZP 400 mg) vs placebo plus MTX Patients were randomized 2:2:1. Concurrent analgesics, NSAIDs or COX2 inhibitors, or oral corticosteroids (≤10 mg/day of prednisone or equivalent) were allowed.			ACR 20 at 52 weeks, ACR 50 and ACR 70 at 24 weeks	units for placebo; *P*<0.001). The HAQ-DI score at 52 weeks was -0.60 with CZP 200 mg, -0.63 with CZP 400 mg and -0.18 with placebo (*P*<0.001). ACR 20 response remained significantly higher with CZP 200 mg over 52 weeks (*P*<0.001 vs placebo). A significantly greater proportion of individuals achieved ACR 50 and ACR 70 with CZP 200 mg (37.1 and 21.4%) and CZP 400 mg (39.9 and 20.6%) compared to placebo (7.6 and 3.0%; *P*<0.001) at week 24. Infections and infestations occurred in 56.4% of CZP 200 mg patients, 58.4% of CZP 400 mg patients and 56.9% of placebo patients with serious infections occurring in 5.3, 7.3 and 2.2% of CZP 200 mg, 400 mg and placebo patients, respectively. The most frequent adverse events reported included headache, hypertension and back pain.
Smolen et al[74] (RAPID 2) Certolizumab 400 mg at weeks 0, 2, and 4 then 200 mg every 2 weeks plus MTX (CZP 200 mg) vs certolizumab 400 mg at weeks 0, 2, and 4 then 400 mg every 2 weeks plus MTX (CZP 400 mg) vs placebo plus MTX Patients were randomized	DB, MC, RCT Patients ≥18 years of age with a diagnosis of RA (defined by ACR 1987 criteria) for ≥6 months and up to 15 years with active disease despite treatment with MTX	N=619 24 weeks	Primary: ACR 20 at 24 weeks Secondary: ACR 50, ACR 70, mTSS, SF-36 Health Survey and individual ACR core set variables, safety	Primary: ACR 20 was attained by significantly more individuals receiving CZP 200 mg (57.3%) and CZP 400 mg (57.6%) compared to placebo (8.7%; *P*≤0.001). Secondary: ACR 50 and ACR 70 were achieved in a significantly greater number of patients in the CZP 200 mg group (32.5 and 15.9%, respectively) and CZP 400 mg group (33.1 and 10.6%, respectively) vs placebo (3.1 and 0.8%, respectively; *P*≤0.01). CZP 200 mg (0.2; 95% CI, -1.0 to 0.6) and CZP 400 mg (-0.4 mg; 95% CI, -0.7 to -0.1) were associated with a significantly lower change in mTSS than placebo (1.2; 95% CI, 0.5 to 2.0; *P*≤0.01 compared to CZP 200 mg; *P*≤0.001 compared to CZP 400 mg). Active treatment resulted in greater improvements in SF-36 scores vs placebo (*P*<0.001) and ACR core components vs placebo *(P*<0.001). Serious infection was reported in 3.2% of CZP 200 mg patients, 2.4% of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
2:2:1. Concurrent analgesics, NSAIDs or COX2 inhibitors, or oral corticosteroids (≤10 mg/day of prednisone or equivalent) were allowed.				CZP 400 mg patients and 0% of placebo patients. Tuberculosis was reported in five patients receiving certolizumab.
Fleischmann et al[75] (FAST4WARD) Certolizumab 400 mg every 4 weeks vs placebo Concurrent analgesics, NSAIDs, or oral corticosteroids (≤10 mg/day of prednisone or equivalent) were allowed.	DB, MC, RCT Patients 18 to 75 years of age with adult onset RA (defined by ACR 1987 criteria) for ≥6 months, with active disease and failed at least one prior DMARD	N=220 24 weeks	Primary: ACR 20 at 24 weeks Secondary: ACR 50, ACR 70, ACR component scores, DAS 28, patient reported outcomes, safety	Primary: ACR 20 achievement at 24 weeks was significantly higher with certolizumab (45.5%) than placebo (9.3%; *P*<0.001). Secondary: A significantly greater proportion of ACR 50 and ACR 70 responders were found in the active treatment group vs the placebo group (22.7 vs 3.7%; *P*<0.001 and 5.5 vs 0%; *P*≤0.05, respectively). A significant improvement in all ACR components was also detected among patients on certolizumab vs placebo (*P*≤0.05). A significantly greater change in DAS 28 was also reported with active treatment (-1.5 vs -0.6 for placebo; *P*<0.001). Patients reported significant improvements in physical function with certolizumab as measured by HAQ-DI (*P*<0.001), arthritis pain (*P*≤0.05) and fatigue (*P*<0.001). Headache, nasopharyngitis, upper respiratory tract infections, diarrhea and sinusitis occurred in at least 5% of certolizumab patients. There were no reports of tuberculosis or opportunistic infections throughout the study.
Weinblatt et al[76] (REALISTIC) Certolizumab 400 mg at weeks 0, 2 and 4, followed by 200 mg every 2 weeks	DB, MC, RCT Patients ≥18 years of age with adult onset RA (defined by ACR 1987 criteria) for ≥3	N=1063 12 weeks	Primary: ACR 20 at 12 weeks Secondary: ACR 50, ACR 70, DAS 28, ACR	Primary: ACR 20 achievement at 12 weeks was significantly higher with certolizumab (51.1%) than placebo (25.9%; *P* < 0.001). Secondary: A significantly greater proportion of ACR 50 and ACR 70 responders were found in the active treatment group vs the placebo group (26.6 vs 9.9%;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	months, with active disease and failed at least one prior DMARD		component scores	*P*<0.001 and 13.0 vs 2.8%; *P*<0.001, respectively). A significant improvement in all ACR components was also detected among patients on certolizumab vs placebo (*P*≤0.05). At 12 weeks, 81.1% of patients on certolizumab achieved a DAS28 improvement of at least 1.2 vs 56.5% with placebo (*P*<0.001). The most common AEs reported were nausea, upper respiratory tract infections, flare of RA and headaches. Injection and infusion-site reactions occurred in 5.8% of certolizumab patients and 1.0% placebo patients.
Tanaka et al[77] (GO-FORTH) Golimumab 50 mg once every four weeks and MTX (Group 3) vs golimumab 100 mg once every four weeks and MTX (Group 2) vs placebo and MTX (Group 1)	DB, MC, PC, RCT Patients 20 to 75 years of age with RA (diagnosed with ACR 1987criteria) with RA for ≥3 months and were receiving 6 to 8 mg/week oral MTX for RA for ≥3 months before study and active RA (≥4/66 swollen joints and ≥4/68 tender joints at screening/ baseline) and ≥2 of the following criteria at screening/ baseline: CRP >1.5 mg/dL, ESR by the Westergren method of >28 mm/hour, morning stiffness lasting ≥30 minute, radiographic	N=269 24 weeks	Primary: Proportion of patients achieving ACR 20 at week 14 Secondary: Proportion of patients achieving an ACR 50 and ACR 70 response, ACR-N Index of Improvement, DAS28(ESR) response DAS28(ESR) remission (score <2.6), HAQ-DI and safety	Primary: There was a significantly higher proportion of patients achieving an ACR 20 in the golimumab 50 and 100 mg groups compared to the placebo group (74.7 and 72.1 vs 27.3%; *P*<0.0001). Secondary: Similarly, more patients in the golimumab 50 and 100 mg groups achieved an ACR 50 compared to the placebo group (43.0 and 37.9 vs 9.1%; *P*≤0.005). More patients receiving golimumab 50 or 100 mg achieved an ACR 70 compared to patients receiving placebo (22.1 and 13.8% vs 2.3%; *P*≤0.005). The ACR-N index of improvement was significantly higher in patients receiving golimumab 50 mg (30%) and golimumab 100 mg (25.85%) compared to placebo (20.00; *P*<0.001 for both). Significantly more patients in the golimumab 50 mg and 100 mg treatment groups achieved DAS28(ESR) scores for response to treatment compared to placebo (79.5 and 85.5 vs 37.6%; *P*<0.0001). A higher proportion of patients receiving golimumab 50 mg or 100 mg achieved DAS28(ESR) for remission compared to placebo at 14 weeks (31.4 and 18.4 vs 3.4%; *P*<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	evidence of bone erosion, or anti-cyclic citrullinated peptide antibody-positive or rheumatoid factor-positive			Patients randomized to golimumab 100 mg and 50 mg treatment groups experienced statistically significant improvements in HAQ-DI scores compared to placebo at 14 weeks (0.32 and 0.39 vs 0.07; *P*<0.0001). By week 16, 72.7, 75.6 and 78.2% of patients receiving placebo, golimumab100 mg and 50 mg, respectively, had adverse events. Infections were the most common adverse event in the placebo (39.8%), golimumab 100 mg (38.4%) and golimumab 50 mg (33.3%) treatment groups at week 24. Serious adverse events were relatively uncommon through week 16, occurring in one patient (1.1%) in receiving placebo (intervertebral disc protrusion), one patient (1.2%) in the golimumab 100 mg group (ileus) and two patients receiving golimumab 50 mg (2.3%). By week 24, 11 (5.5%) of the 201 patients treated with golimumab 50 mg or 100 mg had discontinued golimumab due to the following adverse events: infection (n=2), skin disorders (n=2), liver function abnormality (n=2), injury (n=2), bone neoplasm (n=1), aortic dissection (n=1), gastrointestinal disorder (n=1) and elevated blood pressure (n=1 in combination with skin disorder).
Emery et al[78] Golimumab 100 mg once every 4 weeks and placebo vs golimumab 50 mg once every 4 weeks and MTX vs golimumab 100 mg once every 4 weeks and MTX vs	DB, PC, RCT MTX naïve patients ≥18 years of age with a diagnosis of active RA for ≥3 months and not previously treated with a TNF-blocker	N=637 24 weeks	Primary: ACR 50 response at week 24 Secondary: ACR 20, 70, 90 responses at week 24	Primary: The golimumab monotherapy group was not statistically different from the MTX monotherapy group in ACR response (*P*=0.053). However, post-hoc modified intent-to-treat analysis (excluding three untreated patients) of the ACR 50 response showed statistically significant difference between the two groups (*P*=0.049). Secondary: The combined golimumab and MTX groups had greater proportion of patients achieve an ACR 20 response at week 24 compared to placebo and MTX groups (*P*=0.028 for both groups). ACR 70 response was not significant and ACR 90 response was significant for the golimumab 50 mg and MTX groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo and MTX				
Keystone et al[79] Golimumab 100 mg once every 4 weeks and placebo vs golimumab 50 mg once every 4 weeks and MTX vs golimumab 100 mg once every 4 weeks and MTX vs placebo and MTX	DB, MC, PC, RCT Patients ≥18 years of age with a diagnosis of active RA for ≥3 months despite stable dose of ≥15 mg/week of MTX and not previously treated with a TNF-blocker	N=444 24 weeks	Primary: ACR 20 response at week 14, change from baseline in HAQ at week 24 Secondary: ACR 50, 70, 90 responses and ACR-N EULAR response, remission according to DAS 28, sustained remission (DAS 28 remission at week 14 and maintained through week 24)	Primary: At week 14, an ACR 20 response was achieved by 33.1% of placebo and MTX-treated patients, 44.4% of golimumab 100 mg and placebo-treated patients (*P*=0.059), 55.1% of golimumab 50 mg and MTX-treated patients (*P*=0.001), and 56.2% of golimumab 100 mg and MTX-treated patients (*P*<0.001). At week 24, the median improvements from baseline in the HAQ-DI scores were -0.13 (*P*=0.240), -0.38 (*P*=0.001), and -0.50 (*P*<0.001), respectively. Secondary: ACR 50 and ACR-N response was significant for all the groups except placebo and MTX; ACR 70 was significant for all the groups except the placebo and MTX and golimumab and placebo groups; ACR 90 was not significant for any of the groups. Greater proportion of patients in the golimumab and MTX groups achieved significant EULAR response. At week 24, clinical remission was achieved by 6.0% of placebo and MTX-treated patients, 12.0% (*P*=0.087) of golimumab 100 mg and placebo-treated patients, 20.2% (*P*=0.001) of golimumab 50 mg and MTX-treated patients, and 22.5% (*P*<0.001) of golimumab 100 mg and MTX-treated patients, respectively. Sustained remission was achieved by 0.8%, 6.3% (*P*=0.018), 10.2% (*P*=0.001), and 11.9% (*P*<0.001), respectively.
Smolen et al[80] (GO-AFTER) Golimumab 50 mg once every 4 weeks vs golimumab 100 mg once every 4 weeks	DB, PC, RCT Patients ≥18 years of age with a diagnosis of active RA for ≥3 months previously treated with ≥1 dose of a TNF-blocker without a serious adverse	N=461 24 weeks	Primary: ACR 20 response at week 14 Secondary: ACR 50 response at week 14, DAS 28 response at week 14, ACR 20 response at week	Primary: Golimumab 50 and 100 mg were significantly better than placebo in improving signs and symptoms of RA according to ACR 20 (35.3 and 37.9 vs 18.1%, respectively; *P*<0.001). ACR 20 responders at week 14 among patients who discontinued previous TNF-blocker therapy due to lack of efficacy included 35.7 and 42.7% of patients in the golimumab 50 and 100 mg groups, respectively, compared to 17.7% of patients in the placebo group (*P*=0.006, golimumab 50 mg vs placebo; *P*<0.001, golimumab 100 mg vs placebo).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo Patients were allowed to continue stable doses of concomitant HCQ, MTX, or SSZ during the trial.	reaction		24, improvement from baseline in HAQ scores at week 24	Secondary: ACR 50 response at week 14 was significant for the golimumab-treated groups compared to the placebo group. DAS 28 response was significant for golimumab 50 and 100 mg groups compared to placebo (56.2 and 59.5 vs 30.3%, respectively; *P*<0.001). ACR 20 response at week 24 was significant for the golimumab-treated groups compared to the placebo group. At week 24, golimumab improved physical function and fatigue according to HAQ and FACIT-F scores, respectively.
Smolen et al[81] (GO-AFTER Extension) Golimumab 50 mg once every 4 weeks (Group 1) vs golimumab 50 mg once every 4 weeks. Dose could be increased to 100 mg if <20% improvement in both tender and swollen joint counts at week 16 of the original study occurred. (Group 2) vs golimumab 100 mg once every 4 weeks. (Group 3)	DB, MC, PC, RCT Patients ≥18 years of age with a diagnosis of active RA for ≥3 months previously treated with ≥1 dose of a TNF-blocker without a serious adverse reaction	N=459 160 weeks	Primary: ACR 20 Secondary: ACR 50/70,DAS 28, SDAI, HAQ score	Primary: At week 160, 62.7%, 66.7% and 56.8% of patients achieved ACR20 response and 59%, 65% and 64% had HAQ improvement ≥0.25 unit in Groups 1, 2 and 3, respectively. Secondary: At week 160, 17.3%, 14.8 and 23.5% of patients achieved ACR70 response Groups 1, 2 and 3, respectively. DAS 28 response for groups 1, 2 and 3, response was 71.8%, 83.8% and 71.4% respectively. Remission as measured by DAS 28 for groups 1, 2 and 3, response was 16.9%, 12.5% and 21.5% respectively. SDAI remission for groups 1, 2 and 3, response was 11.4%, 8.8% and 23.1% respectively. SDAI scores for low disease activity (3.3-11) for groups 1, 2 and 3, response was 34.3%, 28.8% and 25.6% respectively. At week 160, 59%, 65% and 64% had HAQ improvement ≥0.25 unit in Groups 1, 2 and 3, respectively.
Weinblatt et al[82] (GO-FURTHER)	DB, MC, PC, RCT Adult patients with	N=592 24 weeks	Primary: Proportion of patients	Primary: There was a significantly higher proportion of patients achieving an ACR 20 in the golimumab group compared to the placebo group (58.5 and 24.9%:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
golimumab 2 mg/kg, at weeks 0 and 4 and every 8 weeks plus MTX vs placebo and MTX	RA for ≥3 months and were receiving 15 to 25 mg/week oral MTX for RA for ≥4 weeks before study and active RA (≥6/66 swollen joints and ≥6/68 tender joints at screening/ baseline) and CRP >1.0 mg/dL, anti- cyclic citrullinated peptide antibody-positive and/or rheumatoid factor-positive		achieving ACR 20 at week 14 Secondary: DAS28 and HAQ-DI week 14, ACR 50 at week 24, and safety	*P*<0.001). Secondary: Significantly more patients in the golimumab treatment groups achieved DAS28 scores for moderate-good response to treatment compared to placebo at 14 weeks (81.3 vs 40.1%; *P*<0.001). Patients randomized to golimumab treatment groups experienced statistically significant improvements in HAQ-DI scores compared to placebo at 14 weeks (0.5 vs 0.19; *P*<0.001). Significantly higher proportion of patients randomized to golimumab groups achieved an ACR 50 compared to the placebo group (34.9 vs 13.2%; *P*≤0.001) at 24 weeks. Significantly higher proportion of patients randomized to golimumab groups achieved an ACR 50 compared to the placebo group (34.9 vs 13.2%; *P*≤0.001) at 24 weeks. Adverse events reported at rates ≥1.0% higher in the golimumab group vs placebo were observed for infections and infestations (24.3 vs 20.8%); nervous system disorders (6.8% vs 4.1%); gastrointestinal disorders (6.6 vs 5.6%); skin and subcutaneous tissue disorders (6.6% vs 3.6%); respiratory, thoracic and mediastinal disorders (4.8 vs 2.5%); vascular disorders (3.8 vs 2.5%); and metabolism and nutrition disorders (2.3 vs 0.0%).
Jones et al[83] (AMBITION) Tocilizumab 8 mg/kg every 4 weeks vs MTX 7.5 to 20 mg every week	DB, DD, PG, RCT Patients ≥18 years of age, with moderate to severe RA for ≥3 months, oral glucocorticoids (up to 10 mg/day of prednisone or equivalent) and	N=673 24 weeks	Primary: Proportion of patients achieving ACR 20 response at week 24 Secondary: Proportion of patients with	Primary: At week 24, 70.6% of tocilizumab patients as compared to 52.1% of MTX patients achieved an ACR 20 response (*P*<0.001). Compared to the placebo arm, a larger proportion of patients treated with tocilizumab also achieved an ACR 20 response at week eight (55.6 vs 13.1%; 95% CI, 0.34 to 0.52). Secondary: The proportion of patients achieving ACR 50 (44.0%) and ACR 70 (28.0%) at week 24 was also statistically significant for tocilizumab as compared to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
or placebo for 8 weeks followed by tocilizumab 8 mg/kg from week nine on	NSAIDs were permitted if the dose was stable for ≥6 weeks		ACR 50/70 responses at week 24 and the time to onset of ACR 20/50/70 responses, changes from baseline at week 24 in 28-joint count DAS 28, the proportion of patients in clinical remission (DAS 28 <2.6), with low disease activity (DAS 28 ≤3.2) and with good/ moderate responses at week 24, improvement in physical function was assessed by change from baseline at week 24 in HAQ-DI, adverse events	MTX (*P*<0.001). Improvements in DAS 28 at week 24 were greater in the tocilizumab group than in the MTX group. Additionally, the proportion of patients in remission at week 24 was higher with tocilizumab (*P*<0.001). By week 24, tocilizumab patients were five times more likely to achieve DAS 28 remission and four times more likely to achieve at least a moderate response (OR vs MTX, 4.24; 95% CI, 2.92 to 6.14). A greater improvement in physical function was seen by a higher mean change in HAQ-DI with tocilizumab when compared to that of MTX. There was no statistically significant difference with regard to the number of adverse events experienced in the tocilizumab group compared to the MTX group (79.9 vs 77.5%; *P*=0.484). Infection rates/patient year were also found to be similar (1.06 vs 1.09). However, skin and subcutaneous infections were reported more frequently in the tocilizumab group (4.1 vs 1.4%; *P* value not reported).
Smolen et al[84] (OPTION) Tocilizumab 8 mg/kg every 4 weeks plus MTX (stable, 10 to 25 mg weekly) vs	DB, PC, PG, RCT Patients ≥18 years of age, with moderate to severe RA >6 months duration, who had an inadequate response to MTX; all	N=622 24 weeks	Primary: ACR 20 response at week 24 Secondary: ACR 50/70, DAS 28, and EULAR responses at	Primary: At week 24, significantly more patients receiving tocilizumab 4 and 8 mg/kg had an ACR 20 response than patients who received placebo (59 vs 48 vs 26% respectively; *P*<0.0001 for both). Secondary: Significantly more patients in both tocilizumab groups achieved ACR 50 (31 vs 44 vs 11%; *P*<0.0001) and ACR 70 at week 24 (12 vs 22 vs 2%; *P*<0.0001) compared to patients in the placebo group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
tocilizumab 4 mg/kg every 4 weeks plus MTX (stable, 10 to 25 mg weekly) vs placebo every 4 weeks plus MTX (stable, 10 to 25 mg weekly)	other DMARDs were discontinued before the start of the study, oral glucocorticoids (≤10 mg/day of prednisone or equivalent) and NSAIDs were permitted if doses were stable for six weeks or more		week 24, difference in HAQ-DI, SF-36, and FACIT-F, scores from baseline, and adverse events	Disease activity was found to be reduced as measured by a DAS 28 score <2.6 in significantly more patients in both tocilizumab groups when compared to the placebo group (13.0 vs 27.0 vs 0.8%; *P*<0.0002 for 4 mg/kg and *P*<0.0001 for 8 mg/kg). EULAR response was also found to be significantly decreased in both tocilizumab groups (21 vs 38 vs 3%; *P*<0.0001 for both). Greater improvements in physical function were seen in both tocilizumab groups as assessed by the HAQ-DI score (-0.52 vs -0.55 vs -0.34; *P*<0.0296 for 4 mg/kg and *P*<0.0082 for 8 mg/kg). Significant differences were seen with regard to changes in the SF-36 physical score in both tocilizumab groups (9.7 vs 9.5 vs 5.0; *P*<0.0001 for both) and in the SF-36 mental score (5.7 vs 7.3 vs 2.7; *P*<0.0394 for 4 mg/kg and *P*<0.0012 for 8 mg/kg). The mean change in FACIT-F score from baseline showed significant improvements in both tocilizumab groups (7.3 vs 8.6 vs 4.0; *P*<0.0063 for 4 mg/kg and *P*<0.0001 for 8 mg/kg). More patients in the tocilizumab groups reported experiencing at least one adverse event when compared to the placebo group (71 vs 69 vs 63%). The rate of all infections/100 patient years was 98.7 in the tocilizumab 4 mg/kg group, 101.9 in the 8 mg/kg group, and 96.1 in the placebo group.
Genovese et al[85] (TOWARD) Tocilizumab 8 mg/kg plus DMARD every 4 weeks vs placebo plus DMARD every 4 weeks	DB, MC, PC, RCT Patients ≥18 years of age, with moderate to severe RA, who received stable doses of permitted DMARDs (MTX, chloroquine, HCQ, parenteral	N=1,220 24 weeks	Primary: ACR 20 responses at week 24 Secondary: ACR 50/70 responses at week 24, number of swollen and	Primary: At week 24, the proportion of patients in the tocilizumab group that were ACR 20 responders was significantly higher than in the control group (61 vs 25%; *P*<0.0001). No obvious differences were seen in ACR 20 response with regard to patients who received two or more DMARDs. Secondary: At week 24, significantly more patients in the tocilizumab group achieved ACR 50 and ACR 70 responses when compared to the placebo group (ACR 50, 30 vs 9%; ACR 70, 21 vs 3%; *P*<0.0001 for both).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	gold, SSZ, azathioprine, and leflunomide) for ≥8 weeks prior to study entry and oral glucocorticoids (≤10 mg/day of prednisone or equivalent) and NSAIDs or COX2 inhibitors if the doses were stable for ≥6 weeks		tender joints, DAS 28, EULAR response, HAQ, FACIT-F score, and SF-36, and adverse events	Compared to baseline, a significant decrease was seen in the number of swollen and tender joints in patients receiving tocilizumab when compared to the placebo group (swollen joint count, -10.3 vs -4.9; tender joint count, -15.7 vs -8.5; *P*<0.0001). Mean DAS 28 improved incrementally over time with greater changes in the tocilizumab group seen by week 24 (-3.17 and -1.16 respectively; *P*<0.0001). Remission rates at week 24 were also higher in the tocilizumab group when compared to the placebo group (30 vs 3%; *P*<0.0001). By week 24, 80% of patients in the tocilizumab group and 38% of patients in the placebo group achieved a good or moderate EULAR response (*P*<0.0001). At week 24, 60% of patients in the tocilizumab group had a clinically meaningful improvement in physical function as compared to 34% with placebo (change from baseline in HAQ ≥0.3). Mean changes from baseline were also significantly higher in the tocilizumab group when compared to the placebo group for the disability index of the HAQ (-0.5 vs -0.2; *P*<0.0001) and FACIT-F scores (8.0 vs 3.6; *P*<0.0001). Mean improvements from baseline in SF-36 scores were higher for both physical and mental components at week 24 in the tocilizumab group (8.9 vs 4.1 and 5.3 vs 2.3 respectively; *P*<0.0001 for both). The occurrence of adverse events was found to be higher with tocilizumab (73 vs 61%). The most frequently occurring adverse events in both groups were infections and infestations (37.4 vs 31.6%), gastrointestinal disorders (20.8 vs 14.7%), and musculoskeletal and connective tissue disorders (13.0 vs 17.9%). Infections with a higher incidence in the tocilizumab group were upper respiratory infections (9 vs 7%), other respiratory infections (12 vs 10%), and skin and subcutaneous tissue infections (5 vs 3%).
Kremer et al[86] (LITHE)	DB, MC, PC, PG, RCT	N=1,196 12 months	Primary: Change from baseline in the	Primary: The proportion of patients without radiographic progression (change in total Genant-modified Sharp score ≤0 from baseline to week 52) was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Tocilizumab 8 mg/kg plus MTX (stable, 10 to 25 mg weekly) for four weeks vs tocilizumab 4 mg/kg plus MTX (stable, 10 to 25 mg weekly) for four weeks vs placebo plus MTX (stable, 10 to 25 mg weekly) for four weeks Oral corticosteroids (≤10 mg/day of prednisone or equivalent) and NSAIDs were permitted if the dosages had been stable for ≥6 weeks before study entry.	Patients with RA, as determined by ACR criteria that was moderate to severe and lasted for ≥6 months; inadequate response to MTX therapy, defined as a swollen joint count of ≥6, a tender joint count of ≥8, and either CRP level ≥1 mg/dl or an ESR ≥28 mm/hour; and had ≥1 radiographically confirmed joint erosion despite having received MTX for ≥12 weeks before baseline		total Genant-modified Sharp score and change in HAQ-DI Secondary: Change from baseline in erosion and JSN scores (at week 24 and 52), total Genant-modified Sharp score at week 24, proportions of patients with no progression of total, erosion, or JSN scores, ACR 20, ACR 50, and ACR 70, change in DAS 28 and proportions of patients with low levels of disease activity (DAS28 ≤3.2) and DAS remission (DAS28 <2.6).	significantly higher in patients treated with tocilizumab 8 or 4 mg/kg (84 and 81 vs 67%; *P*<0.0001). The AUC of the change in the HAQ-DI score from baseline to week 52 demonstrated a significantly greater decrease in the 8 and 4 mg/kg tocilizumab groups compared to the placebo group (-144.1 and -128.4 vs -58.1 units; *P*<0.0001 for both comparisons). Secondary: At week 52, the ACR 20, ACR 50, and ACR 70 response rates were higher in patients treated with tocilizumab compared to placebo; however the difference was only statistically significant for the 8 mg/kg group compared to the placebo group (*P*<0.0001 for all response rate comparisons). The DAS28 scores were reduced over 52 weeks in all treatment groups, with mean improvements of -3.8, -3.0, and -2.0 in the tocilizumab 8 mg/kg, 4 mg/kg and placebo groups, respectively; however, the difference was only significant with the 8 mg/kg dose compared to placebo (*P*<0.0001). At 52 weeks, more patients treated with tocilizumab 8 mg/kg achieved remission (47.2 vs 7.9%; *P*<0.0001) according to the DAS28 score (<2.6) or had low disease activity (DAS28 ≤3.2) compared to placebo (63.6 vs 45.3%; *P*<0.0001). DAS28 remission rates continued to improve between weeks 24 and 52, with the highest proportion of patients in remission in the tocilizumab 8 mg/kg treatment group. The progression of structural damage from baseline to week 52 was reduced by 74 and 70% with tocilizumab 8 and 4 mg/kg, respectively, compared to patients treated with placebo (*P*<0.0001). The total Genant-modified Sharp score at week 52 showed a decreased frequency and severity of disease progression with tocilizumab therapy.
Yazici et al[87] (ROSE) Tocilizumab 8 mg/kg plus	DB, MC, PC, PC, RCT Patients ≥18 years	N=619 24 weeks	Primary: ACR 50 response at week 24	Primary: A significantly higher proportion of patients randomized to receive tocilizumab achieved an ACR 50 response at week 24 compared to placebo (30.1 vs 11.2%; *P*<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
DMARD every four weeks vs placebo plus DMARD every four weeks Permitted DMARD (at stable doses ≥7 weeks before study) included methotrexate, chloroquine, hydroxychloroquine, parenteral gold, sulfasalazine, azathioprine and leflunomide. Doses were required to remain stable throughout the study; however, dose reductions were allowed as clinically warranted for safety reasons.	of age with active RA for ≥6 months and an inadequate clinical response to DMARD in addition to ≥6 swollen joints and ≥6 tender joints at screening and baseline, with either a CRP ≥95.24 nmol/l or an ESR ≥28 mm/h or greater at screening		Secondary: ACR 20, ACR 50, ACR 70, EULAR response, DAS28, clinically meaningful improvement (change from baseline in DAS28 of ≥1.2), patients achieving low disease activity (DAS28 ≤3.2), clinical remission (DAS28 <2.6), ESR and CRP levels, FACIT-F, RAPID3 scores	Secondary: A higher proportion of patients randomized to receive tocilizumab achieved an ACR 20 response at all time points evaluated compared to placebo (*P*<0.0001). Similarly, an ACR 50 response was achieved in significantly more patients in the tocilizumab group compared to placebo at all treatment weeks except week 16 (*P*<0.05 at all time points). A significantly greater proportion of patients in the tocilizumab group compared to the placebo group achieved an ACR 70 response at all time points from week eight onward (*P*<0.05 for all time points). A higher proportions of patients achieved a EULAR good response in the tocilizumab group compared to placebo at all time points starting at week four (13.2 vs 2.0%; *P*<0.0001). The mean DAS28 score decreased from baseline to week 24 in both treatment groups starting at week four; however, the improvement was significantly greater in tocilizumab group compared to placebo (*P*<0.0001). Significantly more patients achieved a clinically meaningful decrease in DAS28 (≥1.2 points from baseline) in the tocilizumab group compared to the placebo group at all time points from week four onward (87.9 vs 53.4%; *P*<0.0001). Moreover, a greater proportion of patients randomized to receive tocilizumab achieved a low disease activity (*P*<0.0001) and clinical remission at week 24 (*P*<0.0001) compared to those in the placebo group. There were significantly greater improvements from baseline in the RAPID3 scores at 24 weeks in the tocilizumab treatment group compared to placebo (-2.33 vs -1.29; *P*<0.0001). There was a statistically significant improvement in mean FACIT-F scores over 24 weeks of treatment with tocilizumab compared to placebo (*P*<0.05). Patients treated with tocilizumab achieved significantly lower mean CRP levels at all time points evaluated compared to the placebo group (*P*<0.0001). Similarly, the mean ESR was significantly reduced from

