Therapeutic Class Overview
Immunomodulators

Therapeutic Class

- **Overview/Summary:** This review will focus on oral and injectable immunomodulators. These agents are used for a variety of inflammatory and immunologic conditions which include: rheumatoid arthritis, psoriatic arthritis, plaque psoriasis, juvenile/systemic idiopathic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, hidradenitis suppurativa, uveitis and several cryopyrin-associated periodic syndromes. Specific Food and Drug Administration (FDA)-approved indications for each agent are summarized in Table 1. Overall, these agents achieve their therapeutic effect via several different mechanisms of action. The majority of oral and injectable immunomodulators inhibit the effect of proinflammatory cytokines, specifically interleukins or tumor necrosis factor (TNF)-α. Interleukin (IL) inhibitors include anakinra (Kineret®), canakinumab (Ilaris®), ixekizumab (Taltz®), rilonacept (Arcalyst®), secukinumab (Cosentyx®), tocilizumab (Actemra®), and ustekinumab (Stelara®) while the TNF-α inhibitors are adalimumab (Humira®), adalimumab-atto (Amjevita®), certolizumab pegol (Cimzia®), etanercept (Enbrel®), etanercept-szzs (Erelzi®), golimumab (Simponi®, Simponi ARIA®), infliximab (Remicade®), and infliximab-dyyb (Inflectra®). Abatacept (Orencia®) is a T-cell activation inhibitor, tofacitinib (Xeljanz®) is a Janus kinase inhibitor, and vedolizumab (Entyvio®) is an α4-β7 integrin receptor antagonist.[1-19]

Table 1. Current Medications Available in the Therapeutic Class[1-20]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Abatacept (Orencia®, Orencia ClickJet®)	Rheumatoid arthritis (adults only); polyarticular juvenile idiopathic arthritis/juvenile rheumatoid arthritis (age ≥six years)	Auto-injector: 125 mg/mL Prefilled syringe: 125 mg/mL Vial: 250 mg	-
Adalimumab (Humira®, Humira Pen®)	Rheumatoid arthritis (adults only); polyarticular juvenile idiopathic arthritis/juvenile rheumatoid arthritis (age ≥two years); psoriatic arthritis (adults only); ankylosing spondylitis (adults only); Crohn's disease (age ≥six years); ulcerative colitis (adults only); plaque psoriasis (adults only); uveitis (adults only); hidradenitis suppurativa (adults only)	Prefilled pen: 40 mg/0.8 mL Prefilled syringe: 10 mg/0.2 mL 20 mg/0.4 mL 40 mg/0.8 mL	-
Adalimumab-atto (Amjevita®, Amjevita SureClick®)	Rheumatoid arthritis (adults only); polyarticular juvenile idiopathic arthritis/juvenile rheumatoid arthritis (age ≥four years); psoriatic arthritis (adults only); ankylosing spondylitis (adults only); Crohn's disease (adults only); ulcerative colitis (adults only); plaque psoriasis (adults only)	Prefilled pen: 40 mg/0.8 mL Prefilled syringe: 20 mg/0.4 mL 40 mg/0.8 mL	-
Anakinra (Kineret®)	Rheumatoid arthritis (adults); cryopyrin-associated periodic syndromes – neonatal-onset multisystem inflammatory disease (no age restriction)	Prefilled syringe: 100 mg/0.67 mL	-
Canakinumab (Ilaris®)	Cryopyrin-associated periodic syndromes – familial cold autoinflammatory syndrome or Muckle-Wells syndrome (age ≥ four years); juvenile idiopathic	Vial: 180 mg (150 mg/mL)	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	arthritis (age ≥ two years)		
Certolizumab (Cimzia®)	Crohn's disease (adults only); rheumatoid arthritis (adults only); psoriatic arthritis (adults only); ankylosing spondylitis (adults only)	Prefilled syringe: 200 mg/mL Vial: 200 mg	-
Etanercept (Enbrel®, Enbrel SureClick®)	Rheumatoid arthritis (adults only); polyarticular juvenile idiopathic arthritis/juvenile rheumatoid arthritis (age ≥two years); psoriatic arthritis (adults only); ankylosing spondylitis (adults only); severe plaque psoriasis (adults only)	Auto-injector: 50 mg/mL Prefilled syringes: 25 mg/0.5 mL 50 mg/mL Vial: 25 mg	-
Etanercept-szzs (Erelzi®, Erelzi Sensoready Pen®)	Rheumatoid arthritis (adults only); polyarticular juvenile idiopathic arthritis/juvenile rheumatoid arthritis (age ≥two years); psoriatic arthritis (adults only); ankylosing spondylitis (adults only); severe plaque psoriasis (adults only)	Auto-injector: 50 mg/mL Prefilled syringes: 25 mg/0.5 mL 50 mg/mL	-
Golimumab (Simponi®, Simponi Aria®)	Rheumatoid arthritis (Simponi® and Simponi Aria® [adults only]); psoriatic arthritis (Simponi® [adults only]); ankylosing spondylitis (Simponi® [adults only]); ulcerative colitis (Simponi® [adults only])	Auto-injector (Simponi®): 50 mg/0.5 mL, 100 mg/mL Prefilled syringe (Simponi®): 50 mg/0.5 mL 100 mg/mL Vial* (Simponi Aria®): 50 mg/4 mL	-
Infliximab (Remicade®)	Crohn's disease (age ≥six years); ulcerative colitis (age ≥six years); rheumatoid arthritis (adults only); ankylosing spondylitis (adults only); psoriatic arthritis (adults only); plaque psoriasis (adults only)	Vial: 100 mg	-
Infliximab (Inflectra®)	Crohn's disease (age ≥six years); ulcerative colitis (adults only); rheumatoid arthritis (adults only); ankylosing spondylitis (adults only); psoriatic arthritis (adults only); plaque psoriasis (adults only)	Vial: 100 mg	-
Ixekizumab (Taltz®)	Plaque Psoriasis (adults)	Auto-injector: 80 mg/mL Prefilled Syringe: 80 mg/mL	-
Rilonacept	Cryopyrin-associated periodic syndromes – familial	Vial:	-

