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**VERMONT**  
**Department of Vermont Health Access**

***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- $\alpha$ , etanercept is a fusion protein that binds to both TNF- $\alpha$  and TNF- $\beta$ , while certolizumab pegol is a pegylated antibody-binding fragment TNF- $\alpha$  blocker.<sup>1,2</sup>

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 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. With the exception of juvenile idiopathic arthritis, infliximab is approved for the same indications as adalimumab and has an additional indication for 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.<sup>3-7</sup>

Anakinra is an interleukin (IL)-1receptor antagonist which 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.<sup>8</sup> For rheumatoid arthritis, anakinra demonstrates modest efficacy compared to TNF-blocking agents.<sup>9</sup> 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.<sup>10</sup> 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. Ustekinumab, the third IL antagonist, 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.<sup>11</sup>

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.<sup>12</sup>

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. As a number of the agents in this class were recently brought to market, or recently had their FDA approved indications expanded, they have not yet been incorporated in clinical practice guidelines.<sup>13</sup>

Because these drugs are made from living organisms, not chemicals, and are extremely difficult to duplicate, Congress has struggled to create regulations to approve generic versions of these agents.

Although at this time none of the agents in this class have a generic formulation, the Heath Care Reform bill that was passed this year gives the FDA a pathway to approve biogenerics.

**Medications**

**Table 1. Medications Included Within Class Review**

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

**Indications**

**Table 2. Food and Drug Administration Approved Indications<sup>3-8,10-12</sup>**

Generic Name	Ankylosing Spondylitis	Crohn's Disease	Juvenile Idiopathic Arthritis	Plaque Psoriasis	Psoriatic Arthritis	Rheumatoid Arthritis	Ulcerative Colitis
Abatacept			✓			✓ *	
Adalimumab	✓	✓ †	✓	✓ ‡	✓	✓	
Anakinra						✓ §	
Certolizumab		✓				✓	
Etanercept	✓		✓	✓ ‡	✓ ¶	✓	
Golimumab	✓				✓	✓ #	
Infliximab	✓	✓		✓ ‡	✓	✓ #	✓
Tocilizumab						✓ **	
Ustekinumab				✓ ‡			

\*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, alone or in combination with DMARDs other than tumor necrosis factor inhibitors.  
 || In patients who have had an inadequate response to conventional therapy.  
 ¶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.

Etanercept is also 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 and Behcet's syndrome.<sup>11</sup>

**Pharmacokinetics****Table 3. Pharmacokinetics**<sup>3-8,10-12,15</sup>

Generic Name	Bioavailability (%)	Time to Peak Concentration	Elimination Half-Life
Abatacept	100	Not reported	8 to 25 days
Adalimumab	64	131±56 hours	10 to 20 days
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 13 days
Ustekinumab	Not reported	7.0 to 13.5 days	14.9 to 45.6 days

**Clinical Trials**

Food and Drug Administration (FDA) 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 Ankylosing Spondylitis (ASAS) response of  $\geq 20\%$  (primary endpoint) with adalimumab (58% vs 21% with placebo;  $P < 0.001$ ). 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 ( $P < 0.001$ ) at week 12. This response was sustained through week 24, with 42% in the adalimumab group achieving a  $\geq 50\%$  improvement in BASDAI score compared to 15% with placebo ( $P < 0.001$ ).<sup>16</sup> An open-label extension study, evaluating the long-term safety and efficacy of etanercept in patients with AS, has been conducted. Safety endpoints included adverse events, serious adverse events, serious infection, and death, while efficacy endpoints included ASAS 20 response, ASAS 5/6 response, and partial remission rates. After up to 192 weeks of treatment, the most common adverse events were injection site reactions, headache and diarrhea. A total of 71% of patients were ASAS 20 responders at week 96 and 81% 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.<sup>19</sup> The FDA approval of golimumab in 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.<sup>20</sup> The efficacy of infliximab in the treatment of AS was demonstrated in 12- and 24-week double-blind placebo-controlled trials. There were significantly more patients that achieved a 50% BASDAI score in the infliximab group compared to placebo at 12 weeks ( $P < 0.0001$ ).<sup>21</sup> At 24 weeks, significantly more patients in the infliximab group achieved ASAS 20 compared to placebo ( $P < 0.001$ ).<sup>22</sup>