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				baseline to a greater degree with tocilizumab compared to the placebo group at week 24 (-34.72 vs -5.70 mm/h; *P*<0.0001).
Emery et al[88] (RADIATE) Tocilizumab 8 mg/kg plus MTX (stable, 10 to 25 mg weekly) for 4 weeks vs tocilizumab 4 mg/kg plus MTX (stable, 10 to 25 mg weekly) for 4 weeks vs placebo plus MTX (stable, 10 to 25 mg weekly) for 4 weeks	DB, PC, PG Patients ≥18 years of age with moderate to severe active RA with failure to respond to one or more TNF antagonists within the past year; patients must have discontinued TNF agents (Enbrel®, Humira®, Remicade®) or DMARDs (other than MTX) before enrolling	N=499 24 weeks	Primary: ACR 20 responses Secondary: DAS 28, number of patients requiring rescue therapy and adverse events	Primary: ACR 20 was achieved at week 24 by 50.0, 30.4 and 10.1% of patients in the 8 mg/kg, 4 mg/kg and control group respectively (*P*<0.001). At week four, more patients achieved ACR 20 in the 8 mg/kg tocilizumab group than those in the control group (*P*<0.001). Patients responded, as measured by ACR 20 response, regardless of the most recently failed TNF antagonist or the number of failed treatments. Secondary: DAS 28 remission rates at week 24 were dose related, being achieved in 30.1, 7.6, and 1.6% of 8 mg/kg, 4 mg/kg and control groups (*P*<0.001 for 8 mg/kg; *P*=0.053 for 4 mg/kg vs control). Rescue therapy with 8 mg/kg of tocilizumab plus MTX was offered at week 16 in all cases of treatment failure (<20% improvement in both tender and swollen joints). More patients in the control group (41%) and in the 4 mg/kg group (19%) received rescue therapy after week 16 compared to 11% of patients in the 8 mg/kg group. Adverse events noted were mild or moderate with overall incidences of 84.0% in the tocilizumab 8 mg/kg group, 87.1% in the tocilizumab 4 mg/kg group, and 80.6% in the placebo plus MTX group. The most common adverse events were infections, gastrointestinal symptoms, rash and headache. The incidence of serious adverse events was higher in the control group (11.3%) than in the tocilizumab 8 mg/kg (6.3%) and 4 mg/kg (7.4%) groups.
Dougados et al[89] (ACT-RAY) Tocilizumab 8 mg/kg plus MTX (stable >15 mg weekly) every 4 weeks	DB, PC, PG Patients ≥18 years of age with active RA with failure to respond to > 12 weeks of MTX	N=556 24 weeks	Primary: DAS 28 remission Secondary: DAS 28 low disease activity,	Primary: DAS 28 remission rates at week 24 were 40.4% with the tocilizumab/MTX group vs. 34.8% with tocilizumab monotherapy (*P*=0.19) Secondary: DAS 28 scored for low disease activity was significantly lower with combination therapy (tocilizumab/MTX) at week 24 that with the with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs tocilizumab 8 mg/kg plus placebo every 4 weeks	treatment (stable dose >15 mg week for 6 weeks prior to study)		ACR 20, ACR 50, ACR 70, ACR 90 and adverse events	tocilizumab monotherapy (61.7 vs. 51.4%; *P*=0.029) ACR 20/50/70/90 was 71.5%/45.5%/24.5%/5.8% with tocilizumab/MTX. ACR 20/50/70/90 was 70.3%/40.2%/25.4%/5.1% with tocilizumab monotherapy. The differences between treatment groups were not considered significant. Adverse events noted were comparable in each treatment group with 6.1% of patients on tocilizumab/MTX reporting a serious adverse event while 5.8% reported a serious adverse event with tocilizumab monotherapy. Discontinuations and dose modifications occurred in 3.6% and 27.4% of tocilizumab/MTX patients and 2.5% and 18.5% of tocilizumab monotherapy patients, respectively. Increases in alanine aminotransferase elevations from normal at baseline to greater than upper limit of normal and to more than three times upper limit of normal at one or more time points during 24 weeks occurred in 48.8% and 7.8% on tocilizumab/MTX and in 27.6% and 1.2% of tocilizumab monotherapy patients, respectively.
Maxwell et al[90] Abatacept 2 to 10 mg/kg alone or in combination with DMARDs or biologics vs placebo or DMARDs or biologics	SR RCTs of patients ≥16 years of age with RA meeting the ACR 1987 revised criteria	N=2,908 (7 trials) ≥3 months	Primary: ACR 50 response and safety Secondary: ACR 20, ACR 70, components of ACR radiographic progression, DAS, EULAR response criteria, changes in HAQ and SF-36	Primary: At three months, the ACR 50 response in the abatacept group was not significantly higher than the control group (RR, 2.50; 95% CI, 0.52 to 11.96). At six and 12 months, the ACR 50 response was significantly higher in the abatacept group compared to the control group (RR, 2.47; 95% CI, 2.00 to 3.07 and RR, 2.21; 95% CI, 1.73 to 2.82, respectively). At one year the NNT in order to achieve ACR 50 was 5 (95% CI, 4 to 7). The RR for adverse events with abatacept compared to controls was 1.05 (95% CI, 1.01 to 1.08). There was a greater number of serious adverse infections with abatacept compared to controls (OR, 1.91; 95% CI, 1.07 to 3.42). However, after removing a study in which patients were treated with combination of etanercept and abatacept, the OR decreased to 1.82 (95% CI, 1.00 to 3.32). Abatacept treated patients had increased number of headaches and infusion reactions (RR, 1.45; 95% CI, 1.20 to 1.74 and RR, 1.30; 95% CI, 1.13 to 1.50). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				ACR 20 response was achieved in significantly more patients treated with abatacept compared to controls at six and 12 months (RR, 1.79; 95% CI, 1.59 to 2.02 and RR, 1.79; 95% CI, 1.55 to 2.07, respectively) but not at three months (RR, 1.70; 95% CI, 0.93 to 3.12). More patients treated with abatacept achieved an ACR 70 at six and 12 months (RR, 3.53; 95% CI, 2.41 to 5.16 and RR, 4.02; 95% CI, 2.62 to 6.18) but not at three months (RR, 5.00; 95% CI, 0.25 to 100.20). There was a statistically significant reduction in the progression of joint damage at 12 months with abatacept (mean difference, -0.27; 95% CI, -0.42 to -0.12). The abatacept treated patients were significantly more likely to reach low DAS (DAS 28 <3.2) compared to controls at six and 12 months (RR, 3.36; 95% CI, 2.28 to 4.96 and RR, 4.33; 95% CI, 2.84 to 6.59), and a NNT of 4 (95% CI, 3 to 5). At 12 months, patients in the abatacept group were significantly more likely to achieve DAS remission (DAS 28 <2.6) with RR of 12.74 (95% CI, 4.76 to 34.15). For clinically meaningful improvement on the HAQ; RR, 1.69 (95% CI, 1.51 to 1.90) in favor of abatacept. There was an absolute difference of 24% (95% CI, 16 to 32) and a NNT to achieve HAQ >0.3 of 5 (95% CI, 4 to 7). Improvement in the physical component of the SF-36 was significantly more likely in the abatacept group (RR, 1.90, 95% CI, 1.52 to 2.39). There was no significant difference between the groups in likelihood of scoring worse. The RR of scoring the same was 0.66 in favor of placebo (95% CI, 0.56 to 0.78). There were significantly fewer patients that scored worse on the mental component of the SF-36 (RR, 0.64; 95% CI, 0.44 to 0.94). Scoring the same was not significantly different between the groups. A score of better was significantly higher in the abatacept group (RR, 1.42; 95% CI, 1.14 to 1.76).
Navarro-Sarabia et al[91] Adalimumab 20, 40, 80	SR RCTs of patients	N=2,381 (6 trials)	Primary: ACR, EULAR responses, DAS	Primary: Adalimumab 40 mg every other week was associated with a RR of 1.52 to 4.63 to attain an ACR 20 response at 24 weeks with a NNT of 1.9 to 5.4.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg every week to every other week, alone or in combination with DMARDs vs placebo or placebo plus DMARDs	with confirmed RA (defined by ACR 1987 criteria), who had active disease and who either failed MTX or other DMARDs therapy, or DMARD naive	12 to 52 weeks	28, components of ACR responses, radiographic data Secondary: Safety	The RR to achieve an ACR 50 response was 4.63 (95% CI, 3.04 to 7.05) and NNT was 3.0 (95% CI, 2.0 to 6.0). The RR to achieve an ACR 70 response was reported as 5.14 (95% CI, 3.14 to 8.41) and a NNT of 7 (95% CI, 5 to 13). At 52 weeks, the RRs were reported for ACR 20, ACR 50 and ACR 70 as 2.46 (95% CI, 1.87 to 3.22), 4.37 (95% CI, 2.77 to 6.91) and 5.15 (95% CI, 2.60 to 10.22) and NNTs were 2.9, 3.1 and 5.3, respectively. A significantly slower rate of radiological progression was detected with either adalimumab 40 mg every other week or 20 mg every week in combination with MTX compared to placebo plus MTX, at 52 weeks. Adalimumab monotherapy (40 mg every other week) was associated with a RR of 1.91 (95% CI, 1.17 to 3.10), 2.84 (95% CI, 1.58 to 5.12) and 7.33 (95% CI, 2.25 to 33.90) to achieve an ACR 20, ACR 50 and ACR 70 response, respectively, with NNTs of 5 (95% CI, 3 to 9), 7 (95% CI, 4 to 20) and 9 (95% CI, 3 to 38), respectively at 24 weeks. Secondary: Only one study demonstrated that adalimumab was associated with a significantly higher risk of developing serious infection (RR, 7.64; 95% CI, 1.02 to 57.18; NNH, 30.2).
Mertens et al[9] Anakinra 50 to 150 mg daily vs placebo	SR RCTs of patients >18 years of age with RA	N=2,876 (5 trials) 24 weeks	Primary: Patients achieving ACR 20 Secondary: Patients achieving ACR 50 and ACR 70, safety	Primary: ACR 20 achievement was noted in significantly more participants taking anakinra (38%) compared to patients taking placebo (23%; RR, 1.61; 95% CI, 1.32 to 1.98). It was concluded that this 15% difference represented a modest yet clinically meaningful difference. Secondary: Both ACR 50 and ACR 70 were obtained at a significantly greater rate with anakinra as opposed to placebo (18 vs 7%; RR, 2.52; 95% CI, 1.56 to 4.03 and 7 vs 2%; RR, 3.71; 95% CI, 1.44 to 9.57, respectively). Anakinra was also associated with significant improvements in HAQ, visual analog score,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Larsen radiographic scores and change in ESR compared to placebo. The number of withdrawals, deaths, adverse events and infections were not significantly different between active treatment and placebo. However, injection site reaction was significantly more prevalent in the anakinra group vs the placebo group (71 vs 28%).
Blumenauer et al[92] Etanercept 10 mg or 25 mg twice weekly alone or in combination with MTX vs MTX or placebo	SR RCTs of patients ≥16 years of age meeting the ACR 1987 revised criteria for RA with evidence of active disease as demonstrated by ≥2 of the following: tender joint count, swollen joint count, duration of early morning stiffness >30 minutes, acute phase reactants such as Westergren ESR or CRP	N=949 (3 trials) ≥6 months	Primary: ACR 20, ACR 50, ACR 70 responses, erosion scores Secondary: Safety	Primary: At six months, 64% of individuals on etanercept 25 mg attained an ACR 20 response vs 15% of patients on control with either MTX alone or placebo (RR, 3.8; 95% CI, 2.5 to 6.0; NNT, 2). ACR 50 was achieved by 39% in the etanercept group compared to 4% in the control group (RR, 8.89; 95% CI, 3.61 to 21.89; NNT, 3). An ACR 70 response was reported in 15 and 1% of etanercept and control patients, respectively (RR, 11.31; 95% CI, 2.19 to 58.30; NNT, 7). Etanercept 10 mg was only associated with significant ACR 20 (51 vs 11% of controls; RR, 4.6; 95% CI, 2.4 to 8.8; NNT, 3) and ACR 50 responses (24 vs 5% of controls; RR, 4.74; 95% CI, 1.68 to 13.36; NNT, 5). Seventy-two percent of patients receiving etanercept had no increase in Sharp erosion score vs 60% of MTX patients. The Sharp erosion scores and JSN were not significantly reduced by either etanercept dose, however etanercept 25 mg was associated with a significantly reduced total Sharp score (WMD, -10.50; 95% CI, -13.33 to -7.67). Secondary: Injection site reactions were reported in 34% of patients on etanercept 10 mg compared to 9% of controls (RR, 3.86; 95% CI, 2.59 to 5.77; NNH, 4) and 41% of patients receiving etanercept 25 mg vs 9% of controls (RR, 4.77; 95% CI, 3.26 to 6.97; NNH, 3.1). The number of withdrawals was reported less frequently in the etanercept 25 mg group (4%) compared to the control group (8%; RR, 0.50; 95% CI, 0.27 to 0.94) and no difference was found between the etanercept 10 mg group and control in the rate of discontinuation.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
van Vollenhoven et al[93] (SWEFOT) Infliximab 3 mg/kg at weeks zero, two and six then every eight weeks plus MTX 20 mg weekly (Group B) vs MTX 20 mg weekly plus sulfasalazine 1,000 mg twice-daily plus hydroxychloroquine 400 mg daily (Group A)	MC, OL, PG, RCT Patients ≥18 years of age with RA (ACR) criteria, no previous DMARD treatment, no oral glucocorticoid treatment or stable glucocorticoid treatment for ≥4 weeks of at most 10 mg daily prednisolone (or equivalent), a DAS28 >3.2	N=487 24 months	Primary: Proportion of patients achieving a EULAR-define good response (a decrease of DAS28 by ≥1.2 and a resulting DAS28 ≤3.2 or less Secondary: EULAR and ACR responses at months 18 and 24, radiological outcomes at months 24	Primary: At month 18, there was no statistically significant difference in the proportion of patients achieving an EULAR-defined good response for patients treated with infliximab compared to conventional therapy (38 vs 29%, respectively; 95% CI, 0.93 to 1.85). Furthermore there was no statistically significant difference between the treatment groups at 24 months (38 vs 31%, respectively; *P*=0.204). Secondary: At 18 months, no statistically significant differences were reported between infliximab and conventional therapy with regard to ACR 20 (45 vs 34%, respectively; 95% CI, 0.99 to 1.82) ACR 70 (17 vs 11%, respectively; 95% CI, 0.86 to 2.98) or EULAR good or moderate response (58 vs 47%, respectively; 95% CI, 0.97 to 1.56). There was, however, a statistically significant difference favoring infliximab with regard to ACR 50 (30 vs 19%, respectively; 95% CI, 1.02 to 2.46). At 24 months there was no statistically significant difference between infliximab and conventional therapy with regard to ACR 20 response (40 vs 33%, respectively; *P*=0.259), ACR 50 (30 vs 22%; *P*=0.134), ACR 70 (16 vs 14%; *P*=0.566) or EULAR good to moderate response (59 vs 50%; *P*=0.166). Radiological outcomes were not statistically significant between infliximab and conventional therapy at 24 months with regard to total score (*P*=0.118), erosion score (*P*=0.0730) or joint-space narrowing score (*P*=0.054).
Wiens et al[94] Infliximab 3 mg/kg at weeks 0, 2 and 6 then every 8 weeks plus MTX vs placebo plus MTX	MA RCTs of adult patients with RA	N=2,129 (7 trials) ≥14 weeks	Primary: ACR 20, ACR 50, ACR 70 response Secondary: Safety and discontinuation of therapy	Primary: Through 30 weeks, the proportion of patients achieving an ACR 20 was 59% in the infliximab group compared to the control group (RR, 1.87; 95% CI, 1.43 to 2.45). An ACR 50 was achieved in 33% of infliximab treated patients and 12% of controls (RR, 2.68; 95% CI, 1.79 to 3.99). The RR of achieving an ACR 70 was 2.68 (95% CI, 1.78 to 4.03) with 17 and 5% of infliximab and control groups achieving an ACR 70, respectively. After ≥1 year of treatment, 62% of patients in the infliximab group and 26% of controls achieved an ACR 20 (RR, 2.33; 95% CI, 1.90 to 2.87). An ACR