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
(Arcalyst®)	cold autoinflammatory syndrome or Muckle-Wells syndrome (age ≥12 years)	220 mg (80 mg/mL)	
Secukinumab (Cosentyx®, Cosentyx SensoReady Pen®)	Ankylosing Spondylitis (adults only); juvenile idiopathic arthritis/juvenile rheumatoid arthritis; plaque psoriasis (adults only)	Auto-injector: 150 mg/mL Prefilled syringe: 150 mg/mL	-
Tocilizumab (Actemra®)	Polyarticular juvenile idiopathic arthritis (age ≥ two years) ; systemic juvenile idiopathic arthritis/juvenile rheumatoid arthritis (age ≥ two years); rheumatoid arthritis (adults only)	Prefilled syringe*: 162 mg/0.9 mL Single use vial: 80 mg/4 mL 200 mg/10 mL 400 mg/20 mL	-
Tofacitinib (Xeljanz®, Xeljanz XR®)	Rheumatoid arthritis (adults only)	Extended-release tablet (Xeljanz XR®): 11 mg Tablet (Xeljanz®): 5 mg	-
Ustekinumab (Stelara®)	Plaque psoriasis (adults only); psoriatic arthritis (adults only)	Prefilled syringe: 45 mg/0.5 mL 90 mg/mL	-
Vedolizumab (Entyvio®)	Crohn's disease (adults only); ulcerative colitis (adults only)	Vial: 300 mg/20 mL	-

*Only indicated for use in patients with rheumatoid arthritis.

Evidence-based Medicine

- The immunomodulators have been shown to be effective for their respective Food and Drug Administration (FDA)-approved indications, particularly in conditions where patients were unresponsive or refractory to traditional 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 traditional DMARD medications, either as monotherapy or in combination with a traditional DMARD. Consistently, immunomodulators have shown greater improvement in symptoms over the respective comparators.[58-168]
- The safety and efficacy of adalimumab for the treatment of non-infectious intermediate, posterior and panuveitis was established in two randomized, double-blind, placebo-controlled clinical trials.[8] The total length of each study was not reported; however, data is reported up to 18 weeks. The primary efficacy endpoint in both studies was time to treatment failure, defined as the development of new inflammatory chorioretinal and/or inflammatory retinal vascular lesions, an increase in anterior chamber (AC) cell grade or vitreous haze (VH) grade or a decrease in best corrected visual acuity (BCVA), on or after week six (study one) or week two (study two). At week 18 in study one, 60 patients (54.5%) failed adalimumab on or after week six compared with 84 patients (78.5%) who received placebo (hazard ratio [HR], 0.50; 95% CI, 0.36 to 0.70). Median time to failure was 5.6 months (95% CI, 3.9 to 9.2) for patients who received adalimumab and 3.0 months (95% CI, 2.7 to 3.7) for patients who received placebo. At week 18 in study two, 45 patients (39.1%) failed adalimumab on or after week two compared with 61 patients (55.0%) who received placebo (HR,

0.57; 95% CI, 0.39 to 0.84). Median time to failure for the adalimumab group was not estimable as fewer than half of the at-risk subjects had an event. Median time to failure for the placebo group was 8.3 months (95% CI, 4.8 to 12.0).[8]