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				50 was achieved in 43% of the infliximab treated patients and 27% of controls (RR, 1.61; 95% CI, 1.14 to 2.27). The RR for reaching ACR 70 was 1.69 (95% CI, 0.87 to 3.28), and 29% of patients in the infliximab group compared to 17% of patients in the control group achieved an ACR 70. Secondary: There were no statistically significant differences in serious adverse events. There was a higher number of patients that withdrew due to adverse events in the infliximab group compared to the placebo group (7 vs 3%; RR, 2.05, 95% CI, 1.33 to 3.16); however, fewer patients in the infliximab group withdrew due to lack of efficacy compared to the control group (4 vs 12%; RR, 0.41; 95% CI, 0.18 to 0.95).
Nixon et al[95] Adalimumab, anakinra, etanercept, or infliximab with or without MTX vs MTX or placebo	MA RCTs of patients with a clinical diagnosis of RA	N=6,694 (13 trials) ≥6 months	Primary: ACR 20 response and ACR 50 response Secondary: Not reported	Primary: The OR for an ACR 20 response was 3.19 (95% CI, 1.97 to 5.48) with adalimumab, 1.70 (95% CI, 0.90 to 3.29) with anakinra, 3.58 (95% CI, 2.09 to 6.91) with etanercept and 3.47 (95% CI, 1.66 to 7.14) with infliximab, all compared to placebo. The OR to achieve an ACR 50 response with adalimumab was 3.97 (95% CI, 2.73 to 6.07), 2.13 (95% CI, 1.27 to 4.22) with anakinra, 4.21 (95% CI, 2.74 to 7.43) with etanercept and 4.14 (95% CI, 2.42 to 7.46) with infliximab, all compared to placebo. The addition of MTX to any of the agents was found to enhance the efficacy of each treatment. The TNF blockers in combination with MTX were associated with higher ACR 20 and ACR 50 responses than anakinra and MTX (OR, 6.35 vs 3.20 and OR, 8.53 vs 4.56, respectively). Further analysis of each agent against another was performed and no significant difference was determined between individual agents in obtaining an ACR 20 and ACR 50 response (adalimumab vs anakinra; OR, 1.88; 95% CI, 0.83 to 4.49 and OR, 1.84; 95% CI, 0.84 to 3.70; adalimumab vs etanercept; OR, 0.89; 95% CI, 0.42 to 1.79 and OR, 0.94; 95% CI, 0.50 to 1.62; adalimumab vs infliximab; OR, 0.92; 95% CI, 0.39 to 2.37 and OR, 0.96; 95% CI, 0.48 to 1.90; etanercept vs anakinra; OR, 2.11; 95% CI, 0.90 to 5.68 and OR, 1.94; 95% CI, 0.87 to 4.36; infliximab vs

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				anakinra; OR, 2.05; 95% CI, 0.74 to 5.50 and OR, 1.93; 95% CI, 0.79 to 4.29; and infliximab vs etanercept; OR, 0.97; 95% CI, 0.34 to 2.33 and OR, 0.98; 95% CI, 0.45 to 1.93. However, the TNF blockers as a class showed a greater ACR 20 and ACR 50 response compared to anakinra (OR, 1.96; 95% CI, 1.03 to 4.01 and OR, 1.93; 95% CI, 1.05 to 3.50; *P*<0.05). Secondary: Not reported
Gabay et al[96] (ADACTA) Tocilizumab 8 mg/kg vs adalimumab 40 mg every 2 weeks	DB, PG, RCT Patients ≥18 years of age with RA > 6 months, intolerant to methotrexate or were inappropriate for continued methotrexate treatment	N=326 24 weeks	Primary: DAS 28 improvement Secondary: Percentage of patients with: a remission response (DAS28< 2.6); low disease activity (DAS28 ≤ 3.2); improvements of at least 20%, 50%, or 70% in ACR Score (ACR20/50/70); and with a EULAR good Response; and a EULAR good or moderate response.	Primary: The change from baseline in DAS28 was significantly greater in the tocilizumab group (—3·3) than in the adalimumab group (−1·8) patients (difference −1·5, 95% CI −1·8 to −1·1; *P*<0·0001). Secondary: DAS 28 remission rates at week 24 were achieved in 39.9% with tocilizumab and 10.5% in the adalimumab group (difference −1·5, 95% CI −1·8 to −1·1; *P*<0·0001). Percentage of patients with low disease activity (DAS 28≤ 3.2) at 24 weeks were achieved in 51.5% with tocilizumab and 19.8% in the adalimumab group (difference −1·5, 95% CI −1·8 to −1·1; *P*<0·0001). Percentage of patients on tocilizumab vs adalimumab with improvements of at least 20% in ACR score was 65.0% vs 49.4% respectively, a 50% improvement was seen in 47.2% vs 27.8% respectively and a 70% improvement was observed in 32.5% vs 17.9% respectively. Percentage of patients on tocilizumab vs adalimumab with a EULAR good response was 51.5% vs 19.8% respectively and percentage with a EULAR good or moderate was response 77.9% vs 54.9% respectively.
Weinblatt et al[97] 25 mg SC abatacept weekly	MC, RCT Patients 18 years of age, had a	N=646 12 months	Primary: Noninferiority, assessed according to	Primary: ACR 20 response was achieved in 86.2% of abatacept compared to controls at 82% with adalimumab (difference 1.8%; 95% CI −5.6% to 9.2%).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs 40 mg SC adalimumab biweekly	confirmed diagnosis of RA for ≤5 years, had an inadequate response to MTX, and had not received previous biologic therapy.		improvement in ACR20 at 1 year Secondary: Improvements in ACR 50, ACR 70, DAS 28, remission response (DAS28< 2.6); low disease activity (DAS28 ≤ 3.2); and HAQ DI.	Secondary: ACR 50 response were comparable and was achieved in 46.2% of abatacept compared to controls at 46% with adalimumab (95% CI not reported). ACR 70 response were comparable and was achieved in 29.2% of abatacept compared to controls at 26% with adalimumab (95% CI not reported). Improvement in DAS 28 was comparable with improvement of −2.30 in the abatacept group and −2.27 adalimumab group. Comparable proportion of patients achieved remission (DAS28< 2.6) between the 2 treatment groups with 43.3% the abatacept group vs 41.9% adalimumab group. In addition, comparable proportion of patients achieved low disease activity (DAS28≤ 3.2) between the 2 treatment groups with 59.3% abatacept patients and 61.4% adalimumab group. Improvements in the HAQ DI score were comparable between treatment groups, improving to 60.4% and 57.0% in the abatacept and adalimumab group respectively.
Ulcerative Colitis				
Rutgeerts et al[92] (ACT 1 and ACT 2) Infliximab 5 to 10 mg/kg at weeks 0, 2, 6 and then every 8 weeks vs placebo	DB, MC, PC, RCT Adult patients with endoscopy confirmed active ulcerative colitis (Mayo score 6 to 12) and moderate to severe active disease on sigmoidoscopy despite concurrent treatment with corticosteroids alone or in combination	N=364 (ACT 1) N=364 (ACT 2) 30 weeks (ACT 2) 54 weeks (ACT1)	Primary: Clinical response at week eight Secondary: Clinical response or clinical remission with discontinuation of corticosteroids at week 30 (ACT 1 and ACT 2) and week 54 (ACT 1), clinical remission and mucosal	Primary: At week eight in ACT 1, the proportion of patients with clinical response was significantly higher in the infliximab 5 and 10 mg/kg groups (69.4 and 61.5%) compared to the placebo group (37.2%; *P*<0.001 for both). In ACT 2 at week eight, the proportion of patients with clinical response was significantly higher in the infliximab 5 and 10 mg/kg groups (64.5 and 69.2%) compared to the placebo group (29.3%; *P*<0.001 for both). Secondary: In ACT 1, the proportion of patients with clinical response at week 30 was significantly higher in the infliximab 5 and 10 mg/kg groups (52.1 and 50.8%) compared to the placebo group (29.8%; *P*<0.001 and *P*=0.002, respectively). In ACT 2 at week 30, the proportion of patients with clinical response was significantly higher in the infliximab 5 and 10 mg/kg groups (47.1 and 60.0%) compared to the placebo group (26.0%; *P*<0.001 for