- The safety and efficacy of adalimumab in the treatment of hidradenitis suppurativa was established in two clinical trials PIONEER I and PIONEER II. Both were 36-week, multicenter, randomized, double-blind clinical trials with a total of 633 adult patients with moderate to severe (Hurley Stage II and III) hidradenitis suppurativa who had an inadequate response to a trial of oral antibiotics, total abscess and inflammatory nodule count of ≥3 and lesions present in ≥2 body areas. At 12 weeks, therapy was evaluated and effectiveness was defined as improvement in abscesses and inflammatory nodules at 12 weeks using the Hidradenitis Suppurativa Clinical Response (HiSCR). Treatment with adalimumab resulted in a significantly higher proportion of patients achieving clinical response compared to placebo (PIONEER I: 41.8% vs 26.0%, P=0.003; PIONEER II: 58.9% vs 27.6%, P<0.001), regardless of whether patients continued baseline antibiotic therapy or not, and regardless of their baseline Hurley stage. [58]
- The safety and efficacy of canakinumab in the treatment of systemic juvenile idiopathic arthritis was confirmed in two parallel clinical trials. At day 15 of the first trial, a total of 36 patients in the canakinumab group (84%), as compared with four in the placebo group (10%), had an adapted ACR30 response, which was sustained at day 29 (P<0.001). The second study concluded that There was a 64% relative reduction in the risk of flare for patients in the canakinumab group as compared to those in the placebo group (hazard ratio of 0.36; 95% CI: 0.17 to 0.75).[89]
- Secukinumab for the treatment of ankylosing spondylitis in patients 18 years of age or older was evaluated in two similar, double-blind, placebo controlled trials, MEASURE 1 and 2. The primary endpoint in both studies was the proportion of patients who had an Assessment of Spondyloarthritis International Society (ASAS) criteria improvement ≥20% (ASAS20) at week 16. In MEASURE 1, ASAS20 was significantly greater at week 16 in the secukinumab 150 mg group (61%) and 75 mg group (60%) than the placebo group (29%, P<0.001 for both vs placebo). In MEASURE 2, ASAS20 at week 16 was significantly greater in the secukinumab 150 mg group (61%) when compared to the placebo group (28%, P<0.001). There was no significant difference between the placebo group and the secukinumab 75 mg group (41%, P=0.10).[70]
- The safety and efficacy of secukinumab for the treatment of plaque psoriasis was evaluated in four multicenter, randomized, double-blind, placebo-controlled trials. The proportion of patients who achieved PASI 75 was statistically significantly greater in the secukinumab 300 mg group (81.6%, 77.1%, 75.9% and 86.7%) and secukinumab 150 mg group (71.6%, 67.0%, 69.5%, and 71.7%) compared with placebo (4.5%, 4.9%, 0%, 3.3%; P<0.001 for all secukinumab comparisons compared to placebo). In one of the trials, secukinumab 300 mg and 150 mg groups were compared to etanercept. Both secukinumab groups (77.1% and 67.0%) had a higher proportion of patients that achieved PASI 75 compared with etanercept (44%; P<0.001 for both secukinumab comparisons). Results were similar when IGA mod 2011 scores were compared.[5,100-0102]
- Secukinumab for the treatment of psoriatic arthritis in patients 18 years of age or older was evaluated in two similar, double-blind, placebo controlled trials, FUTURE 1 and 2. The primary endpoint for both studies was the proportion of patients who had an American College of Rheumatology (ACR) improvement ≥20% (ACR20 response) at week 24.[115,116] In FUTURE 1, ACR20 response at week 24 was significantly greater in the secukinumab 150 mg group (50%) and 75 mg group (50.5%) than the placebo group (17.3%, P<0.001 for both vs placebo).[115] In FUTURE 2, ACR20 response at week 24 was significantly greater in the secukinumab 300 mg group (54%), the secukinumab 150 mg group (51%) and the secukinumab 75 mg group (29%), when compared to placebo (15%, P<0.001 for 300 mg and 150 mg groups vs placebo and P=0.0399 for the 75 mg group vs placebo).[116]
- The safety and efficacy of ixekizumab, for the treatment of moderate-to-severe psoriasis, was established in three multicenter, randomized, double-blind, placebo-controlled trials in patients 18 years of age or older (UNCOVER-1, UNCOVER-2 and UNCOVER-3). Patients had to have body surface area (BSA) involvement ≥10%, static Physician's Global Assessment (sPGA) ≥3 and Psoriasis Area Severity Index (PASI) ≥12. The three trials evaluated two different induction phase doses of ixekizumab: 80 mg every two weeks and 80 mg every four weeks over 12 weeks. In addition, two of the trials (UNCOVER-1 and UNCOVER-2) evaluated two different maintenance phase doses of 80 mg every four weeks and 80 mg every 12 weeks over 48 weeks. Two of the trials

(UNCOVER-2 and UNCOVER-3) had etanercept as an active comparator arm during the induction phase.[93-95] In UNCOVER-1, treatment with ixekizumab, with an initial dose of 160 mg and subsequent induction period dosages of 80 mg every two weeks or 80 mg every four weeks resulted in significant improvement during the induction period. Across all efficacy end points, response rates associated with the dosage of 80 mg every two weeks were higher than those associated with the 80 mg every four weeks dose. In UNCOVER-1 and UNCOVER-2, for ixekizumab week 12 responders, efficacy was also maintained through the 60-week maintenance period.[93,94] In UNCOVER-2 and UNCOVER-3, treatment with both induction doses of ixekizumab (80 mg every two weeks and 80 mg every four weeks) demonstrated significantly greater efficacy than etanercept. Across all efficacy endpoints, response rates associated with 80 mg every two weeks was higher than those associated with 80 mg every four weeks.[93,95]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[22-48]
    - Support the use of the immunomodulators with respect to their Food and Drug Administration (FDA)-approved indications.
    - As more recent guidelines are published, the recommendations for use tumor necrosis factor-blockers earlier in therapy is becoming a more common occurance.[31,33,36] The adverse event profiles are similar across the class; however, routes of administration and dosing frequency may vary.
    - In general, no one agent is preferred over another.

- Other Key Facts:
    - The recently upheld Patient Protection and Affordable Care Act provides a legal framework for regulatory approval of biosimilar drugs.[53]
    - While none of the agents in this class are available generically, biosimilars for adalimumab, etanercept, and infliximab (i.e., Amjevita®, Erelzi®, and Inflectra®, respectively) were recently approved by the FDA and are not considered interchangeable with the reference product. In addition, none of the biosimilar agents are commercially available due to ongoing patent litigation.[9,13,16] Specifically, the manufacturer of adalimumab-atto (Amjevita®) does not expect biosimilar adalimumab to be available until at least 2018 .[169]
    - Dosing and administration varies both by drug and by dosage form.[1-19]
        - Oral: tofacitinib (tablet, extended-release tablet)
        - Intravenous Injection: abatacept, golimumab (Simponi ARIA®), infliximab, infliximab-dyyb, tocilizumab, and vedolizumab. Each is infused over 30 minutes, with the exception of infliximab and infliximab-dyyb, which are infused over two hours.
        - Most injectables require infrequent dosing, ranging from one to 12 weeks. Anakinra is the only injectable immunomodulator that requires daily dosing.
        - Tofacitinib immediate release is taken twice daily while the extended-release formulation can be taken once daily.
        - The majority of these agents have not been studied in renal or hepatic dysfunction.
        - Anakinra and tofacitinib require renal dose adjustment for creatinine clearances less than 30 mL or 40 mL, respectively.
        - Tofacitinib requires a dose adjustment in patients with moderate hepatic dysfunction, however, it has not been studied in patients with severe hepatic dysfunction and no dosing recommendations are available.
    - The safety and efficacy of these agents in pediatric patients varies based on drug and indication.[1-19]
        - Anakinra, canakinumab and rilonacept are FDA-approved for the treatment of Cryopyrin-Associated Periodic Syndromes. Anakinra does not have a minimum age associated with its use while canakinumab is approved for use in children aged four or older and rilonacept is approved for use in children 12 to 17 years old.
        - Safety and efficacy in pediatric patients to treat juvenile idiopathic arthritis has been established for abatacept (age six or older), adalimumab (age 2 to 17 years),

adalimumab-atto (age 4 to 17 years), canakinumab, etanercept (age two or older), etanercept-szzs (age two or older), and tocilizumab (all two or older).
    - Adalimumab, infliximab, and infliximab-dyyb have been FDA-approved for the treatment of pediatric Crohn's disease in pediatric patients aged six or older. Additionally, infliximab is also indicated to treat pediatric ulcerative colitis in pediatric patients 6 to 17 years of age.
- Anakinra is the only FDA-approved agent for neonatal-onset multisystem inflammatory disease. Canakinumab and rilonacept are the only FDA-approved agents for the treatment of familial cold autoinflammatory syndrome and Muckle-Wells syndrome.