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	with azathioprine or mercaptopurine (ACT 1) or despite concurrent treatment with corticosteroids alone or mercaptopurine and medications containing 5-aminosalicylates (ACT 2)		healing at weeks eight and 30 (ACT 1 and ACT 2) and week 54 (ACT 1), and clinical response at week eight in patients with a history of corticosteroid refractory disease	both). In ACT 1 at week 54, the clinical response rate was significantly higher in the infliximab 5 and 10 mg/kg groups compared to the placebo group (45.5 and 44.3 vs 19.8%; *P*<0.001 for both). In ACT 1, the proportion of patients with clinical remission at week eight was significantly higher in the infliximab 5 and 10 mg/kg groups (38.8 and 32.0%) compared to the placebo group (14.9%; *P*<0.001 and *P*=0.002, respectively). In ACT 2 at week eight, the proportion of patients with clinical remission was significantly higher in the infliximab 5 and 10 mg/kg groups (33.9 and 27.5%) compared to the placebo group (5.7%; *P*<0.001 for both). In ACT 1, the proportion of patients with clinical remission at week 30 was significantly higher in the infliximab 5 and 10 mg/kg groups (33.9 and 36.9%) compared to the placebo group (15.7%; *P*=0.001 and *P*<0.001, respectively). In ACT 2 at week 30, the proportion of patients with clinical remission was significantly higher in the infliximab 5 and 10 mg/kg groups (25.6 and 35.8%) compared to the placebo group (10.6%; *P*=0.003 and *P*<0.001, respectively). In ACT 1 at week 54, the clinical remission rate was significantly higher in the infliximab 5 and 10 mg/kg groups compared to the placebo group (34.7 and 34.4 vs 16.5%; *P*=0.001 for both). In ACT 1 at week eight, the proportion of patients refractory to corticosteroids that had a clinical response was significantly higher in the infliximab 5 and 10 mg/kg groups compared to the placebo group (77.4 and 67.7 vs 35.3%; *P*<0.001 and *P*=0.010, respectively). In ACT 2 at week eight when compared to the placebo group (37.5%), the proportion of patients refractory to corticosteroids that had a clinical response was significantly higher in the infliximab 10 mg/kg (65.5%; *P*=0.011), but not 5 mg/kg group (63.3%; *P*=0.053). In ACT 1, the proportion of patients with mucosal healing at week eight was significantly higher in the infliximab 5 and 10 mg/kg groups (62.0 and 59.0%) compared to the placebo group (33.9%; *P*<0.001 for both). In ACT 2 at week eight, the proportion of patients with mucosal healing was significantly higher in the infliximab 5 and 10 mg/kg groups (60.3 and 61.7%) compared to the placebo group (30.9%; *P*<0.001 for both). In ACT 1, the proportion of patients with mucosal healing at week 30 was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				significantly higher in the infliximab 5 and 10 mg/kg groups (50.4 and 49.2%) compared to the placebo group (24.8; *P*<0.001 for both). In ACT 2 at week 30, the proportion of patients with mucosal healing was significantly higher in the infliximab 5 and 10 mg/kg groups (46.3 and 56.7%) compared to the placebo group (30.1%; *P*=0.009 and *P*<0.001, respectively). In ACT 1 at week 54, the mucosal healing rate was significantly higher in the infliximab 5 and 10 mg/kg groups compared to the placebo group (45.5 and 46.7 vs 18.2%; *P*=0.001 for both).
Hyams et al[99] (abstract) Infliximab 5 mg/kg at weeks 0, 2 and 6 then 5 mg/kg every 8 weeks through week 46 vs infliximab 5 mg/kg at weeks 0, 2 and 6 then 5 mg/kg every 12 weeks through week 42	MC, OL, Randomized Patients 6 to 17 years of age with active ulcerative colitis (Mayo score 6 to 12, including endoscopic subscore ≥2) who failed to respond to or tolerate treatment with mercaptopurine, azathioprine, corticosteroids, and/or 5-aminosalicylates	N=60 54 weeks	Primary: Clinical response at week eight (decrease from baseline in Mayo score ≥30% and ≥3 points, with a decrease in rectal bleeding subscore of 0/1) compared to baseline Secondary: Not reported	Primary: At week eight, 73.3% of patients had a clinical response with infliximab (95% CI, 62.1 to 84.5). Clinical remission by Mayo score was achieved in 33.3% of patients. At week 54, there was a greater proportion of patients achieving clinical remission with infliximab 5 mg/kg every eight weeks compared to infliximab 5 mg/kg every 12 weeks; though, this difference was not significant (*P*=0.146). Secondary: Not reported
Reinisch et al[94] Adalimumab 160 mg at week 0, 80 mg at week 2, 40 mg at weeks 4 and 6 (ADA 160/80 group) vs Adalimumab 80 mg at	DB, MC, PC, RCT Adult with moderate-severe active ulcerative colitis, (Mayo score of 6 to 12 with an endoscopy subscore of 2–3) who failed concurrent and	N=390 8 weeks	Primary: Proportion of patients in remission (Mayo score ≤2 and no subscore >1) compared to baseline Secondary:	Primary: At week eight, 18.5% of patients in the ADA 160/80 group (*P*=0.031 vs placebo) and 10.0% in the ADA 80/40 group (*P*=0.833 vs placebo) were in remission compared to placebo (9.2%). Secondary: At week eight, 54.6% of patients in the ADA 160/80 group (*P* vs placebo not reported), 51.5% in the ADA 80/40 group (*P* vs placebo not reported) and 44.6% in the placebo group had a clinical response.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
week 0, 40 mg at weeks 2, 4 and 6 (ADA 80/40 group) vs placebo	stable treatment with oral corticosteroids and/or immunomodulators		Proportion of patients with a clinical response (decrease in Mayo Score ≥3 points and ≥30% from baseline plus decrease in rectal bleeding subscore ≥1 or an absolute rectal bleeding subscore of 0 or 1); proportion of patients with mucosal healing (endoscopy subscore of 0 or 1); proportion of patients with rectal bleeding subscore ≤1, PGA subscore ≤1, or stool frequency subscore ≤1	At week eight, 46.9% of patients in the ADA 160/80 group (*P* vs placebo not reported), 37.7% in the ADA 80/40 group (*P* vs placebo not reported) and 41.5% in the placebo group had mucosal healing. At week eight, 77.7% of patients in the ADA 160/80 group (*P*=0.038 vs placebo), 70.0% in the ADA 80/40 group (*P* vs placebo not reported) and 66.2% in the placebo group had a rectal bleeding subscore of ≤ 1. At week eight, 60.0% of patients in the ADA 160/80 group (*P*=0.035 vs placebo), 53.8% in the ADA 80/40 group (*P* vs placebo not reported) and 46.9% in the placebo group had a PGA subscore of ≤ 1 At week eight, 48.5% of patients in the ADA 160/80 group (*P* vs placebo not reported), 36.2% in the ADA 80/40 group (*P* vs placebo not reported) and 37.7% in the placebo group had a stool frequency subscore of ≤ 1
Sandborn et al[101] Adalimumab 160 mg at week 0, 80 mg at week 2, then 40 mg every other week vs placebo	DB, MC, PC, RCT Adult with moderate-severe active ulcerative colitis > 3months, (Mayo score of 6 to 12 with an endoscopy subscore > 2) despite concurrent	N=494 52 weeks	Primary: Proportion of patients in remission (Mayo score ≤2 and no subscore >1) at week 8 and 52 Secondary: Proportion of	Primary: At week 8, 16.5% of patients in the adalimumab group were in remission compared to placebo (9.3%; *P*=0.019; 95% CI: 1.2−12.9). At week 52, 17.3% of patients in the adalimumab group were in remission compared to placebo (8.5%; *P*=0.004; 95% CI: 2.8−14.5). Secondary: At week 8 and 52, 8.5% of patients in the adalimumab group (*P*=0.47 vs

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	treatment with oral corticosteroids and/or azathioprine or 6-mercaptopurine.		patients in remission at week 8 and 52; proportion of patients with a clinical response (decrease in Mayo Score ≥3 points and ≥30% from baseline plus decrease in rectal bleeding subscore ≥1 or an absolute rectal bleeding subscore of 0 or 1); proportion of patients with mucosal healing (endoscopy subscore of 0 or 1); proportion of patients who discontinued corticosteroid; proportion of patients with rectal bleeding subscore ≤1, PGA subscore ≤1, or stool frequency subscore ≤1	placebo) and 4.1% in the placebo group were in sustained remission. At week 8, 50.4% of patients in the adalimumab group (*P*<0.001 vs placebo) and 34.6% in the placebo group had a clinical response. At week 52, 30.2% of patients in the adalimumab group and 18.3% in the placebo group had a clinical response. (*P*=0.002). At week 8 and 52, 23.8% of patients in the adalimumab group (*P*<0.001 vs placebo) and 12.2% in the placebo group were in sustained remission. Mucosal healing was achieved at week 8 in 41.1% of patients in the adalimumab group and 31.7% of patients receiving placebo (*P*=0.032). At week 52, 25% of patients in the adalimumab group and 15.4% of patients receiving placebo (*P*=0.009) had mucosal healing. Mucosal healing at week 8 and 52, 18.5% of patients in the adalimumab group (*P*<0.013 vs placebo) and 10.6% in the placebo group. At week 8, 46.0% of patients in the adalimumab group (*P*=0.028 vs placebo) and 37.4% in the placebo group had a PGA subscore of ≤ 1. At week 8, 37.9% of patients in the adalimumab group (*P*=0.058 vs placebo) and 28.5% in the placebo group had a stool frequency subscore of ≤ 1. At week 8, 70.2% of patients in the adalimumab group (*P*=0.006 vs placebo) and 58.1% in the placebo group had a rectal bleeding subscore of ≤ 1. Proportion of patients that discontinued corticosteroid use before week 52 and achieved remission at week 52 was13.3% of patients in the adalimumab group (*P*=0.35 vs placebo) and 5.7% in the placebo group. Proportion of patients that for ≥90 days before week 52 and achieved remission at week 52 was 13.3% of patients in the adalimumab group (*P*=0.35 vs placebo) and 5.7% in the placebo group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Neonatal-Onset Multisystem Inflammatory Disease				
Sibley et al[102] Anakinra 1 to 5 mg/kg/day	OL Patients with NOMID with at least 2 of the following clinical manifestations: urticaria-like rash, CNS involvement (papilledema, cerebrospinal fluid CSF pleocytosis, or sensorineural hearing loss), or epiphyseal and/or patellar overgrowth on radiographs	N=43 60 months	Primary: Sustained improvements in diary scores, parent's/patient's and physician's global scores of disease activity, CHAQ scores, parent's/patient's pain scores, and inflammatory markers (CRP level, ESR, and SAA) Secondary: Reduction or elimination CNS organ inflammation and damage and the absence of leptomeningeal enhancement on MRI, and in the eyes as the absence of eye inflammation on examination. Other endpoints include improvements in hearing, vision, bone lesions and	Primary: Scores for daily diaries, parent's and physician's global assessment of disease activity, parent's assessment of pain, and C-HAQ decreased significantly from baseline to 36 months (P=0.0016 for C-HAQ and P<0.001 for all other assessments). These parameters did not show significant change from month 36 to month 60. Significant decreases in inflammatory markers (CRP level, ESR, and SAA) were observed from baseline to 12 months and from baseline to 36 months (all P<0.001). These parameters did not show significant change from month 36 to month 60. Secondary: CNS inflammation, including CSF leukocyte count and elevated opening pressure, decreased significantly at the study end points 36 and 60 months compared to baseline (P=0.0026 and P=0.0076, respectively, for CSF WBC count and P=0.0012 and P< 0.001, respectively, for opening pressure). These parameters did not show significant change from month 36 to month 60. The number of patients with leptomeningeal enhancement decreased to three of 26 patients at 36 months (P=0.039) and one of 20 patients at 60 months (P=0.016). Improvement in hearing occurred in 30% of ears, and progression of hearing loss was halted in the majority of the patients. Visual acuity and peripheral vision improved or stabilized in most patients over five years. One patient had worsening of visual acuity, and two other patients had worsening of peripheral vision in the absence of clinically detectable intraocular inflammation. (Note-All three of these patients had severely atrophic nerves at baseline). Bony overgrowth was present in 10 of 26 patients, and during the study period the volume of the bony lesions increased significantly; however, no

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			growth, and safety.	new bone lesions developed in patients while they were receiving anakinra therapy. No dose-limiting toxicity was observed during the study. Upper respiratory infections (58 to 62%), rash (27 to 32%), malaise (17 to 19%) gastroenteritis (11 to 12%), and urinary tract infections (4 to 12%), nausea/vomiting (10 to 11%) injection site reactions (1 to 10%) were frequently observed.

* Not currently available in the United States.
Study abbreviations: CI=confidence interval, DB=double-blind, DD=double dummy, ES=extension study, HR=hazard ratio, MA=meta-analysis, MC=multicenter, NNH=number needed to harm, NNT=number needed to treat, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel group, RCT=randomized controlled trial, RD=risk difference, RR=relative risk, SD=standard deviation, SR=systematic review, WMD=weighted mean difference
Miscellaneous abbreviations: ACR=American College of Rheumatology, ACR-N=numeric index of the ACR response, ACR pedi 30=American College of Rheumatology pediatric 30% improvement criteria, ALT=Alanine transaminase, AS=ankylosing spondylitis, ASAS=Assessment of Spondyloarthritis International Society criteria; BSA=body surface area, BASDAI=Bath Ankylosing Spondylitis Disease Activity Index, BASFI=Bath Ankylosing Spondylitis Functional Index, BASMI=Bath Ankylosing Spondylitis Metrology Index, BSA=body surface area, CCP=cyclic citrullinated protein CD=Crohn's disease, CDAI=Crohn's disease activity index, CHAQ=Childhood Health Assessment Questionnaire, CNS=central nervous system, COX=cyclooxygenase, CR-70=complete response, CR-100=complete response 100, CRP=C-reactive protein, CSF=cerebrospinal fluid, DAS 28=Disease Activity Score in 28 joints, DMARD=disease-modifying antirheumatic drug, DOI=definition of improvement, ECL= electrogenerated chemiluminescence, EIM=extra-intestinal manifestations, ELISA=enzyme-linked immunosorbent assay, ESR=erythrocyte sedimentation rate, EULAR=European League Against Rheumatism Response criteria, FACIT-F=Functional Assessment of Chronic Illness Therapy-Fatigue, HAQ=health assessment questionnaire, HAQ-DI=health assessment questionnaire–disability index, HBI= Harvey-Bradshaw index, HCQ=hydroxychloroquine, IBDQ=inflammatory bowel disease questionnaire, IOIBD=international organization for the study of inflammatory bowel disease, ITT=intent to treat, JRA=juvenile rheumatoid arthritis, JSN=joint space narrowing, mTSS=modified Total Sharp Scores, MTX=methotrexate, NOMID=neonatal-onset multisystem inflammatory disease, NSAIDs=nonsteroidal anti-inflammatory drugs, PASI=psoriasis area and severity index, PCDAI=pediatric Crohn's disease activity index, PGA=physician global assessment, PsA=psoriatic arthritis, PsARC=psoriatic arthritis response criteria, PSSI=psoriasis scalp severity index, RA=rheumatic arthritis, RF=rheumatoid factor, SF-36=short form-36, SF-36 MCS=short form-36-mental component, SF-36 PCS=short form-36-physical component, SAA= Serum amyloid A, SSZ=sulfasalazine, TB=tuberculosis, TNF=tumor necrosis factor, VAS=visual analog scale

Special Populations

Table 5. Special Populations[3-8,10-12]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Abatacept	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. The frequency of serious infection and malignancy was higher in patients ≥65 years of age. Approved for use in children ≥6 years of age for the treatment of juvenile rheumatoid arthritis. Safety and efficacy in the pediatric population not been established for other indications.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Unknown
Adalimumab	No evidence of overall differences in efficacy observed between elderly and younger adult patients. The frequency of serious infection and malignancy was higher in patients ≥65 years of age. Approved for use in children ≥4 years of age for the treatment of juvenile rheumatoid arthritis. Safety and efficacy in the pediatric population have not been established for other indications.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	B	Unknown
Anakinra	No evidence of overall differences in efficacy observed between elderly and younger adult patients. Approved for use in	Renal dose adjustment is required; for creatinine clearances <30 mL/ minute, a	Not studied in hepatic dysfunction.	B	Unknown

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	children for the treatment of neonatal onset multisystem inflammatory disease. Safety and efficacy in the pediatric population have not been established for other indications.	dose of 100 mg for rheumatoid arthritis or 1 to 2 mg/kg for neonatal onset multisystem inflammatory disease every other day is recommend-ed.			
Certolizumab	Safety and efficacy in elderly patients have not been established. Safety and efficacy in the pediatric population have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	B	Unknown
Etanercept	No evidence of overall differences in efficacy observed between elderly and younger adult patients. Approved for use in children ≥2 years of age for the treatment of juvenile rheumatoid arthritis. Safety and efficacy in the pediatric population have not been established for other indications.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	B	Unknown
Golimumab	No evidence of overall differences in efficacy observed between elderly and younger adult patients. Safety and efficacy in the pediatric population have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	B	Unknown
Infliximab	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients for the treatment of	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	B	Unknown

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	rheumatoid arthritis and psoriasis. Safety and efficacy in elderly patients have not been established for the treatment of ankylosing spondylitis, Crohn's disease, psoriatic arthritis or ulcerative colitis. Approved for use in children ≥6 years of age for the treatment of Crohn's disease and ulcerative colitis. Safety and efficacy in the pediatric population have not been established for other indications.				
Tocilizumab	Frequency of serious infection and malignancy was higher in patients ≥65 years of age. Approved for use in children ≥2 years of age for the treatment of juvenile rheumatoid arthritis. Safety and efficacy in the pediatric population have not been established for other indications.	No dosage adjustment required in mild renal impairment. Not studied in patients with moderate to severe renal dysfunction.	Not studied in hepatic dysfunction.	C	Unknown
Ustekinumab	Safety and efficacy in elderly patients have not been established. Safety and efficacy in the pediatric population have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	B	Unknown

Adverse Drug Events

The anti tumor necrosis factor-α agents (adalimumab, certolizumab, etanercept, golimumab and infliximab) share similar adverse event profiles including risk of reactivation of latent tuberculosis, severe infection, heart failure, lupus-like syndrome, and lymphoma. Table 6 highlights the adverse drug events with a focus on those noted in ≥5% of study populations.

Table 6. Adverse Drug Events (%)[3-8,10-12]

Adverse Event	Abatacept	Adalimumab	Anakinra†	Certolizumab	Etanercept	Golimumab*	Infliximab	Tocilizumab	Ustekinumab
Gastrointestinal									
Abdominal pain	-	7	5	-	5 to 10	-	12	-	-
Diarrhea	-	-	7	-	8 to 16	-	12	-	-
Dyspepsia	6	-	-	-	4 to 11	-	10	-	-
Nausea	≥10	9	8	-	9 to 15	-	21	-	-
Vomiting	-	-	14‡	-	3 to 5	-	-	-	-
Laboratory Tests									
Abnormal test	-	8	-	-	-	-	-	3 to 6	-
Alkaline phosphatase increased	-	5	-	-	-	-	-	-	-
Hematuria	-	5	-	-	-	-	-	-	-
Hypercholesterolemia	-	6	-	-	-	-	-	-	-
Hyperlipidemia	-	7	-	-	-	-	-	-	-
Respiratory									
Bronchitis	5 to 13	-	-	3	-	-	10	-	-
Coughing	8	-	-	-	5 to 6	-	12	-	-
Flu syndrome	-	7	-	-	-	-	14	-	-
Nasopharyngitis	12	-	-	5	-	-	-	4 to 7	7 to 8
Non-upper respiratory infection	-	-	-	-	21 to 54	-	-	-	-
Pharyngitis	-	-	11.6‡	3	6 to 7	6	-	-	-
Respiratory disorder	-	-	-	-	5	-	-	-	-
Rhinitis	-	-	-	-	12 to 16	-	-	-	-
Sinusitis	5 to 13	11	7	-	3 to 5	-	14	-	-
Upper respiratory infection	≥10	17	14	6	38 to 65	7	32	6 to 8	4 to 5
Skin									
Pruritus	-	-	-	-	-	-	7	-	-
Rash	-	12	-	3	3 to 13	-	10	-	-
Other									
Accidental injury	-	10	-	-	-	-	-	-	-

Adverse Event	Abatacept	Adalimumab	Anakinra†	Certolizumab	Etanercept	Golimumab*	Infliximab	Tocilizumab	Ustekinumab
Alopecia	-	-	-	-	1 to 6	-	-	-	-
Arthralgia	-	-	6, 11.6‡	-	-	-	-	-	-
Asthenia	-	-	-	-	5 to 11	-	-	-	-
Back pain	7	6	-	4	-	-	8	-	-
Body pain	-	-	-	-	-	-	8	-	-
Dizziness	9	-	-	-	7 to 8	-	-	-	-
Fatigue	-	-	-	3	-	-	9	-	-
Fever	-	-	11.6‡	3	2 to 3	-	7	-	-
Flu like symptoms	-	-	6	-	-	-	-	-	-
Headache	18	12	12, 14‡	5	17 to 24	-	18	5 to 7	5
Hypertension	7	5	-	5	-	-	7	4 to 6	-
Injection site pain	-	12	-	-	-	-	-	-	-
Injection site reaction	-	8	16‡, 71	-	37 to 43	-	-	-	-
Moniliasis	-	-	-	-	-	-	5	-	-
Mouth ulcer	-	-	-	-	2 to 6	-	-	-	-
Peripheral edema	-	-	-	-	2 to 8	-	-	-	-
Urinary tract infection	6	8	-	-	-	-	8	-	-
Worsening of rheumatoid arthritis	-	-	19	-	-	-	-	-	-

-Event not reported or incidence <5%.
*With or without disease modifying antirheumatic agents.
†Unless otherwise specified, adverse reaction observed in patients treated for rheumatoid arthritis.
‡ Neonatal-onset multisystem inflammatory disease during the first six months of therapy.

Contraindications/Precautions

The immunomodulators are contraindicated in patients with a known hypersensitivity to any of the agents or to any component of the individual products.[3-8,10-12] Patients treated concomitantly with abatacept or anakinra and anti-tumor necrosis factor (TNF) agents experienced more infections than patients treated with TNF agents alone. There was no significant increase in efficacy with combination therapy; therefore, concomitant administration of abatacept or anakinra and TNF agents is not recommended.[3-8,12]

Serious and sometimes fatal infections have been reported with abatacept. Live vaccines should not be given concurrently or within three months of discontinuation with abatacept. Patients with chronic pulmonary obstructive disease treated with abatacept developed adverse reactions associated with worsening of their respiratory symptoms. Due to the inhibition of T-cell activation by abatacept, host defenses against infections and malignancies may be affected.[12]

Anakinra is contraindicated in patients with a known hypersensitivity to *Escherichia coli*-derived proteins. Serious infections have been associated with anakinra and should not be initiated in patients with active infections. In RA, discontinue use if serious infection develops. In NOMID patients, the risk of a NOMID flare when discontinuing anakinra treatment should be weighed against the potential risk of continued treatment. Hypersensitivity reactions, including anaphylactic reactions and angioedema, have occurred with anakinra. Live vaccines are not recommended to be given concurrently with anakinra. Combination therapy with a TNF blocking agent is not recommended Decreases in neutrophil count have been reported with anakinra.[8]

Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including tocilizumab for rheumatoid arthritis. Additionally, viral reactivation, gastrointestinal perforations, and increased lipid levels were reported with tocilizumab. The impact of tocilizumab on demyelinating disorders is not known, although multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were rarely reported in clinical trials. Caution should be used when considering tocilizumab in patients with preexisting or recent onset demyelinating disorders. Treatment is not recommended in patients with an increased incidence of neutropenia, reduced platelets, increased transaminase levels, or in patients with active hepatic disease or hepatic impairment. Hypersensitivity reactions, including anaphylaxis reactions and death, have been reported with tocilizumab. Live vaccines are not recommended to be given concurrently with tocilizumab.[10]

Ustekinumab is associated with an increase risk of infections and reactivation of latent infections. In addition, hypersensitivity reactions, including anaphylaxis and angioedema, have been reported with ustekinumab. Ustekinumab may increase the risk of malignancies. Live vaccines are not recommended to be given concurrently with ustekinumab.[11]

Numerous precautions are associated with the TNF agents (adalimumab, certolizumab, etanercept, golimumab and infliximab), many of which are shared throughout the class and include:

- Infection, active or chronic (including localized), or history of recurrent infection; increased risk of developing a serious infection.
- Infections, serious (sepsis, tuberculosis, fungal, and other opportunistic infections); fatalities have been reported; discontinue if serious infection develops.
- Tuberculosis, history of latent or active; increased risk of developing infection; initiate treatment for latent tuberculosis before starting anti-TNF therapy.
- Tuberculosis, risk factors or potential exposure; infection should be ruled out prior to initiation of therapy.
- Central nervous system demyelinating disorder, preexisting or recent onset; risk for exacerbation.
- Close personal contact with person with active tuberculosis.
- Congestive heart failure; new-onset or worsening reported in patients with and without history.
- Hematologic abnormalities (e.g., pancytopenia, aplastic anemia) have been reported; discontinue if significant abnormalities develop.