References

1. Kineret® [package insert]. Stockholm (Sweden): Swedish Orphan Biovitrum AB; 2016 May.
2. Ilaris® [package insert]. East Hanover (NJ): Novartis Pharmaceuticals Corp.; 2016 Jul.
3. Arcalyst® [package insert]. Tarrytown (NY): Regeneron Pharmaceuticals, Inc.; 2014 Sep.
4. Actemra® [package insert]. South San Francisco (CA): Genetech, Inc.; 2014 Nov.
5. Cosentyx® [package insert]. East Hanover (NJ): Novartis Pharmaceuticals Corp.; 2016 Jan.
6. Taltz® [package insert]. Indianapolis (IN): Eli Lilly and Company; 2016 Mar.
7. Stelara® [package insert]. Horsham (PA): Janssen Biotech, Inc.; 2014 March.
8. Humira® [package insert]. North Chicago (IL): Abbvie Inc; 2016 Jul.
9. Amjevita® [package insert]. Thousand Oaks (CA): Amgen Inc; 2016 Sep.
10. Simponi® [package insert]. Horsham (PA): Janssen Biotech, Inc.; 2016 Jan.
11. Simponi Aria® [package insert]. Horsham (PA): Janssen Biotech, Inc.; 2016 Aug.
12. Remicade® [package insert]. Horsham (PA): Janssen Biotech, Inc; 2015 Nov.
13. Inflectra® [package insert]. Lake Forest (IL): Hospira; 2016 Apr.
14. Cimzia® [package insert]. Smyrna (GA): UCB, Inc.; 2016 Apr.
15. Enbrel® [package insert]. Thousand Oaks (CA): Immunex Corporation; 2015 Mar.
16. Erelzi® [package insert]. Princeton (NJ): Sandoz; 2016 Aug.
17. Orencia® [package insert]. Princeton (NJ): Bristol-Myers Squibb; 2016 Jun.
18. Xeljanz® [package insert]. New York (NY): Pfizer, Inc.; 2016 Feb.
19. Entyvio® [package insert]. Deerfield (IL): Takeda Pharmaceuticals America, Inc.; 2014 May.
20. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2015 [cited 2015 Jul 29]. Available from: http://www.clinicalpharmacology.com.
21. Grosser T, Smyth E, FitzGerald GA. Chapter 34. Anti-inflammatory, Antipyretic, and Analgesic Agents; Pharmacotherapy of Gout. In: Brunton LL, Chabner BA, Knollmann BC. eds. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12e. New York, NY: McGraw-Hill; 2011 [cited 2015 Jul 29]. Available from: http://accessmedicine.mhmedical.com/content.aspx?bookid=374&Sectionid=41266242.
22. 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.
23. 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.
24. 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).
25. 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
26. National Institute for Health and Care Excellence (NICE). TNF-alpha inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis. London (UK): National Institute for Health and Care Excellence (NICE); 2016 Feb.
27. 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.
28. 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.
29. 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.
30. Ringold S, Weiss PF, Beukelman T, Dewitt EM, Ilowite NT, Kimura Y, et al. 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications.
31. 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.
32. Gossec L, Smolen JS, Ramiro S, de Wit M, Cutolo M, Dougados M, et al. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. Ann Rheum Dis. 2016 Mar;75(3):499-510.
33. 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.