- Hepatitis B virus carriers; risk of reactivation including after discontinuation of therapy, fatal outcomes have occurred; monitor for signs and symptoms of Hepatitis B virus infections during and for several months after adalimumab therapy and discontinue if Hepatitis B virus is reactivated.
- Live vaccine use; not recommended.
- Malignancy; increased risk of lymphoma and possibly other malignancies such as breast, colon, prostate, lung, and melanoma.
- Lupus-like syndrome may occur secondary to autoantibodies (adalimumab, certolizumab, and etanercept).[3-7]

Some of the immunomodulators are associated with boxed warnings, which are outlined below.

Black Box Warning for Adalimumab and Infliximab[7]

WARNING
Postmarketing cases of hepatosplenic T-cell lymphoma, a rare type of T-cell lymphoma, have been reported in patients treated with tumor necrosis factor blockers including Humira® and Remicade®. These cases have had a very aggressive disease course and have been fatal. All reported Remicade® cases have occurred in patients with Crohn's disease or ulcerative colitis and the majority was in adolescent and young adult males. All of these patients had received treatment with azathioprine or 6-mercaptopurine concomitantly with Humira® or Remicade® at or prior to diagnosis.

Black Box Warning for Tocilizumab[10]

WARNING
Serious Infections Patients treated with Actemra® are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. If a serious infection develops, interrupt Actemra® until the infection is controlled. Reported infections include: • Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before Actemra® use and during therapy. Treatment for latent infection should be initiated prior to Actemra® use. • Invasive fungal infections, including candidiasis, aspergillosis, and pneumocystis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease. • Bacterial, viral and other infections due to opportunistic pathogens. The risks and benefits of treatment with Actemra® should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with Actemra®, including the possible development of tuberculosis in patients who tested negative for infection prior to initiating therapy.

Black Box Warning for Adalimumab, Certolizumab, Etanercept, Golimumab, Infliximab[3-7,98]

WARNING
Serious Infection Patients treated with Cimzia®, Enbrel®, Humira®, Remicade® or Simponi® are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. Cimzia®, Enbrel®, Humira®, Remicade® and Simponi® should be discontinued if a patient develops a serious infection or sepsis. Reported infections include:

WARNING

- Active tuberculosis, including reactivation of latent tuberculosis. Patients with tuberculosis have frequently presented with disseminated or extrapulmonary disease. Patients should be tested for latent tuberculosis before Cimzia®, Enbrel®, Remicade®, or Simponi® use and during therapy. Treatment for latent infection should be initiated prior to Cimzia®, Enbrel®, Humira®, Remicade®, or Simponi® use.
- Invasive fungal infections, including histoplasmosis, coccidioidomycosis, candidiasis, aspergillosis, blastomycosis, and pneumocystosis. Patients with histoplasmosis or other invasive fungal infections may present with disseminated, rather than localized disease. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. Empiric anti-fungal therapy should be considered in patients at risk for invasive fungal infections who develop severe systemic illness.
- Bacterial, viral and other infections due to opportunistic pathogens, including Legionella and Listeria.

The risks and benefits of treatment with Cimzia®, Enbrel®, Humira®, Remicade®, or Simponi® should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.
Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with Cimzia®, Enbrel®, Humira®, Remicade® or Simponi®, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

Malignancy
Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with tumor necrosis factor blockers, of which Cimzia®, Enbrel®, Humira®, Remicade® or Simponi® are members.

Drug Interactions
Cytokines such as interleukin (IL)-6 have been shown to decrease the expression of CYP450 isoenzymes in patients with infections and inflammatory conditions such as rheumatoid arthritis. Inhibition of IL-6 signaling in rheumatoid arthritis patients treated with tocilizumab may restore CYP450 activities to normal levels which would have the potential to increase the metabolism of CYP450 substrates. In vitro studies showed that tocilizumab has the potential to affect expression of multiple CYP enzymes (1A2, 2B6, 2C9, 2C19, 2D6, and 3A4). Upon initiation or discontinuation of tocilizumab it is recommended that therapeutic monitoring for any medication with a narrow therapeutic index be initiated and the dose of the medication be adjusted as needed.[10]

Table 7. Drug Interactions[31]

Generic Name	Interacting Medication or Disease	Potential Result
Abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, tocilizumab, ustekinumab	Live vaccines	Concomitant use may result in an increased risk of secondary transmission of infection by the live vaccine.
Adalimumab, anakinra, etanercept, golimumab, infliximab	Abatacept	Concurrent use may increase the risk of infections.
Adalimumab, certolizumab, etanercept, golimumab, infliximab	Anakinra	Concurrent use may increase the risk of infections.
Adalimumab, etanercept, infliximab	Rilonacept	Concurrent use may increase the risk of serious infections and neutropenia.
Anakinra	Etanercept	Concurrent use may increase the risk of serious infections and neutropenia.
Etanercept	Cyclophosphamide	Concurrent administration may result in a higher incidence of developing

Generic Name	Interacting Medication or Disease	Potential Result
		noncutaneous solid malignancies.
Infliximab	Tocilizumab	Concurrent use may increase immunosuppression and the risk of infections.

Dosage and Administration

Table 8. Dosing and Administration[3-8,10-12]

Generic Name	Adult Dose	Pediatric Dose	Availability
Abatacept	Rheumatoid arthritis: Prefilled syringe and single use vial: initial (<60 kg), 500 mg IV over 30 minutes at weeks zero, two and four; (60 to 100 kg), 750 mg IV over 30 minutes at weeks zero, two and four; (>100 kg), 1,000 mg IV over 30 minutes at weeks zero, two and four; maintenance (<60 kg), 500 mg IV over 30 minutes every four weeks; (60 to 100 kg), 750 mg IV over 30 minutes every four weeks; (>100 kg), 1,000 mg IV over 30 minutes every four weeks or initial (<60 kg), 500 mg IV over 30 minutes followed by 125 mg SC within 24 hours; 750 mg IV over 30 minutes followed by 125 mg SC within 24 hours; (>100 kg), 1,000 mg IV over 30 minutes followed by 125 mg SC within 24 hours; maintenance 125 mg SC every four weeks	Juvenile idiopathic arthritis (six to 17 years of age): Prefilled syringe and single use vial: initial, (<75 kg),10 mg/kg IV over 30 minutes at weeks zero, two and four; (≥75 kg), follow adult dosing not to exceed 1,000 mg/dose; maintenance (<75 kg), 10 mg/kg IV over 30 minutes every four weeks; (≥75 kg), follow adult dosing not to exceed 1,000 mg/dose	Prefilled syringe: 125 mg/mL Single use vial: 250 mg
Adalimumab	Ankylosing spondylitis, psoriatic arthritis: Prefilled pen and syringe, single use vial: initial/maintenance, 40 mg SC every other week Crohn's disease: Prefilled pen and syringe, single use vial: initial, 160 mg SC at week zero (may administer as four injections in one day or two injections daily for two consecutive days), followed by 80 mg SC during week two (day 15); maintenance, 40 mg SC every other week starting at week four (day 29) Plaque psoriasis: Prefilled pen and syringe, single use vial: initial, 80 mg SC; maintenance, 40 mg SC every other week starting one week after the initial dose Rheumatoid arthritis: Prefilled pen and syringe, single use vial: initial/maintenance, 40 mg SC every other	Juvenile idiopathic arthritis (four to 17 years of age): 15 to <30 kg, 20 mg SC every other week; ≥30 kg, 40 mg SC every other week There is limited data in pediatric patients with a weight <15 kg.	Prefilled pen: 40 mg/0.8 mL Prefilled syringe: 20 mg/0.4 mL 40 mg/0.8 mL Single use vial: 40 mg/0.8 mL

Generic Name	Adult Dose	Pediatric Dose	Availability
	week; may increase to 40 mg SC every week in patients not receiving concomitant methotrexate Ulcerative colitis: Prefilled pen and syringe, single use vial: initial, 160 mg SC at week zero (may administer as four injections in one day or two injections daily for two consecutive days), followed by 80 mg SC during week two (day 15); maintenance, 40 mg SC every other week starting at week four (day 29)		
Anakinra	Rheumatoid arthritis: Prefilled syringe: initial/maintenance, 100 mg SC daily Neonatal-onset multisystem inflammatory disease: Prefilled syringe: initial: 1-2 mg/kg daily; maintenance, dose can be individually adjusted to a maximum of 8 mg/kg daily	Neonatal-onset multisystem inflammatory disease: Prefilled syringe: initial: 1-2 mg/kg daily; maintenance, maximum of 8 mg/kg daily	Prefilled syringe: 100 mg/0.67 mL
Certolizumab	Crohn's disease: Prefilled syringe and vial: initial, 400 mg SC (as two SC injections of 200 mg) once, repeat at weeks two and four; maintenance, 400 mg SC (as two SC injections of 200 mg) once every four weeks Rheumatoid arthritis: Prefilled syringe and vial: initial, 400 mg SC (as two SC injections of 200 mg) once and then repeat at weeks two and four; maintenance, 200 mg SC once every other week or 400 mg (as two SC injections of 200 mg) every four weeks	Safety and efficacy in the pediatric population have not been established.	Prefilled syringe: 200 mg/mL Vial (powder for injection): 200 mg
Etanercept	Ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis: Prefilled autoinjector and syringe and vial: initial/maintenance, 50 mg SC weekly Plaque psoriasis: Prefilled autoinjector and syringe and vial: initial, 50 mg SC twice weekly for three months; maintenance, 50 mg SC weekly	Juvenile idiopathic arthritis (two to 17 years of age): Prefilled autoinjector and syringe and vial: initial and maintenance (<63 kg), 0.8 mg/kg SC weekly; (≥63 kg), 50 mg SC weekly	Prefilled "SureClick" autoinjector: 50 mg/mL Prefilled syringes: 25 mg/0.5 mL 50 mg/mL Vial (powder for injection): 25 mg
Golimumab	Ankylosing spondylitis, psoriatic arthritis: Prefilled autoinjector and syringe: initial/maintenance, 50 mg SC once monthly	Safety and efficacy in the pediatric population have not been established.	Prefilled "SmartJect" autoinjector: 50 mg/0.5 mL

Generic Name	Adult Dose	Pediatric Dose	Availability
	Rheumatoid arthritis: Prefilled autoinjector and syringe: initial/maintenance, 50 mg SC once monthly in combination with methotrexate		Prefilled syringe: 50 mg/0.5 mL
Infliximab	Ankylosing Spondylitis: Vial: initial, 5 mg/kg IV over two hours at weeks zero, two, and six; maintenance, 5 mg/kg IV over two hours every six weeks Crohn's disease: Vial: initial, 5 mg/kg IV over two hours at weeks zero, two, and six; maintenance, 5 mg/kg IV over two hours every eight weeks; may be increased to 10 mg/kg in patients that respond then lose response Plaque psoriasis, psoriatic arthritis, ulcerative colitis : Vial: initial, 5 mg/kg IV over two hours at weeks zero, two, and six; maintenance, 5 mg/kg IV over two hours every eight weeks Rheumatoid arthritis: Vial: initial, 3 mg/kg IV over two hours at weeks zero, two, and six; maintenance, 3 mg/kg IV over two hours every eight weeks; may be increased to 10 mg/kg IV over two hours every eight weeks or 3 mg/kg IV over two hours every four weeks if incomplete response; all in combination with methotrexate	Crohn's disease, ulcerative colitis (≥6 years of age): Vial: initial, 5 mg/kg IV over two hours at weeks zero, two and six; maintenance, 5 mg/kg IV over two hours every eight weeks	Single use vial: 100 mg
Tocilizumab	Rheumatoid arthritis: Vial: initial/maintenance, 4 mg/kg IV every four weeks as a 60 minute infusion; dose may be increased to 8 mg/kg IV every four weeks; maximum, 800 mg/infusion	Juvenile idiopathic rheumatoid arthritis (≥2 years of age): Vial: initial/ maintenance (<30 kg), 12 mg/kg IV every two weeks as a 60 minute infusion; (≥30 kg) 8 mg/kg IV every two weeks as a 60 minute infusion	Single use vials: 80 mg/4 mL 200 mg/10 mL 400 mg/20 mL
Ustekinumab	Plaque psoriasis: Prefilled syringe and single use vial: initial (≤100 kg), 45 mg SC followed by 45 mg four weeks later; (>100 kg), 90 mg SC followed by 90 mg SC four weeks later; maintenance (≤100 kg), 45 mg SC every 12 weeks; (>100 kg), 90 mg SC every 12 weeks	Safety and efficacy in the pediatric population have not been established.	Prefilled syringe: 45 mg/0.5 mL 90 mg/mL Single use vials: 45 mg/0.5 mL 90 mg/mL

IV-intravenous, SC=subcutaneous

Clinical Guidelines

Table 9. Clinical Guidelines

Clinical Guideline	Recommendations
Assessment of Spondyloarthritis International Society/European League Against Rheumatism: **2010 Update of the Assessment of Spondyloarthritis International Society/European League Against Rheumatism Recommendations for the Management of Ankylosing Spondylitis (2010)**[13]	• Treatment of ankylosing spondylitis (AS) should be tailored according to: o Current manifestations of the disease (axial, peripheral, entheseal, extra-articular symptoms and signs). o Level of current symptoms, clinical findings, and prognostic indicators (disease activity/inflammation, pain, function [disability, handicap], structural damage [hip involvement, spinal deformities]. o General clinical status (age, sex, comorbidity, concomitant drugs). o Wishes and expectations of the patient. • Disease monitoring of patients with AS should include: patient history, clinical parameters, laboratory tests, and imaging, all according to the clinical presentation, as well as the Assessment of Spondyloarthritis International Society core set. The frequency of monitoring should be decided on an individual basis depending on symptoms, severity, and drug treatment. • Optimal management of AS requires a combination of non-pharmacological and pharmacological treatments. • Non-pharmacological treatment of AS should include patient education and regular exercise. Physical therapy with supervised exercises, individually or in a group preferred. Patient associations and self help groups may be useful. • Nonsteroidal anti-inflammatory drugs (NSAIDs), including selective cyclooxygenase (COX)-2 inhibitors, are recommended as first line drug treatment for patients with AS with pain and stiffness. Continuous treatment with an NSAID is preferred for patients with persistently active, symptomatic disease. Cardiovascular, gastrointestinal and renal risks should be taken into account. • Analgesics, such as opioids and paracetamol, might be considered for pain control in patients in whom NSAIDs are insufficient, contraindicated, and/or poorly tolerated. • Corticosteroid injections directed to the local site of musculoskeletal inflammation may be considered. The use of systemic corticosteroids for axial disease is not supported by evidence. • There is no evidence for the efficacy of disease modifying antirheumatic drugs (DMARDs), including methotrexate and sulfasalazine, for the treatment of axial disease. Sulfasalazine may be considered in patients with peripheral arthritis. • Anti-tumor necrosis factor α (TNF-α inhibitor) treatment should be given to patients with persistently high disease activity despite conventional treatments according to the Assessment of Spondyloarthritis International Society recommendations. There is no evidence to support the obligatory use of DMARDs before, or concomitant with, TNF-α inhibitor treatment in patients with axial disease. There is no evidence to support a different efficacy of the various TNF-α inhibitors on the axial and articular/entheseal disease manifestations; but in the presence of inflammatory bowel disease a difference in gastrointestinal efficacy needs to be taken into consideration. Switching to a second TNF-α inhibitor might be

Clinical Guideline	Recommendations
	beneficial, especially in patients that have lost response. There is no evidence to support biologic agents other than TNF-α inhibitor in AS. • Total hip arthroplasty should be considered in patients with refractory pain or disability and radiographic evidence of structural damage, independent of age. Spinal corrective osteotomy may be considered in patients with severe disabling deformity. A spinal surgeon should be consulted in patients with AS and an acute vertebral fracture.
Assessment of Spondyloarthritis International Society: **2010 Update of the International Assessment of Spondyloarthritis International Society Recommendations for the Use of Anti-Tumor Necrosis Factor Agents in Patients with Axial Spondyloarthritis (2010)**[14]	• All patients should have had adequate therapeutic trials of at least two NSAIDs. An adequate therapeutic trial is defined as at least two NSAIDs over a four-week period in total at a maximum recommended dose unless contraindicated. • Patients with pure axial manifestations do not have to take DMARDs before TNF-α inhibitor treatment can be started. • Patients with symptomatic peripheral arthritis should have an insufficient response to at least one local corticosteroid injection if appropriate, and should normally have had an adequate therapeutic trial of a DMARD, preferably sulfasalazine. • Patients with symptomatic enthesitis must have failed appropriate local treatment.
National Institute for Health and Clinical Excellence: **Adalimumab, Etanercept and Infliximab for Ankylosing Spondylitis (2008)**[15]	• Adalimumab or etanercept are recommended as treatment options for adults with severe active AS only if all of the following criteria are fulfilled: o The patient's disease satisfies the modified New York criteria for diagnosis of AS. o There is confirmation of sustained active spinal disease, demonstrated by: a score of at least four units on the Bath AS Disease Activity Index and at least 4 cm on the 0 to 10 cm spinal pain visual analogue scale (these should both be demonstrated on two occasions at least 12 weeks apart without any change of treatment). o Conventional treatment with two or more NSAIDs taken sequentially at maximum tolerated or recommended dosage for four weeks has failed to control symptoms. • It is recommended that the response to adalimumab or etanercept treatment should be assessed 12 weeks after treatment is initiated, and that treatment should only be continued in the presence of an adequate response. • Infliximab is not recommended for the treatment of AS; patients currently receiving infliximab for the treatment of AS should have the option to continue therapy until they and their clinicians consider it appropriate to stop. • Golimumab was not incorporated into the guidelines at last publication due to the recent Food and Drug Administration (FDA) approval (April 24, 2009).
National Institute for Health and Clinical Excellence: **Golimumab for the treatment of Ankylosing Spondylitis (2011)**[16]	• Golimumab is recommended as an option for the treatment of severe, active ankylosing spondylitis in adults only if it is used as described for adalimumab and etanercept in NICE Guideline (2008) 'Adalimumab, etanercept and infliximab for ankylosing spondylitis'.
American College of Gastroenterology: **Management of Crohn's**	<u>Mild to moderate active disease</u> • Ileal, ileocolonic, or colonic disease has commonly been treated in clinical practice with oral mesalamine 3.2 to 4.0 g daily or

Clinical Guideline	Recommendations
Disease in Adults(2009)[17]	sulfasalazine for ileocolonic or colonic disease as 3 to 6 g daily in divided doses. • Despite the use of oral mesalamine treatment in the past, new evidence suggests that this approach is minimally effective as compared to placebo and less effective than budesonide or conventional corticosteroids. • Alternatively, metronidazole at a dose of 10 to 20 mg/kg/day has been used in a proportion of patients not responding to sulfasalazine. • Controlled ileal release budesonide (9 mg/day) is effective when active disease is confined to the ileum and/or right colon. • Anti-tuberculous therapy has not been effective for either induction of remission or maintenance of remission in patients with Crohn's disease. <u>Moderate to severe disease</u> • Patients with moderate to severe disease are treated with prednisone 40 to 60 mg daily until resolution of symptoms and resumption of weight gain (generally seven to 28 days). • Infection or abscess requires appropriate antibiotic therapy or drainage (percutaneous or surgical). • Elemental diets are less effective than corticosteroids, but can avoid corticosteroid-induced toxicities. • Azathioprine and 6-mercaptopurine are effective for maintaining a steroid induced remission, and parenteral methotrexate at a dose of 25 mg/week is effective for steroid-dependent and steroid-refractory Crohn's disease. • The TNF-α inhibitors, adalimumab, certolizumab, and infliximab are effective in the treatment of moderate to severely active Crohn's disease in patients who have not responded despite complete and adequate therapy with a corticosteroid or an immunosuppressive agent. • Infliximab monotherapy and infliximab in combination with azathioprine are more effective than azathioprine in the treatment of patients with moderate to severe Crohn's disease who have failed to respond to first-line therapy with mesalamine and/or corticosteroids. • Adalimumab, certolizumab, and infliximab may be used as alternatives to steroid therapy in selected patients in whom corticosteroids are contraindicated or not desired. • The anti-alpha 4 integrin antibody, natalizumab, is effective in the treatment of patients with moderate to severely active Crohn's disease who have had an inadequate response or are unable to tolerate conventional Crohn's disease therapies and TNF-α inhibitor therapy. <u>Severe/fulminant disease</u> • Because of the acuteness and diversity of presentation of patients with severe Crohn's disease and the potential for development of complications, the management decisions for these patients are based more on practicality than controlled trial evidence. • Patients with persistence of Crohn's related symptoms despite introduction of conventional oral steroids or an TNF-α inhibitor (adalimumab or infliximab), or those presenting with high fever,

Clinical Guideline	Recommendations
	frequent vomiting, evidence of intestinal obstruction, rebound tenderness, cachexia, or evidence of an abscess should be hospitalized. • Surgical evaluation is warranted for patients with intestinal obstruction or who have a tender abdominal mass. • An abdominal mass should be evaluated through transabdominal ultrasound, magnetic resonance imaging scan. • Once the presence of an abscess has been excluded or if the patient has been receiving oral corticosteroids, parenteral corticosteroids equivalent to 40 to 60 mg of prednisone daily or its equivalent are administered in divided doses or as a continuous infusion. • There is no specific role for total parenteral nutrition in addition to steroids. Nutritional support through elemental feeding or parenteral hyperalimentation is indicated, after five to seven days, for patients who are unable to maintain adequate nutritional requirements. <u>Perianal and fistulizing disease</u> • Acute suppuration is an indication for surgical drainage with or without placement of non-cutting setons. • Nonsuppurative, chronic fistulization, or perianal fissuring is treated medically with antibiotics, immunosuppressives or infliximab. <u>Maintenance therapy</u> • Mesalamine and sulfasalazine have not had consistent maintenance benefits after medical inductive therapy. • Conventional corticosteroids should not be used as long-term agents to prevent relapse of Crohn's disease. • Budesonide at a dose of 6 mg/day reduces the time to relapse in ileal and/or right colonic disease, but does not provide significant maintenance benefits after six months. • Azathioprine/6-mercaptopurine and methotrexate have demonstrable maintenance benefits after inductive therapy with corticosteroids. • Azathioprine can maintain remissions induced by infliximab in steroid-naive patients. • Maintenance therapy with adalimumab, certolizumab, and infliximab is effective. • Infliximab monotherapy and infliximab combined with azathioprine are more effective than azathioprine for maintenance of patients with moderate to severe Crohn's disease who have failed to respond to first-line therapy with mesalamine and/or corticosteroids. • Maintenance therapy with natalizumab is effective. • Infliximab, mesalamine, metronidazole or azathioprine/mercaptopurine should be considered after ileocolonic resections to reduce the likelihood of symptomatic recurrence, whereas conventional corticosteroids and budesonide at a dose of 6 mg/day are not effective.
National Institute for Health and Clinical Excellence: **Crohn's disease Management in adults, children and young**	<u>Monotherapy</u> • Offer monotherapy with a conventional glucocorticosteroid (prednisolone, methylprednisolone or intravenous hydrocortisone) to induce remission in people with a first presentation or a single inflammatory exacerbation of Crohn's disease in a 12-month period.

Clinical Guideline	Recommendations
people (2012)[18]	• Consider enteral nutrition as an alternative to a conventional glucocorticosteroid to induce remission for: o Children in whom there is concern about growth or side effects. o Young people in whom there is concern about growth. • In people with one or more of distal ileal, ileocaecal or right-sided colonic disease who decline, cannot tolerate or in whom a conventional glucocorticosteroid is contraindicated, consider budesonide for a first presentation or a single inflammatory exacerbation in a 12-month period. • In people who decline, cannot tolerate or in whom glucocorticosteroid treatment is contraindicated, consider 5-aminosalicylate (5-ASA) treatment for a first presentation or a single inflammatory exacerbation in a 12-month period. • Do not offer budesonide or 5-ASA treatment for severe presentations or exacerbations. • Do not offer azathioprine, mercaptopurine or methotrexate as monotherapy to induce remission. <u>Combination therapy</u> • Consider adding azathioprine or mercaptopurine to a conventional glucocorticosteroid or budesonide to induce remission of Crohn's disease if: o There are two or more inflammatory exacerbations in a 12-month period, or o The glucocorticosteroid dose cannot be tapered. • Assess thiopurine methyltransferase (TPMT) activity before offering azathioprine or mercaptopurine. Do not offer azathioprine or mercaptopurine if TPMT activity is deficient (very low or absent). Consider azathioprine or mercaptopurine at a lower dose if TPMT activity is below normal but not deficient (according to local laboratory reference values). • Consider adding methotrexate to a conventional glucocorticosteroid or budesonide to induce remission in people who cannot tolerate azathioprine or mercaptopurine, or in whom TPMT activity is deficient, if: o There are two or more inflammatory exacerbations in a 12-month period, or o The glucocorticosteroid dose cannot be tapered. <u>Infliximab and adalimumab</u> • Infliximab and adalimumab, within their licensed indications, are recommended as treatment options for adults with severe active Crohn's disease whose disease has not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments), or who are intolerant of or have contraindications to conventional therapy. • Infliximab or adalimumab should be given as a planned course of treatment until treatment failure (including the need for surgery), or until 12 months after the start of treatment, whichever is shorter. • People should then have their disease reassessed to determine whether ongoing treatment is still clinically appropriate. People whose disease relapses after treatment is stopped should have the

Clinical Guideline	Recommendations
	option to start treatment again. Remission maintenance • For patients that choose maintenance therapy, offer azathioprine or mercaptopurine as monotherapy to maintain remission when previously used with a conventional glucocorticosteroid or budesonide to induce remission or to maintain remission in patients not previously treated with these medications. • Consider methotrexate to maintain remission only in patients who: o Needed methotrexate to induce remission. o Did not tolerate azathioprine or mercaptopurine for maintenance. o Contraindicated to azathioprine or mercaptopurine. • Do not offer conventional glucocorticosteroids or budesonide to maintain remission. Remission maintenance following surgery • After surgery ,consider azathioprine or mercaptopurine to maintain remission in people with factors such as: o More than one resection. o Previously complicated or debilitating disease (e.g. abscess, involvement of adjacent structures, fistulising or penetrating disease). • Consider 5-ASA treatment to maintain remission after surgery. • Do not offer budesonide or enteral nutrition to maintain remission after surgery.
American College of Rheumatology: **Recommendations for the Treatment of Juvenile Idiopathic Arthritis: Initiation and Safety Monitoring of Therapeutic Agents for the Treatment of Arthritis and Systemic Features (2011)**[19]	General considerations • Recommendations for the treatment of juvenile idiopathic arthritis (JIA) are divided into five treatment groups that were developed by the core expert panel responsible for the literature review in the recommendation development. The treatment groups are as follows: history of arthritis of four or fewer joints, history of arthritis of five or more joints, active sacroiliac arthritis, systemic arthritis with active systemic features (and without active arthritis) and systemic arthritis with active arthritis (and without active systemic features). • Glucocorticoid joint injections for active arthritis are recommended regardless of concurrent therapy (no DMARD, nonbiologic DMARD, biologic DMARD) or JIA treatment group. Due to its “superior” efficacy, triamcinolone hexacetonide should be used. • When initiating a TNF-α inhibitor (etanercept or adalimumab), continuation of methotrexate is recommended for patients that had a partial previous response. History of arthritis in four or fewer joints • For patients with low disease activity, no joint contractures and without features of poor prognosis, initiation of therapy with NSAID monotherapy is recommended as a treatment option. Therapy with an NSAID without additional therapy is not recommended longer than two months. • For all patients regardless of disease activity level, prognostic features or joint contractures, initiation of intra-articular joint injections (with or without additional therapy is recommended. • For patients with high disease activity and poor prognostic features,

Clinical Guideline	Recommendations
	methotrexate is recommended as initial treatment (without prior therapy). For patients with high disease activity without poor prognostic features or with moderate disease activity and poor prognostic features, methotrexate is recommended after initial joint injection. For patients with low disease activity and poor prognostic features or moderate disease activity without poor prognostic features, methotrexate is recommended after repeated joint injections. • For patients with enthesitis-related arthritis category of JIA with moderate or high disease activity with and without poor prognostic features, sulfasalazine is recommended after glucocorticoid injections or an adequate trial of NSAIDs. • Initiation of a TNF-α inhibitor is recommended for patients with moderate or high disease activity with poor prognostic features after receiving glucocorticoid joint injections and three months of methotrexate at maximum tolerated dose. Initiation of a TNF-α inhibitor is also recommended in patients with high disease activity without poor prognostic features after receiving glucocorticoid joint injections and six months of methotrexate. For patients with enthesitis-related arthritis category of JIA and moderate or high disease activity, regardless of prognostic features, TNF-α inhibitors are recommended after receiving glucocorticoid joint injections and an adequate trial of sulfasalazine (without prior methotrexate). <u>History of arthritis of five or more joints</u> • Initial treatment with methotrexate is recommended in patients with high disease activity with or without poor prognostic features and in patients with moderate disease activity and poor prognostic features. For patients with low disease activity and poor prognostic features, methotrexate therapy is recommended after one month of therapy with NSAIDs. In patients with moderate disease activity without poor prognostic features, methotrexate is recommended after one to two months of therapy with NSAIDs. • Leflunomide is a treatment alternative to methotrexate as initial therapy in patients with high disease activity and poor prognostic features. In patients with high disease activity without poor prognostic features or moderate disease activity with poor prognostic features, leflunomide is a treatment alternative after a brief trial with NSAIDs. • For patients with moderate or high disease activity, regardless of prognostic features, TNF-α inhibitors are recommended after receiving methotrexate or leflunomide for three months at the maximum tolerated typical doses. For patients with low disease activity with or without poor prognostic features, TNF-α inhibitors are recommended after receiving methotrexate or leflunomide for six months. • For patients with moderate or high disease activity regardless of prognostic features, switching from one TNF-α inhibitor to another is recommended as a treatment option after receiving four months of therapy with current TNF-α inhibitor. • Abatacept is recommended as a treatment option after receiving four months of therapy with a TNF-α inhibitor in patients with high disease activity regardless of prognostic features or moderate

Clinical Guideline	Recommendations
	disease activity and poor prognostic features. For patients with moderate or high disease activity regardless of prognostic features or patients with low disease activity with features of poor prognosis, abatacept is recommended as a treatment option after receiving more than one TNF-α inhibitor sequentially. • Switching to a TNF-α inhibitor is recommended as a treatment option in patients that received abatacept for three months and have high disease activity with poor prognostic features and in patients that received abatacept for six months and have moderate to high disease activity with or without features of poor prognosis. Active sacroiliac arthritis • For patients with high disease activity and features of poor prognosis, TNF-α inhibitors are recommended after receiving an adequate trial of NSAIDs. • A TNF-α inhibitor is recommended in patients with high disease activity regardless of prognostic features or moderate disease activity with features of poor prognosis that have received three months of methotrexate, or in patients with moderate disease without poor prognosis that received six months of methotrexate. • A TNF-α inhibitor is recommended in patients with moderate or high disease activity regardless of prognostic features that have received three months of sulfasalazine, or in patients with low disease with poor prognosis that received six months of sulfasalazine. Systemic arthritis with active systemic features • NSAID monotherapy is appropriate during clinical evaluation for possible systemic arthritis. NSAID monotherapy is not recommended for patients with active fever and physician global assessment of overall disease activity ≥7 of 10. In patients with active fever, continuation of NSAID monotherapy longer than one month is not appropriate. • Initial therapy with systemic glucocorticoids (with or without additional concurrent therapy) is recommended for patients with active fever and physician global assessment of seven or greater. For all patients with active fever, systemic glucocorticoids are recommended following up to two weeks of NSAIDs. • Anakinra is recommended for all patients with active fever and poor prognostic features, regardless of current therapy. For patients that sustain or develop fever while receiving systemic glucocorticoid, anakinra is recommended. Systemic arthritis with active arthritis • NSAID monotherapy (with or without glucocorticoid joint injections) for up to one month is recommended for patients with low disease activity without features of poor prognosis. • For all patients with active arthritis, regardless of prognostic features, methotrexate is recommended after one month or less of NSAID monotherapy (with or without glucocorticoid injections). • After three months of methotrexate, anakinra is recommended for patients with moderate or high disease activity with or without poor prognostic features. Anakinra is recommended for patients with high or moderate disease activity, regardless of prognostic features, and

Clinical Guideline	Recommendations
	have received methotrexate and a TNF-α inhibitor or methotrexate and abatacept. Initiation of anakinra later in the disease course may be less appropriate compared to nearer to the onset of disease. • For patients with moderate or high disease activity with or without poor prognosis features, TNF-α inhibitors are recommended after receiving three months of methotrexate. Switching from anakinra to TNF-α inhibitors may be appropriate for patients with moderate to high disease activity regardless of prognostic features. • Abatacept is recommended for patients that received methotrexate and a TNF-α inhibitor and have high disease activity regardless of prognostic features or moderate disease activity and poor prognostic features.
European League Against Rheumatism: **Recommendations for the Management of Psoriatic Arthritis with Pharmacological Therapies (2012)**[20]	Recommendations for treatment • In patients with psoriatic arthritis, NSAIDs may be used to relieve musculoskeletal signs and symptoms. • In patients with active disease (particularly those with many swollen joints, structural damage in the presence of inflammation, high erythrocyte sedimentation rate/C-reactive protein and/or clinically relevant extraarticular manifestations), treatment with DMARDs, such as methotrexate, sulfasalazine, leflunomide, should be considered at an early stage. • In patients with active psoriatic arthritis and clinically relevant psoriasis, a DMARD that also improves psoriasis, such as methotrexate, should be preferred. • Local corticosteroid injections should be considered as adjunctive therapy in psoriatic arthritis; systemic steroids at the lowest effective dose may be used with caution. • In patients with active arthritis and an inadequate response to at least one synthetic DMARD, such as methotrexate, therapy with a TNF-α inhibitor should be commenced. • In patients with active enthesitis and/or dactylitis and insufficient response to NSAIDs or steroid injections, a TNF-α inhibitor may be considered. • In patients with predominantly axial disease that is active and has insufficient response to NSAIDs, a TNF-α inhibitor should be considered. • A TNF-α inhibitor might be considered for a very active patient treatment naïve to DMARDs (particularly those with many swollen joints, structural damage in the presence of inflammation, and/ or clinically relevant extra-articular manifestations, especially extensive skin involvement). • In patients who fail to respond adequately to one TNF-α inhibitor, switching to another TNF-α inhibitor should be considered. • When adjusting therapy, factors apart from disease activity, such as comorbidities and safety issues, should be taken into account.
National Psoriasis Foundation: **Consensus Guidelines for the Management of Plaque Psoriasis (2012)**[21]	Oral therapies • Acitretin is the only antipsoriatic retinoid available for systemic use in the United States. The use of acitretin is limited due to its slow onset of action and persistence of residual plaque psoriasis even when plaque thinning is noted. The combination of acitretin with topical calcipotriene or biological therapy or phototherapy may increase rates of clearance. Acitretin is especially useful in patients with severely sun-damaged skin, in which it may suppress actinic

Clinical Guideline	Recommendations
	keratoses and even invasive malignant neoplasms. • Although it can be effective in the long term, continuous use of cyclosporine is associated with cumulative renal toxic effects, hypertension and hyperglycemia. Cyclosporine should normally be reserved for intermittent use of no longer than 12 weeks as a short-term treatment agent to control a flare of psoriasis, after which therapy is switched for long-term maintenance. When used in this intermittent fashion, a course of cyclosporine treatment can induce an average decrease of more than 75% in psoriasis severity. • Methotrexate is directly anti- inflammatory because of its effects on T-cell gene expression patterns. Compared to cyclosporine, methotrexate has a more modest effect on psoriasis severity, but can be used continuously for many years with durable benefits. A major safety issue with methotrexate is the cumulative toxic effects to the liver. <u>Biologic agents</u> • Adalimumab may be used as first-line systemic treatment of plaque psoriasis and has a higher efficacy and lower rate of adverse effects compared to methotrexate. • Etanercept is commonly used as a first-line systemic drug for chronic plaque psoriasis. • Infliximab is administered via intravenous infusion, is a fast-acting drug that is often used as a second- or third-line biological for chronic plaque psoriasis • Ustekinumab is associated with favorable results when compared to etanercept in terms of efficacy and safety. It may be used as first-line systemic treatment for chronic plaque psoriasis. • Alefacept is generally used for intermittent use. There is little evidence to support use to achieve full clearance, and it is often used in combination regimens. It may be used as first-line systemic drug for chronic plaque psoriasis.
American Academy of Dermatology: **Guidelines of Care for the Management of Psoriasis and Psoriatic Arthritis, Sections 2, 3 and 4 (2008-2009)**[22-24]	<u>Topical therapies</u> • Approximately 80% of patients are affected with mild to moderate psoriasis with the majority of cases able to be successfully treated with topical agents. • Topical agents are also used adjunctively to either ultraviolet light or systemic medications for resistant lesions in patients with more severe disease. • Treatment needs vary depending on body location of disease, characteristics of the psoriasis being treated including lesion thickness, degree of erythema and amount of scaling, as well as patient preferences. • Topical corticosteroids are the cornerstone of treatment for the majority of patients with psoriasis. • Other topical agents include anthralin, coal tar, nonmedicated topical moisturizers, pimecrolimus, salicylic acid, tacrolimus, tazarotene, vitamin D analogues, and combination products. • Salicylic acid is a topical keratolytic agent that has been used for many years and has no specific FDA indication. • There are no placebo-controlled trials verifying the safety and efficacy of salicylic acid however the agent is typically used in combination with other topical therapies.