34. 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.
35. 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.
36. 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. J Am Acad Dermatol. 2009 Sep;61(3):451-85.
37. 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.
38. Singh JA, Saag KG, Bridges SL, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol. 2016;68(1):1-26.
39. 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.
40. 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.
41. 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
42. National Institute for Health and Care Excellence (NICE). Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed. London (UK): National Institute for Health and Care Excellence (NICE); 2016 Jan.
43. 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.
44. Press release AbbVie's Humira (adalimumab) receives first and only US Food and Drug Administration approval for moderate to severe Hidradenitis Suppurativa [press release on the Internet]. North Chicago (IL): Novartis: 2015 Sep 10 [cited 2015 Sep 17]. Available from: http://abbvie.mediaroom.com/2015-09-10-AbbVies-HUMIRA-Adalimumab-Receives-First-and-Only-U-S-Food-and-Drug-Administration-Approval-for-Moderate-to-Severe-Hidradenitis-Suppurativa.
45. Zouboulis CC, Desai N, Emtestam L, Hunger RE, Ioannides D, Juhász I, et al. European S1 guideline for the treatment of hidradenitis suppurativa/acne inversa. J Eur Acad Dermatol Venereol. 2015 Apr;29(4):619-44. doi: 10.1111/jdv.12966. Epub 2015 Jan 30.
46. Smith JR and Rosenbaum JT. Management of uveitis: a rheumatologic perspective. Arthritis Rheum. 2002;46(2):309-18.
47. Jabs DA, Rosenbaum JT, Foster CS, Holland GN, Jaffe GJ, Louie JS, et al. Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel. Am J Ophthalmol. 2000 Oct;130(4):492-513.
48. Levy-Clarke G, Jabs DA, Read RW, Rosenbaum JT, Vitale A, and Van Gelder RN. Expert panel recommendations for the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders. Ophthalmology. 2014;121(3):785-96.
49. Rambhatla PV, Lim HW, Hamzavi I. A Systematic Review of Treatments for Hidradenitis Suppurativa. Arch Dermatol. 2011 Dec;E1-E8.
50. Margesson LJ, F William Danby. Treatment of hidradenitis suppurativa. In: Berman RS, Dellavalle RP (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2015 [cited 2015 Sep 17]. Available from: http://www.utdol.com/utd/index.do.
51. Alikhan A, Lynch PJ, Eisen DB. Hidradenitis suppurativa: a comprehensive review. J Am Acad Dermatol. 2009 Apr;60(4):539-61.
52. Zouboulis C, Deasai N, Emtestam L. European S1 guideline for the treatment of hidradenitis suppurativa/acne inversa. J Eur Acad Derm Ven. 2015 Jan;29(4):619-44.
53. 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.
54. Karampetsou MP, Liossis SN, Sfikakis PP. TNF-α antagonists beyond approved indications: stories of success and prospects for the future. QJM. 2010 Dec;103(12):917-28.
55. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2014 June 15]. Available from: http://clinicaltrials.gov.
56. Micromedex® Healthcare Series [intranet database]. Version 5.1. Greenwood Village, (CO): Thomson Healthcare[cited 2014 Jun 15]. Available from: http://www.thomsonhc.com/.
57. Drug Facts and Comparisons [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2014 [cited 2014 June 15]. Available from: http://online.factsandcomparisons.com.
58. Kimball AB, Okun MM, Williams DA, Gottlieb AB, Papp KA, Zouboulis CC, et al. Two Phase 3 Trials of Adalimumab for Hidradenitis Suppurativa. N Engl J Med. 2016 Aug 4;375(5):422-34.
59. 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.
60. Landewé R, Braun J, Deodhar A, Dougados M, Maksymowych WP, Mease PJ, et al. Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomised placebo-controlled Phase 3 study. Ann Rheum Dis. 2013 Nov 14.
61. 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.

62. 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.
63. 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.
64. 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.
65. 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.
66. 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.
67. 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.
68. Machado MA, Barbosa MM, Almeida AM, de Araújo VE, Kakehasi AM, Andrade EI, et al. Treatment of ankylosing spondylitis with TNF blockers: a meta-analysis. Rheumatol Int. 2013 Sep;33(9):2199-213.
69. Wang Y, Wang H, Jiang J, Zhao D, and Liu Y. Comparative Efficacy and Acceptability of Anti-TNF-Alpha Therapy in Ankylosing Spondylitis: A Mixed-Treatments Comparison. Cell Physiol Biochem. 2016 Sep 19;39(5):1679-1694.
70. Baeten D, Sieper J, Braun J, Baraliakos X, Dougados M, Emery P, et al. Secukinumab, an Interleukin-17A Inhibitor, in Ankylosing Spondylitis. N Engl J Med. 2015 Dec 24;373(26):2534-48. doi: 10.1056/NEJMoa1505066.
71. 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.
72. 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.
73. 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.
74. 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.
75. 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.
76. 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.
77. 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.
78. 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.
79. Behm BW, Bickston SJ. Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD006893.
80. Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Eng J Med. 2013;369:711-21..
81. Sands BE, Feagan BG, Rutgeerts P, Colombel JF, Sandborn WJ, Richmond Sy, et al. Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment had failed. Gastroenterology. 2014 May 21; [Epub ahead of print].
82. 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.
83. 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.
84. 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.
85. 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.
86. 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.
87. 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.
88. Brunner H, Ruperto N, Zuber Z, Keane C, Harari O, Kenwright A, et al. Efficacy and safety of tocilizumab in patients with polyarticular juvenile idiopathic arthritis: data from a phase 3 trial [abstract]. Arthritis Rheum. 2012 Oct;64(10 Suppl):S682. Abstract no. 1597.
89. Ruperto N, Brunner HI, Quartier P, Constantin T, Wulffraat N, Horneff G, et al. Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. N Engl J Med. 2012 Dec 20;367(25):2396-406. doi: 10.1056/NEJMoa1205099.
90. 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.

91. 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.
92. de Vries AC, Thio HB, de Kort WJ, Opmeer BC, van der Stok HM, de Jong EM, et al. A prospective randomised controlled trial comparing infliximab and etanercept in patients with moderate to severe chronic plaque type psoriasis Psoriasis Infliximab versus Etanercept Comparison Evaluation, the PIECE study. Br J Dermatol. 2016 Jul 15.
93. Taltz® (ixekizumab) product dossier. Eli Lilly. Data on file.
94. Gordon K, Blauvelt A, Langley RG, et al. Ixekizumab for Treatment of Moderate-to-Severe Plaque Psoriasis: 12-Week Results From a Phase 3 Study (UNCOVER-1). Presented at: 23rd World Congress of Dermatology; June 8–13, 2015; Vancouver, Canada.
95. Griffiths CE, Reich K, Lebwohl M, et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. Lancet. 2015;386(9993):541-551.
96. 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.
97. 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.
98. 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.
99. 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.
100. Langley RG, Elewski BE, Lebwohl M, Reich K, Griffiths CE, Papp K, et al. Secukinumab in plaque psoriasis--results of two phase 3 trials. N Engl J Med. 2014 Jul 24;371(4):326-38. doi: 10.1056/NEJMoa1314258. Epub 2014 Jul 9.
101. Blauvelt A, Prinz JC, Gottlieb AB, Kingo K, Sofen H, Ruer-Mulard M, et al. Secukinumab administration by pre-filled syringe: efficacy, safety and usability results from a randomized controlled trial in psoriasis (FEATURE). Br J Dermatol. 2015 Feb;172(2):484-93. doi: 10.1111/bjd.13348. Epub 2014 Dec 11.
102. Paul C, Lacour JP, Tedremets L, Kreutzer K, Jazayeri S, Adams S, et al. Efficacy, safety and usability of secukinumab administration by autoinjector/pen in psoriasis: a randomized, controlled trial (JUNCTURE). J Eur Acad Dermatol Venereol. 2015 Jun;29(6):1082-90. doi: 10.1111/jdv.12751. Epub 2014 Sep 22.
103. Blauvelt A, Reich K, Tsai TF, Tyring S, Vanaclocha F, Kingo K, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate-to-severe plaque psoriasis up to 1 year: Results from the CLEAR study. J Am Acad Dermatol. 2016 Sep 20. pii: S0190-9622(16)30624-7.
104. Strober BE, Bissonnette R, Fiorentino D, Kimball AB, Naldi L, Shear NH, et al. Comparative effectiveness of biologic agents for the treatment of psoriasis in a real-world setting: Results from a large, prospective, observational study (Psoriasis Longitudinal Assessment and Registry [PSOLAR]). J Am Acad Dermatol. 2016 May;74(5):851-61.e4.
105. Gomez-Garcia F, Epstein D, Isla-Tejera B, Lorente A, Velez Garcia-Nieto A, and Ruano J. Short-term efficacy and safety of new biologic agents targeting IL-23/Th17 pathway for moderate to severe plaque psoriasis: a systematic review and network meta-analysis. Br J Dermatol. 2016 Jun 13.
106. 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.
107. 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.
108. Mease PJ, Fleischmann R, Deodhar AA, Wollenhaupt J, Khraishi M, Kielar D, et al. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). Ann Rheum Dis. 2013 Oct 16.
109. van der Heijde D, Fleischmann R, Wollenhaupt J, Deodhar A, Kielar D, Woltering F, et al. Effect of different imputation approaches on the evaluation of radiographic progression in patients with psoriatic arthritis: results of the RAPID-PsA 24-week phase III double-blind randomised placebo-controlled study of certolizumab pegol. Ann Rheum Dis. 2013 Oct 15.
110. 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.
111. 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.
112. 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.
113. 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.
114. 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.
115. Mease PJ, McInnes IB, Kirkham B, Kavanaugh A, Rahman P, van der Heijde D, et al. Secukinumab Inhibition of Interleukin-17A in Patients with Psoriatic Arthritis. N Engl J Med. 2015 Oct;373(14):1329-39. doi: 10.1056/NEJMoa1412679.
116. McInnes IB, Mease PJ, Kirkham B, Kavanaugh A, Ritchlin CT, Rahman P, et al. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2015 Sep 19;386(9999):1137-46. doi: 10.1016/S0140-6736(15)61134-5. Epub 2015 Jun 28.

117. McInnes IB, Kavanaugh A, Gottlieb AB, Puig L, Rahman P, Ritchlin C, et al. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. Lancet. 2013 Aug 31;382(9894):780-9.
118. 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.
119. 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.
120. 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.
121. 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.
122. Keystone EC, van der Heijde D, Kavanaugh A, Kupper H, Liu S, Guérette B, Mozaffarian N. Clinical, functional, and radiographic benefits of longterm adalimumab plus methotrexate: final 10-year data in longstanding rheumatoid arthritis. J Rheumatol. 2013 Sep;40(9):1487-97.
123. 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.
124. 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.
125. 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.
126. 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.
127. 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.
128. Tanaka Y, Harigai M, Takeuchi T, Yamanaka H, Ishiguro N, Yamamoto K, et al. Clinical efficacy, radiographic progression, and safety through 156 weeks of therapy with subcutaneous golimumab in combination with methotrexate in Japanese patients with active rheumatoid arthritis despite prior methotrexate therapy: final results of the randomized GO-FORTH trial. Mod Rheumatol. 2016 Jul;26(4):481-90.
129. 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.
130. 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.
131. 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.
132. 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.
133. 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.
134. 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.
135. 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.
136. 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.
137. 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.
138. 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.
139. 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.