Clinical Guideline	Recommendations
	Systemic therapies • Although biologics are often less toxic and not teratogenic, traditional systemic therapies (acitretin, cyclosporine, methotrexate) are still used more often due to oral route of administration and low cost. • Used more than 50 years ago, methotrexate is most commonly prescribed for severe, recalcitrant, disabling psoriasis when used in a weekly, single low-dose regimen for its effect on the immune system; concurrent folate supplementation may be warranted. • Though highly effective and known for its rapid effects, cyclosporine is associated with nephrotoxicity and hypertension; its use is restricted to one and two years in the United States and United Kingdom, respectively. • When used in conjunction with ultraviolet radiation B or psoralen and ultraviolet radiation A phototherapy or biologics, acitretin is effective for psoriasis and the treatment of choice in human immunodeficiency virus-positive patients with severe psoriasis due to its lack of significant immunosuppression; effects are dose-dependent and response is observed after three to six months. • Agents not FDA-indicated but used in psoriasis with limited supporting evidence include: azathioprine, fumarates (not approved in the United States), leflunomide, mycophenolate mofetil, sulfasalazine, tacrolimus, and 6-thioguanine. Biologics • Three TNF-α inhibitors are FDA-approved for the treatment of psoriatic arthritis; adalimumab, etanercept, and infliximab (please note that the publication of these guidelines was before FDA-approval of golimumab). • Psoriatic arthritis is an inflammatory seronegative spondyloarthropathy associated with psoriasis that if left untreated can lead to persistent inflammation with progressive joint damage that can result in severe physical limitations and disability. • NSAIDs and/or intra-articular injections of corticosteroids may be appropriate treatment options in patients with milder, localized disease. • Patients with moderate to severe psoriatic arthritis that is more extensive or aggressive in nature or that significantly impacts quality of life should be treated with methotrexate, TNF-α inhibitors, or both. These treatment options are considered the standard of care. • Other DMARDs which may be used in the treatment of psoriatic arthritis include leflunomide and sulfasalazine. Antimalarials, cyclosporine, and gold are used less frequently due to the evidence for their efficacy being less convincing than for leflunomide, methotrexate, and sulfasalazine. • Although expensive, there are potential long-term cost savings and benefits associated with the use of biologics in the treatment of psoriatic arthritis, including reduced need for joint replacement surgery; reduced demands on medical, nursing, and therapy services; reduced needs for concomitant medicines; reduced demands on social services and careers; improved quality of life; improved prospect of remaining in the work force; and increased life

Clinical Guideline	Recommendations
	expectancy. • Because the clinical trial efficacy data (primary endpoint of American College of Rheumatology 20% improvement) with all three FDA-approved TNF-α inhibitors are roughly equivalent, the choice of which agent to use is an individual one with the degree and severity of cutaneous involvement an important consideration. • Adalimumab and infliximab both demonstrated significant benefit for the treatment of psoriatic arthritis in clinical trials, while etanercept demonstrated significant improvements in signs and symptoms of psoriatic arthritis.
American College of Rheumatology: **2012 Update of the 2008 American College of Rheumatology Recommendations for the Use of Disease-Modifying Antirheumatic Drugs and Biologic Agents in the Treatment of Rheumatoid Arthritis (2012)[25]**	<u>Initiating and switching among DMARDs</u> • If a patient deteriorates from low to moderate/high disease activity after three months of DMARD monotherapy (in patients without poor prognostic features), then methotrexate, hydroxychloroquine, or leflunomide should be added. • Add another non-methotrexate DMARD or switch to a different non-methotrexate DMARD if the patient still experiences moderate or high disease activity following three months of methotrexate or methotrexate/DMARD combination therapy. <u>Switching from DMARDs to biologic agents</u> • For patients with continued moderate or high disease activity following three months of methotrexate monotherapy or DMARD combination therapy, an alternative to DMARD therapy is adding or changing therapy to a TNF-α inhibitor, abatacept or rituximab. • Add or switch to a TNF-α inhibitor if a patient continues to have moderate or high disease activity, following three months of intensified DMARD combination therapy or after a second DMARD has been tried. <u>Switching among biologic agents due to lack of benefit or loss of benefit</u> • In patients with moderate or high disease activity despite three months of TNF-α inhibitor therapy and this is due to a lack or loss of benefit, switching to another TNF-α inhibitor or a non-TNF-α inhibitor biologic is recommended. • In patients with moderate or high disease activity despite six months of a non-TNF-α inhibitor biologic and the failure is due to a lack or loss of benefit, the patient should switch to another non-TNF-α inhibitor biologic or a TNF-α inhibitor. <u>Switching among biologic agents due to harms/adverse events</u> • Patients with high disease activity following treatment failure of a TNF-α inhibitor due to a serious adverse event, an attempt should be made to switch to a non-TNF-α inhibitor biologic. • In patients with moderate or high disease activity after failing an TNF-α inhibitor because of a nonserious adverse event, switch to another anti-TNF-α inhibitor or a non-TNF-α inhibitor biologic. • Patients with moderate or high disease activity after failing a non-TNF-α inhibitor biologic because of an adverse event (serious or nonserious) should be switched to another non-TNF-α inhibitor biologic or a TNF-α inhibitor. <u>Biologic use in Hepatitis B or C</u>

Clinical Guideline	Recommendations
	• Etanercept could potentially be used in rheumatoid arthritis patients with hepatitis C requiring rheumatoid arthritis treatment; however, biologic agents should not be used in rheumatoid arthritis patients with untreated chronic hepatitis B and in rheumatoid arthritis patients with treated chronic hepatitis B with Child-Pugh class B and higher. Malignancies • Patients treated for solid malignancies more than five years ago or who have been treated for nonmelanoma skin cancer more than five years ago, treatment with a biologic agent may be initiated or continued if the patient would otherwise qualify for biologic therapy. • Rituximab should only be started or initiated in rheumatoid arthritis patients with a previously treated solid malignancy within the last five years, a previously treated nonmelanoma skin cancer within the last five years, a previously treated melanoma skin cancer, or a previously treated lymphoproliferative malignancy. • Little is known about the effects of biologic therapy in patients with a history of a solid cancer within the past five years. Congestive heart failure • Anti-TNF biologic in rheumatoid arthritis patients with congestive heart failure is not recommended in those with a New York Heart Association class III or IV and who have an ejection fraction of 50% or less.
National Institute for Health and Clinical Excellence: **Rheumatoid Arthritis National Clinical Guideline for Management and Treatment in Adults (2009)**[26]	• In people with newly diagnosed active rheumatoid arthritis, offer a combination of DMARDs (including methotrexate and at least one other DMARD, plus short-term glucocorticoids) as first-line treatment as soon as possible, ideally within three months of the onset of persistent symptoms. • In people with recent-onset rheumatoid arthritis receiving combination DMARD therapy and in whom sustained and satisfactory levels of disease control have been achieved, cautiously try to reduce drug doses to levels that still maintain disease control. • In people with newly diagnosed rheumatoid arthritis for which combination DMARD therapy is not appropriate, start DMARD monotherapy; placing greater emphasis on fast escalation to a clinically effective dose rather than on the choice of DMARD. • In people with established rheumatoid arthritis whose disease is stable, cautiously reduce dosages of disease modifying or biological drugs. Return promptly to disease-controlling dosages at the first sign of a flare. • When introducing new drugs to improve disease control into the treatment regimen of a person with established rheumatoid arthritis, consider decreasing or stopping their pre-existing rheumatological drugs once the disease is controlled. • In any person with established rheumatoid arthritis in whom disease-modifying or biological drug doses are being decreased or stopped, arrangements should be in place for prompt review. • Consider offering short-term treatment with glucocorticoids (oral, intramuscular or intra-articular) to rapidly improve symptoms in people with newly diagnosed rheumatoid arthritis if they are not already receiving glucocorticoids as part of DMARD combination therapy.

Clinical Guideline	Recommendations
	• Offer short-term treatment with glucocorticoids for managing flares in people with recent onset or established disease, to rapidly decrease inflammation. • In people with established rheumatoid arthritis, only continue long-term treatment with glucocorticoids when the long-term complications of glucocorticoid therapy have been fully discussed, and all other treatment options (including biological drugs) have been offered. • On the balance of its clinical benefits and cost effectiveness, anakinra is not recommended for the treatment of rheumatoid arthritis, except in the context of a controlled, long-term clinical study. • Patients currently receiving anakinra for rheumatoid arthritis may suffer loss of wellbeing if their treatment were discontinued at a time they did not anticipate. Therefore, patients should continue therapy with anakinra until they and their consultant consider it is appropriate to stop. • Do not offer the combination of TNF-α inhibitor therapy and anakinra for rheumatoid arthritis. • Oral NSAIDs or COX-2 inhibitors should be used at the lowest effective dose for the shortest possible period of time. • When offering treatment with an oral NSAID or COX-2 inhibitor, the first choice should be either a standard NSAID or a COX-2 inhibitor. In either case, these should be co-prescribed with a proton pump inhibitor, choosing the one with the lowest acquisition cost. • All oral NSAIDs or COX-2 inhibitors have analgesic effects of a similar magnitude but vary in their potential gastrointestinal, liver and cardio-renal toxicity; therefore, when choosing the agent and dose, healthcare professionals should take into account individual patient risk factors, including age. When prescribing these drugs, consideration should be given to appropriate assessment and/or ongoing monitoring of these risk factors. • If a person with rheumatoid arthritis needs to take low-dose aspirin, healthcare professionals should consider other analgesics before substituting or adding an NSAID or COX-2 inhibitor (with a proton pump inhibitor) if pain relief is ineffective or insufficient. • If NSAIDs or COX-2 inhibitors are not providing satisfactory symptom control, review the disease-modifying or biological drug regimen. • The TNF-α inhibitors adalimumab, etanercept and infliximab are recommended as options for the treatment of adults who have both of the following characteristics: o Active rheumatoid arthritis as measured by disease activity score (DAS 28) >5.1 confirmed on at least two occasions, one month apart. o Have undergone trials of two DMARDs, including methotrexate (unless contraindicated). A trial of a DMARD is defined as being normally of six months, with two months at standard dose, unless significant toxicity has limited the dose or duration of treatment. • TNF-α inhibitors should normally be used in combination with methotrexate. Where a patient is intolerant of methotrexate or where methotrexate treatment is considered to be inappropriate,

Clinical Guideline	Recommendations
	adalimumab and etanercept may be given as monotherapy. • Treatment with TNF-α inhibitors should be continued only if there is an adequate response at six months following initiation of therapy. An adequate response is defined as an improvement in DAS 28 of 1.2 points or more. • After initial response, treatment should be monitored no less frequently than six-monthly intervals with assessment of DAS 28. Treatment should be withdrawn if an adequate response is not maintained. • An alternative TNF-α inhibitor may be considered for patients in whom treatment is withdrawn due to an adverse event before the initial six-month assessment of efficacy provided the risks and benefits have been fully discussed with the patient and documented. • Escalation of dose of the TNF-α inhibitors above their licensed starting dose is not recommended. • Treatment should normally be initiated with the least expensive drug (taking into account administration costs, required dose and product price per dose). This may need to be varied in individual cases due to differences in the mode of administration and treatment schedules. • Use of the TNF-α inhibitors for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate or other DMARDs is not recommended. • Initiation of TNF-α inhibitors and follow-up of treatment response and adverse events should be undertaken only by a specialist rheumatological team with experience in the use of these agents.
National Institute for Health and Clinical Excellence: **Adalimumab, Etanercept, Infliximab, Rituximab and Abatacept for the Treatment of Rheumatoid Arthritis After the Failure of a Tumor Necrosis Factor Inhibitor (2010)**[27]	• Rituximab in combination with methotrexate is recommended as an option in adult patients with severe active rheumatoid arthritis that have had inadequate response or intolerance to other DMARDs including at least one TNF-α inhibitor. • Treatment with rituximab should be given no more frequently that every six months and should be continued only if an adequate response is maintained at this dosing interval. • Abatacept, adalimumab, etanercept and infliximab each in combination with methotrexate, are recommended as treatment options only in patients with severe active rheumatoid arthritis that have had inadequate response or intolerance to other DMARDs including at least one TNF-α inhibitor and cannot receive rituximab because of a contraindication to or adverse event with rituximab. • Adalimumab and etanercept monotherapy are recommended as treatment options only in patients with severe active rheumatoid arthritis that have had inadequate response or intolerance to other DMARDs including at least one TNF-α inhibitor and cannot receive rituximab because of a contraindication to or adverse event with methotrexate. • Treatment with abatacept, adalimumab, etanercept and infliximab should be continued only if there is an adequate response six months after therapy. • Abatacept, adalimumab, etanercept, infliximab and rituximab should be initiated, supervised and treatment response assessed by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis.
National Institute for Health	• Golimumab in combination with methotrexate is recommended as an

Clinical Guideline	Recommendations
and Clinical Excellence: **Golimumab for the Treatment of Rheumatoid Arthritis After the Failure of Previous Disease-Modifying Antirheumatic Drugs (2011)**[28]	option for the treatment of rheumatoid arthritis in adults whose rheumatoid arthritis has responded inadequately to conventional DMARDs only, including methotrexate, if: o It is used as described for other TNF inhibitor treatments in NICE Guideline (2010) 'Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor'. o The manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose, agreed as part of the patient access scheme. • Golimumab in combination with methotrexate is recommended as an option for the treatment of rheumatoid arthritis in adults whose rheumatoid arthritis has responded inadequately to other DMARDs, including a TNF inhibitor, if: o It is used as described for other TNF inhibitor treatments in NICE Guideline (2010) 'Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor'. o The manufacturer provides the 100 mg dose of golimumab at the same cost as the 50 mg dose, agreed as part of the patient access scheme.
American College of Gastroenterology, Practice Parameters Committee: **Ulcerative Colitis Practice Guidelines in Adults (2010)**[29]	Management of mild-moderate distal colitis • Topical mesalamine agents are “superior” to topical steroids or oral aminosalicylates. • The combination of oral and topical agents is “superior” to each agent used alone. • Mesalamine enemas or suppositories may still be effective in patients refractory to oral aminosalicylates or to topical corticosteroids. One meta-analysis demonstrated topical mesalamine to be “superior” to oral aminosalicylates in achieving clinical improvement in patients with mild-moderate distal colitis. • Patients who are refractory to the above therapies may require oral prednisone 40 to 60 mg daily or infliximab with an induction regimen of 5 mg/kg at weeks zero, two and six. • Oral therapy effective for achieving and maintaining remission include aminosalicylates, balsalazide, mesalamine, olsalazine and sulfasalazine. Maintenance of remission in distal disease • Balsalazide, mesalamine and sulfasalazine are effective in maintaining remission; combination oral and topical mesalamine is more effective than oral mesalamine alone. • Mesalamine suppositories are effective for maintenance of remission in patients with proctitis and mesalamine enemas are effective in patients with distal colitis. • Topical corticosteroids, including budesonide, have not been proven effective at maintaining remission. • When patients fail to maintain remission with the above therapies, thiopurines (6-mercaptopurine or azathioprine) and infliximab may be effective. Management of mild-moderate extensive colitis: active disease • Oral sulfasalazine is considered first line.

Clinical Guideline	Recommendations
	• Reserve oral steroids for patients refractory to oral aminosalicylates or patients who require rapid improvement. • 6-mercaptopurine or azathioprine can be used for patients refractory to oral prednisone and are acutely ill, requiring intravenous therapy. • Infliximab is effective in patients who are steroid refractory or steroid dependent despite the use of thiopurine at adequate doses or who are intolerant to these medications. <u>Maintenance of remission for mild-moderate extensive colitis</u> • Balsalazide, mesalamine, olsalazine and sulfasalazine are effective in reducing the number of relapses. • 6-mercaptopurine or azathioprine can be used for steroid sparing in steroid dependent patients and have been shown to effectively maintain remission in patients not adequately sustained on aminosalicylates. • Infliximab effectively maintains remission in patient who responded to the infliximab induction regimen. <u>Management of severe colitis</u> • If a patient is refractory to maximum oral treatment of aminosalicylates, oral prednisone, and topical medications may be treated with infliximab if urgent hospitalization is not required. • Patients that show signs of toxicity should be hospitalized to receive intravenous steroids. • Failure to significantly improve within three to five days indicates need for intravenous cyclosporine (or colectomy - weaker evidence). • Infliximab may also be used to avoid colectomy in patients failing intravenous steroids; however, long-term efficacy in this setting is unknown.

Conclusions

Immunomodulators inhibit the pro-inflammatory response involved in the pathophysiology of several chronic inflammatory diseases. The immunomodulators interfere with this inflammatory pathway through slightly different mechanisms.[3-8,10-12] To date, there are a lack of head-to-head trials amongst these agents, making it difficult to compare the efficacy, although each have been shown to be efficacious compared to placebo for their respective Food and Drug Administration (FDA)-approved indication(s).[32-102] Current clinical guidelines do not distinguish among the different agents for any indication for which the specific agent is approved.[13-29]The adverse event profiles are similar across the class. Currently, adalimumab and infliximab have the most FDA-approved indications among the agents in the class.

References:

1. Overview of biologic agents in the rheumatic diseases. In: Furst DE, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2012 [cited 2012 Sept 3]. Available from: http://www.utdol.com/utd/index.do.
2. Tumor necrosis factor-alpha inhibitors: An overview of adverse effects. In: Furst DE, editor. UpToDate [database on the Internet]. Waltham (MA): UpToDate; 2012 [cited 2012 Sept 3]. Available from: http://www.utdol.com/utd/index.do.
3. Humira® [package insert]. North Chicago (IL): Abbott Laboratories; 2013 May.
4. Cimzia® [package insert]. Smyrna (GA): UCB, Inc.; 2012 Apr.
5. Enbrel® [package insert]. Thousand Oaks (CA): Immunex Corporation; 2011 Dec.
6. Simponi® [package insert]. Horsham (PA): Janssen Biotech, Inc.; 2011 Sep.
7. Remicade® [package insert]. Horsham (PA): Janssen Biotech, Inc; 2011 Oct.
8. Kineret® [package insert]. Thousand Oaks (CA): Swedish Orphan Biovitrum AB; 2012 Dec.
9. Mertens M, Singh JA. Anakinra for rheumatoid arthritis. Cochrane Database of Systematic Reviews 2009, Issue 1. Art. No.: CD005121. DOI: 10.1002/14651858. CD005121.pub3.
10. Actemra® [package insert]. South San Francisco (CA): Genetech, Inc.; 2011 Apr.
11. Stelara® [package insert]. Horsham (PA): Janssen Biotech, Inc.; 2012 Jun.
12. Orencia® [package insert]. Princeton (NJ): Bristol-Myers Squibb; 2011 Dec.
13. Braun J, van den Berg R, Baraliakos X, Boehm H, Burgos-Vargas R, Collantes-Estevez E, et al. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. Ann Rheum Dis. 2011 Jun;70(6):896-904.
14. van der Heijde D, Sieper J, Maksymowych WP, Dougados M, Burgos-Vargas R, Landewé R, et al. Assessment of SpondyloArthritis international Society. 2010 Update of the international ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis. Ann Rheum Dis. 2011 Jun;70(6):905-8.
15. National Institute for Health and Clinical Excellence (NICE). Adalimumab, etanercept and infliximab for ankylosing spondylitis. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 May. 47 p. (Technology appraisal guidance; no. 143).
16. National Institute for Health and Clinical Excellence (NICE). Golimumab for the treatment of ankylosing spondylitis. London (UK): National Institute for Health and Clinical Excellence (NICE); 2011 Aug. Available at: http://www.nice.org.uk/guidance/TA233
17. Lichtenstein GR, Hanauer SB, Sandborn WJ; Practice Parameters Committee of the American College of Gastroenterology. Management of Crohn's disease in adults. Am J Gastroenterol. 2009;104:465-83.
18. National Institute for Health and Clinical Excellence (NICE). Crohn's disease Management in adults, children and young people. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Oct. Available at: http://www.nice.org.uk/guidance/TA225
19. Beukelman T, Patkar NM, Saag KG, Tolleson-Rinehart S, Cron RQ, DeWitt EM, et al. 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. Arthritis Care Res (Hoboken). 2011 Apr;63(4):465-82.
20. Gossec L, Smolen JS, Gaujoux-Viala C, Ash Z, Marzo-Ortega H, van der Heijde D, et al. European League Against Rheumatism recommendations for the management of psoriatic arthritis with pharmacological therapies. Ann Rheum Dis. 2012 Jan;71(1):4-12.
21. Hsu S, Papp KA, Lebwohl MG, Bagel J, Blauvelt A, Duffin KC, et al. Consensus guidelines for the management of plaque psoriasis. Arch Dermatol. 2012 Jan;148(1):95-102.
22. Gottlieb A, Korman NJ, Gordon KB, Feldman SR, Lebwohl M, Koo JYM, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 2. Psoriatic arthritis: Overview and guidelines of care for treatment with an emphasis on the biologics. J Am Acad Dermatol. 2008;58(5):851-64.
23. Menter A, Korman NJ, Elmets CA, Feldman SR, Gelfand JM, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 3. Guidelines of care for the management and treatment of psoriasis with topical therapies. J Am Acad Dermatol. 2009;60:643-59.
24. Menter A, Korman NJ, Elmets CA, Feldman SR, Gelfand JM, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 4. Guidelines of care for the management and treatment of psoriasis with traditional systemic agents [article in press]. J Am Acad Dermatol. 2009.

May 30 [cited 2012 Sept 3]; Available from: http://www.aad.org/research/guidelines/documents/pso4tsys609.pdf.
25. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken). 2012 May;64(5):625-39.
26. National Institute for Health and Clinical Excellence (NICE). National Collaborating Centre for Chronic Conditions. Rheumatoid arthritis: national clinical guideline for management and treatment in adults. London: Royal College of Physicians, February 2009.
27. National Institute for Health and Clinical Excellence (NICE). Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor. August 2010 Available from http://guidance.nice.org.uk/CG79.
28. National Institute for Health and Clinical Excellence (NICE). Golimumab for the treatment of rheumatoid arthritis after the failure of previous disease-modifying anti-rheumatic drugs. London (UK): National Institute for Health and Clinical Excellence (NICE); 2011 Jun. Available at: http://www.nice.org.uk/guidance/TA225
29. Kornbluth A, Sachar DB; Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol. 2010 Mar;105(3):501-23.
30. H.R. 5894-112th Congress: Patient Protection and Affordable Care Act Education and Outreach Campaign Repeal Act of 2012. (2012). In GovTrack.us (database of federal legislation). Retrieved September 4, 2012, from http://www.govtrack.us/congress/bills/112/hr5894.
31. Micromedex® Healthcare Series [intranet database]. Version 5.1. Greenwood Village, (CO): Thomson Healthcare. Cited 2013 Jun]. Available from: http://www.thomsonhc.com/.
32. van der Heijde D, Kivitz A, Schiff MH, Sieper J, Dijkmans BAC, Braun J, et al. Efficacy and safety of adalimumab in patients with ankylosing spondylitis. Arthritis Rheum. 2006;54(7):2136-46.
33. Van Assche G, Vermeire S, Ballet V, Gabriels F, Noman M, D'Haens G, et al. Switch to adalimumab in patients with Crohn's disease controlled by maintenance infliximab: prospective randomised SWITCH trial. Gut. 2012 Feb;61(2):229-34.
34. Gorman JD, Sack KE, Davis JC. Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor α. N Engl J Med. 2002;346(18):1349-56.
35. Calin A, Dijkmans BAC, Emery P, Hakala M, Kalden J, Leirisalo-Repo M, et al. Outcomes of a multicentre randomized clinical trial of etanercept to treat ankylosing spondylitis. Ann Rheum Dis. 2004; 63:1594-600.
36. Davis JC, van der Heijde DM, Braun J, Dougados M, Clegg DO, Kivitz AJ, et al. Efficacy and safety of up to 192 weeks of etanercept therapy in patients with ankylosing spondylitis. Ann Rheum Dis. 2008;67:346-52.
37. Braun J, van der Horst-Bruinsma IE, Huang F, Burgos-Vargas R, Vlahos B, Koenig AS, et al. Clinical efficacy and safety of etanercept vs sulfasalazine in patients with ankylosing spondylitis: a randomized, double-blind trial. Arthritis Rheum. 2011 Jun;63(6):1543-51.
38. Inman RD, Davis JC Jr, van der Heijde D, Diekman L, Sieper J, Kim SI, et al. Efficacy and safety of golimumab in patients with ankylosing spondylitis: results of a randomized, double-blind, placebo-controlled, phase III trial. Arthritis Rheum. 2008 Nov;58(11):3402-12.
39. Braun J, Brandt J, Listing J, Zink A, Alten R, Golder W, et al. Treatment of active ankylosing spondylitis with infliximab: a randomized controlled multicentre trial. Lancet. 2002 Apr 6;359(9313):1187-93.
40. van der Heijde D, Dijkmans B, Geusens P, Sieper J, DeWoody K, Williamson P, Braun J; Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy Study Group. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). Arthritis Rheum. 2005 Feb;52(2):582-91.
41. Ma C, Panaccione R, Heitman SJ, Devlin SM, Ghosh S, Kaplan GG. Systematic review: the short-term and long-term efficacy of adalimumab following discontinuation of infliximab. Aliment Pharmacol Ther. 2009;30:977-86.
42. Löfberg R, Louis EV, Reinisch W, Robinson AM, Kron M, Camez A, Pollack PF. Adalimumab produces clinical remission and reduces extraintestinal manifestations in Crohn's disease: results from CARE. Inflamm Bowel Dis. 2012 Jan;18(1):1-9.

43. Watanabe M, Hibi T, Lomax KG, Paulson SK, Chao J, Alam MS, et al. Adalimumab for the induction and maintenance of clinical remission in Japanese patients with Crohn's disease. J Crohn's Colitis. 2012 Mar;6(2):160-73.
44. Shao L-M, Chen M-Y, Chen Q-Y, Cai J-T. Meta-analysis: the efficacy and safety of certolizumab pegol in Crohn's disease. Aliment Pharmacol Ther. 2009;29(6):605-14.
45. Targan SR, Hanauer SB, van Deventer SJ, Mayer L, Present DH, Braakman T, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. N Engl J Med. 1997 Oct 9;337(15):1029-35.
46. Present DH, Rutgeerts P, Targan S, Hanauer SB, Mayer L, van Hogezand RA, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med. 1999 May 6;340(18):1398-405.
47. Hyams J, Crandall W, Kugathasan S, Griffiths A, Olson A, Johanns J, et al; REACH Study Group. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. Gastroenterology. 2007 Mar;132(3):863-73;quiz 1165-6.
48. Behm BW, Bickston SJ. Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease. Cochrane Database of Systematic Reviews 2008, Issue 1. Art. No.: CD006893. DOI: 10.1002/14651858. CD006893.
49. Ruperto N, Lovell DJ, Quartier P, Paz E, Rubio-Pérez N, Silva CA, et al; Pediatric Rheumatology International Trials Organization; Pediatric Rheumatology Collaborative Study Group. Abatacept in children with juvenile idiopathic arthritis: a randomized, double-blind, placebo-controlled withdrawal trial. Lancet. 2008 Aug 2;372(9636):383-91.
50. Lovell D, Ruperto N, Goodman S, Reiff A, Jung L, Jarosova K, et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. N Engl J Med. 359;8:810-20.
51. Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. N Engl J Med. 2000;342:763-9.
52. Lovell DJ, Reiff A, Jones OY, Schneider R, Nocton J, Stein L, et al. Long-term safety and efficacy of etanercept in children with polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum. 2006;54:1987-94.
53. Horneff G, Schmeling H, Biedermann T, Foeldvari I, Ganser G, Girschick, et al. The German etanercept registry for treatment of juvenile idiopathic arthritis. Ann Rheum Dis. 2004 Dec; 63(12):1638-44.
54. De Benedetti, Brunner H, Ruperto N, Calvo I, Cuttica R, Schneider R, et al. Tocilizumab in patients with systemic juvenile idiopathic arthritis: efficacy data from the placebo-controlled 12-week part of the phase 3 TENDER trial [abstract]. Arthritis Rheum. 2010 Oct; 62(10 Suppl):596S. Abstract no. 1434.
55. Bagel J, Lynde C, Tyring S, Kricorian G, Shi Y, Klekotka P. Moderate to severe plaque psoriasis with scalp involvement: a randomized, double-blind, placebo-controlled study of etanercept. J Am Acad Dermatol. 2012 Jul;67(1):86-92.
56. Saurat JH, Stingl G, Dubertret L, Papp K, Langley RG, Ortonne JP, et al; CHAMPION Study Investigators. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs methotrexate vs placebo in patients with psoriasis (CHAMPION). Br J Dermatol. 2008 Mar;158(3):558-66.
57. Leonardi C, Kimball A, Papp K, Yeilding N, Guzzo C, Wang Y, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomized, double-blind, placebo-controlled trial (PHOENIX 1). Lancet. 2008;371:1665-74.
58. Papp K, Langley R, Lebwohl M, Krueger G, Szapary P, Yeilding N, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomized, double-blind, placebo-controlled trial (PHOENIX 2). Lancet. 2008;371:1675-84.
59. Griffiths CE, Strober BE, van de Kerkhof P, Ho V, Fidelus-Gort R, Yeilding N, Guzzo C, Xia Y, Zhou B, Li S, Dooley LT, Goldstein NH, Menter A; ACCEPT Study Group. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. N Engl J Med. 2010 Jan 14;362(2):118-28.
60. Schmitt J, Zhang Z, Wozel, G, Meurer M, Kirch W. Efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate-to-severe psoriasis: meta-analysis of randomized controlled trials. Br J Derm. 2008;159:513-26.
61. Genovese MC, Mease PJ, Thomson GTD, Kivitz AJ, Perdok RJ, Weinberg MA, et al. Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy. J Rheum. 2007;34:1040-50.

62. Mease PJ, Gladman DD, Ritchlin CT, Ruderman EM, Steinfeld SD, Choy EHS, et al. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis. Arthritis Rheum. 2005; 52(10):3279-89.
63. Mease PJ, Goffe BS, Metz J, VanderStoep A, Finck B, Burge DJ. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomized trial. The Lancet. 2000;356;385-90.
64. Mease PJ, Kivitz AJ, Burch FX, Siegel EL, Cohen SB, Ory P, et al. Etanercept treatment of psoriatic arthritis: safety, efficacy and effect on disease progression. Arthritis Rheum. 2004;50:2264-72.
65. Kavanaugh A, McInnes I, Mease P, Krueger GG, Gladman D, Gomez-Reino J, et al. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four week efficacy and safety results of a randomized, placebo-controlled study. Arthritis Rheum. 2009;60(4):976-86.
66. Antoni C, Krueger GG, de Vlam K, Birbara C, Beutler A, Guzzo C, et al; IMPACT 2 Trial Investigators. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. Ann Rheum Dis. 2005 Aug;64(8):1150-7.
67. Baranauskaite A, Raffayová H, Kungurov NV, Kubanova A, Venalis A, Helmle L, et al. Infliximab plus methotrexate is superior to methotrexate alone in the treatment of psoriatic arthritis in methotrexate-naive patients: the RESPOND study. Ann Rheum Dis. 2012 Apr;71(4):541-8.
68. Westhovens R, Robles M, Ximenes AC, Nayiager S, Wollenhaupt J, Durez P, et al. Clinical efficacy and safety of abatacept in methotrexate-naive patients with early rheumatoid arthritis and poor prognostic factors. Ann Rheum Dis. 2009 Dec;68(12):1870-7.
69. Genovese MC, Covarrubias A, Leon G, Mysler E, Keiserman M, Valente R, et al. Subcutaneous abatacept vs intravenous abatacept: A phase IIIb noninferiority study in patients with an inadequate response to methotrexate. Arthritis Rheum. 2011 Oct;63(10):2854-64.
70. Keystone EC, Kremer JM, Russell A, Box J, Abud-Mendoza C, Elizondo MG, et al. Abatacept in subjects who switch from intravenous to subcutaneous therapy: results from the phase IIIb ATTUNE study. Ann Rheum Dis. 2012 Jun;71(6):857-61.
71. Haraoui B, Cividino A, Stewart J, Guérette B, Keystone EC. Safety and effectiveness of adalimumab in a clinical setting that reflects Canadian standard of care for the treatment of rheumatoid arthritis (RA): results from the CanACT study. BMC Musculoskelet Disord. 2011 Nov 17;12:261.
72. van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, García Meijide JA, Wagner S, et al. Tofacitinib or adalimumab vs placebo in rheumatoid arthritis. N Engl J Med. 2012 Aug 9;367(6):508-19.
73. Keystone E, van der Heijde D, Mason D, Landewe R, van Vollenhoven R, Combe B, et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis. Arthritis Rheum. 2008;58(11):3319-29.
74. Smolen J, Landewe R, Mease P, Brzezicki J, Mason D, Luijtens K, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomized controlled trial. Ann Rheum Dis. 2009;68:797-804.
75. Fleishmann R, Vencovsky J, van Vollenhoven RF, Borenstein D, Box J, Coteur G, et al. Efficacy and safety of certolizumab pegol monotherapy every four weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. Ann Rheum Dis. 2009; 68:805-11.
76. Weinblatt ME, Fleischmann R, Huizinga TW, Emery P, Pope J, Massarotti EM, et al. Efficacy and safety of certolizumab pegol in a broad population of patients with active rheumatoid arthritis: results from the REALISTIC phase IIIb study. Rheumatology. 2012 Dec; 51(12):2204-14.
77. Tanaka Y, Harigai M, Takeuchi T, Yamanaka H, Ishiguro N, GO-FORTH Study Group, et al. Golimumab in combination with methotrexate in Japanese patients with active rheumatoid arthritis: results of the GO-FORTH study. Ann Rheum Dis. 2012 Jun;71(6):817-24.
78. Emery P, Fleischmann RM, Moreland LW, Hsia EC, Strusberg I, Durez P, et al. Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. Arthritis Rheum. 2009 Aug;60(8):2272-83.
79. Keystone EC, Genovese MC, Klareskog L, Hsia EC, Hall ST, Miranda PC, et al. Golimumab, a human antibody to tumor necrosis factor {alpha} given by monthly subcutaneous injections, in active

rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. Ann Rheum Dis. 2009 Jun;68(6):789-96.
80. Smolen JS, Kay J, Doyle MK, Landewé R, Matteson EL, Wollenhaupt J, et al; GO-AFTER study investigators. Golimumab in patients with active rheumatoid arthritis after treatment with tumor necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomized, double-blind, placebo-controlled, phase III trial. Lancet. 2009 Jul 18;374(9685):210-21.
81. Smolen JS, Kay J, Landewé RB, Matteson EL, Gaylis N, Wollenhaupt J,et al. Golimumab in patients with active rheumatoid arthritis who have previous experience with tumour necrosis factor inhibitors: results of a long-term extension of the randomized, double-blind, placebo-controlled GO-AFTER study through week 160. Ann Rheum Dis. 2012 Oct;71(10):1671-9.
82. Weinblatt ME, Bingham CO 3rd, Mendelsohn AM, Kim L, Mack M, Lu J, et al. Intravenous golimumab is effective in patients with active rheumatoid arthritis despite methotrexate therapy with responses as early as week 2: results of the phase 3, randomised, multicentre, double-blind, placebo-controlled GO-FURTHER trial. Ann Rheum Dis. 2013 Mar; 72(3):381-9.
83. Jones G, Sebba A, Gu J, Lowenstein MB, Calvo A, Gomez-Reino JJ, et al. Comparison of tocilizumab monotherapy vs methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: The AMBITION study. Ann Rheum Dis. 2010 Jan;69(1):88-96.
84. Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, Aleckck E, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomized trial. Lancet. 2008 Mar;371(9617):987-97.
85. Genovese M, McKay J, Nasonov E, Mysler EF, da Silva NA, Alecock E, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs. Arthritis and Rheumatism. 2008 Oct;58(10):2968-80.
86. Kremer JM, Blanco R, Brzosko M, Burgos-Vargas R, Halland AM, Vernon E, et al. cilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structural joint damage at one year. Arthritis Rheum. 2011 Mar;63(3):609-21.
87. Yazici Y, Curtis JR, Ince A, Baraf H, Malamet RL, Teng LL, Kavanaugh A. Efficacy of tocilizumab in patients with moderate to severe active rheumatoid arthritis and a previous inadequate response to disease-modifying antirheumatic drugs: the ROSE study. Ann Rheum Dis. 2012 Feb;71(2):198-205.
88. Emery P, Keystone E, Tony H, Cantagrel A, R van Vollenhoven, Sanchez A, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumor necrosis factor biological: results from a 24-week multicenter randomized placebo-controlled trial. Ann Rheum Dis. 2008 July;67:1516-23.
89. Dougados M, Kissel K, Sheeran T, Tak PP, Conaghan PG, Mola EM, et al. Adding tocilizumab or switching to tocilizumab monotherapy in methotrexate inadequate responders: 24-week symptomatic and structural results of a 2-year randomised controlled strategy trial in rheumatoid arthritis (ACT-RAY). Ann Rheum Dis. 2013 Jan;72(1):43-50.
90. Maxwell L, Singh JA. Abatacept for rheumatoid arthritis. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD007277.
91. Navarro-Sarabia F, Ariza-Ariza R, Hernandez-Cruz B, Villanueva I. Adalimumab for treating rheumatoid arthritis. Cochrane Database of Systematic Review 2005, Issue 3. Art. No.: CD005113. DOI: 10.1002/14651858.CD005113.pub2.
92. Blumenauer BTB, Cranney A, Burls A, Coyle D, Hochberg MC, Tugwell P, et al. Etanercept for the treatment of rheumatoid arthritis. Cochrane Database of Systematic Reviews 2003, Issue 3. Art. No.: CD004525. DOI: 10.1002/14651858.CD004525.
93. van Vollenhoven RF, Geborek P, Forslind K, Albertsson K, Ernestam S, Swefot study group et al. Conventional combination treatment vs biological treatment in methotrexate-refractory early rheumatoid arthritis: two year follow-up of the randomised, non-blinded, parallel-group Swefot trial. Lancet. 2012 May 5;379(9827):1712-20.
94. Wiens A, Correr CJ, Venson R, Grochocki MC, Otuki MF, Pontarolo R. A meta-analysis of the efficacy and safety of using infliximab for the treatment of rheumatoid arthritis. Clin Rheumatol. 2009 Dec;28(12):1365-73.

95. Nixon R, Bansback N, Brennan A. The efficacy of inhibiting tumor necrosis factor α and interleukin 1 in patients with rheumatoid arthritis: a meta-analysis and adjusted indirect comparisons. Rheumatology. 2007;46:1140-7.
96. Gabay C, Emery P, van Vollenhoven R, Dikranian A, Alten R, Pavelka K, et al. ADACTA Study Investigators. Tocilizumab monotherapy vs adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. Lancet. 2013 May 4; 381(9877):1541-50.
97. Weinblatt ME, Schiff M, Valente R, van der Heijde D, Citera G, Zhao C, et al. Head-to-head comparison of subcutaneous abatacept vs adalimumab for rheumatoid arthritis: findings of a phase IIIb, multinational, prospective, randomized study. Arthritis Rheum. 2013 Jan; 65(1):28-38.
98. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005 Dec 8;353(23):2462-76.
99. Hyams JS, Damaraju L, Blank M, Johanss J, Guzzo C, Winter H, et al. A randomized multicenter, open-label phase 3 study to evaluate the safety and efficacy of infliximab in pediatric patients with moderate to severe ulcerative colitis [abstract]. Gastroenterology. 2011 May;140(5 Suppl. 1):124S-5S. Abstract no. 747.
100. Reinisch W, Sandborn WJ, Hommes DW, D'Haens G, Hanauer S, Schreiber S, et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. Gut. 2011 Jun;60(6):780-7.
101. Sandborn WJ, van Assche G, Reinisch W, Colombel JF, D'Haens G, Wolf DC,et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2012 Feb;142(2):257-65.
102. Sibley CH, Plass N, Snow J, Wiggs EA, Brewer CC, King KA, et al. Sustained response and prevention of damage progression in patients with neonatal-onset multisystem inflammatory disease treated with anakinra: a cohort study to determine three- and five-year outcomes. Arthritis Rheum. 2012 Jul;64 (7):2375-86.
103. Drug Facts and Comparisons [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2013 [cited 2013 Jun]. Available from: http://online.factsandcomparisons.com.