140. 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.
141. Maxwell L, Singh JA. Abatacept for rheumatoid arthritis. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD007277.
142. Navarro-Sarabia F, Ariza-Ariza R, Hernandez-Cruz B, Villanueva I. Adalimumab for treating rheumatoid arthritis. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD005113.
143. Mertens M, Singh JA. Anakinra for rheumatoid arthritis. Cochrane Database Syst Rev. 2009 Jan 21;(1):CD005121.
144. Blumenauer BTB, Cranney A, Burls A, Coyle D, Hochberg MC, Tugwell P, et al. Etanercept for the treatment of rheumatoid arthritis. Cochrane Database Syst Rev. 2003;(4):CD004525.
145. 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.
146. 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.
147. 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.
148. 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.
149. 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.
150. Schiff M, Weinblatt ME, Valente R, van der Heijde D, Citera G, Elegbe A, et al. Head-to-head comparison of subcutaneous abatacept vs adalimumab for rheumatoid arthritis: two-year efficacy and safety findings from AMPLE trial. Ann Rheum Dis. 2013 Aug 20.
151. Fleischmann R, Kremer J, Cush J, Schulze-Koops H, Connell CA, Bradley JD, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. N Engl J Med. 2012 Aug 9;367(6):495-507.
152. 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.
153. Burmester GR, Blanco R, Charles-Schoeman C, Wollenhaupt J, Zerbini C, Benda B, et al. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. Lancet. 2013 Feb 9;381(9865):451-60.
154. van der Heijde D, Tanaka Y, Fleischmann R, Keystone E, Kremer J, Zerbini C, et al. Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study. Arthritis Rheum. 2013 Mar;65(3):559-70.
155. Kremer J, Li ZG, Hall S, Fleischmann R, Genovese M, Martin-Mola E, et al. Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. Ann Intern Med. 2013 Aug 20;159(4):253-61.
156. He Y, Wong AY, Chan EW, Lau WC, Man KK, Chui CS, et al. Efficacy and safety of tofacitinib in the treatment of rheumatoid arthritis: a systematic review and meta-analysis. BMC Musculoskelet Disord. 2013 Oct 18;14:298.
157. Berhan A. Efficacy, safety and tolerability of tofacitinib in patients with an inadequate response to disease modifying anti-rheumatic drugs: a meta-analysis of randomized double-blind controlled studies. BMC Musculoskelet Disord. 2013 Nov 26;14:332.
158. 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.
159. 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.
160. 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.
161. 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.
162. Sandborn WJ, Feagan BG, Marano C, Zhang H, Strauss R, Johanns J, et al. Subcutaneous Golimumab Induces Clinical Response and Remission in Patients With Moderate-to-Severe Ulcerative Colitis. Gastroenterology. 2013 Jun 2.
163. Sandborn WJ, Feagan BG, Marano C, Zhang H, Strauss R, Johanns J, et al. Subcutaneous Golimumab Maintains Clinical Response in Patients With Moderate-To-Severe Ulcerative Colitis. Gastroenterology. 2013 Jun 14.
164. Feagan BG, Rutgeerts P, Sands BE, Hanauer S, Colombel JF, Sandborn WJ, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Eng J Med. 2013;369(8):699-710.
165. 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.
166. Lachmann HJ, Kone-Paut I, Keummerle-Deschner JB, et al. Use of Canakinumab in the Cryopyrin Associated Periodic Syndrome. N Engl J Med 2009;360:2416-25.
167. Jaffe GJ, Dick AD, Brezin AP, Nguyen QD, Thorne JE, Kestelyn P, et al Adalimumab in Patients with Active Noninfectious Uveitis. N Engl J Med. 2016 Sep 8;375(10):932-43.
168. Nguyen QD, Merrill PT, Jaffe GJ, Dick AD, Kurup SK, Sheppard J, et al. Adalimumab for prevention of uveitic flare in patients with inactive non-infectious uveitis controlled by corticosteroids (VISUAL II): a multicentre, double-masked, randomised, placebo-controlled phase 3 trial. Lancet. 2016 Sep 17;388(10050):1183-92.
169. Edney A. Moves Closer to Selling Competitor for AbbVie's Humira. Bloomberg News. July 12, 2016. [cited 2012 Mar 30] Available from: http://www.bloomberg.com/news/articles/2016-07-12/amgen-moves-closer-to-selling-competitor-for-abbvie-s-humira.