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.<sup>23</sup> Shao et al performed a meta-analysis evaluating certolizumab use over 12 to 26 weeks for the treatment of Crohn's disease and demonstrated that the agent was associated with an increased rate of induction of clinical response (relative risk [RR], 1.36;  $P = 0.004$ ) and remission (RR, 1.95;  $P < 0.0001$ ) over placebo. However, risk of infection was higher with certolizumab use.<sup>24</sup> In a trial evaluating infliximab for induction of remission, significantly more patients achieved remission at four weeks with infliximab compared to placebo ( $P < 0.005$ ).<sup>25</sup> In a trial by Present et al, significantly more patients treated with infliximab 5 and 10 mg/kg had a reduction of  $\geq 50\%$  in the number of fistulas compared to placebo ( $P = 0.002$  and  $P = 0.02$ , respectively).<sup>26</sup> 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.<sup>27</sup> Additionally, 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;  $P=0.000019$ ; adalimumab, data not reported) over placebo in recipient's with Crohn's disease. Adalimumab and infliximab also had a steroid-sparing effect.<sup>28</sup>

In a trial by Ruperto et al in pediatric patients (6 to 17 years) with juvenile idiopathic arthritis, the patients treated with placebo had significantly more flares than the patients treated with abatacept ( $P=0.0003$ ). The time to flare was significantly different favoring abatacept ( $P=0.0002$ ).<sup>29</sup> Adalimumab was studied in a group of patients (4 to 17 years of age) with active juvenile rheumatoid arthritis who had previously received treatment with nonsteroidal anti-inflammatory drugs (NSAIDs). Patients were stratified according to methotrexate (MTX) use and received 24 mg/m<sup>2</sup> (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 method 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.<sup>30</sup> 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%;  $P=0.003$ ).<sup>31</sup> 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.<sup>32</sup>

More than 2,200 patients were enrolled in two published pivotal phase III trials that served as the primary basis for the FDA approval of ustekinumab in psoriasis. PHOENIX 1 and PHOENIX 2 enrolled patients with moderate to severe psoriasis to randomly receive ustekinumab 45 mg, 90 mg or placebo at weeks 0, four and every 12 thereafter.<sup>34,35</sup> In PHOENIX 1, patients who were initially randomized to ustekinumab at week 0 and achieved long-term response (at least 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 Psoriasis Area and Severity Index (PASI) 75 compared to placebo 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 ( $P<0.0001$ ).<sup>34</sup> 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 mg and 90 mg compare to 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 such response to changes in dosing intensity in partial responders treated with 45 mg. Adverse events were similar between groups.<sup>35</sup> 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 mg (67.5%) and 90 mg (73.8%) compared to etanercept (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).<sup>36</sup> 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

placebo ( $P < 0.0001$ ). The withdrawal rate was 0.5% with adalimumab, 0.4 to 0.5% with etanercept and 1.3% with infliximab.<sup>37</sup>

In two trials, psoriatic arthritis patients receiving adalimumab 40 mg every other week achieved an ACR 20 at a higher rate than with placebo. Thirty-nine percent in the active treatment group vs 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 ( $P < 0.001$ ).<sup>38,39</sup> Adalimumab use was also 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;  $P < 0.001$ ).<sup>39</sup> 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 with 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 vs 0% ( $P = 0.0154$ ) and 13% ( $P < 0.0001$ ) of placebo-treated patients.<sup>40</sup> In a second trial, the mean annualized rate of change in the mTSS with etanercept was -0.03 unit, compared with 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 with 3% of placebo patients ( $P = 0.001$ ). Additionally, 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%;  $P < 0.001$ ).<sup>41</sup> 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 with 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.<sup>42</sup> In a trial by Antoni et al, more infliximab treated patients achieved ACR20 at weeks 12 and 24 compared to placebo ( $P < 0.001$ ).<sup>43</sup>

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. A significantly greater proportion of patients on certolizumab 400 mg plus MTX at weeks 0, 2, and 4 then 200 or 400 mg every two weeks attained greater ACR 20, ACR 50 and ACR 70 responses over placebo and MTX after 24 weeks ( $P \leq 0.01$ ). The response rates were sustained with active treatment over 52 weeks.<sup>44</sup> The mTSS' were significantly lower with certolizumab in combination with MTX therapy compared to MTX in combination with placebo.<sup>44,45</sup> Fleischmann, et al evaluated certolizumab monotherapy vs 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.<sup>46</sup> The FDA approval of golimumab for rheumatoid arthritis was based on three multicenter, double-blind, randomized, controlled trials in 1,542 patients  $\geq 18$  years of age 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 vs patients treated with MTX alone.<sup>47-49</sup> Additionally, the golimumab 50 mg groups demonstrated a greater improvement compared to the control groups in the change in mean Health Assessment Questionnaire Disability Index.<sup>48,49</sup> 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 given 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.<sup>50-54</sup> AMBITION evaluated the safety and efficacy of tocilizumab monotherapy versus MTX in patients with active rheumatoid arthritis for whom previous treatment with MTX/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 when 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. Additionally, more patients treated with tocilizumab achieved remission at week 24 when compared to patients treated with MTX.<sup>50</sup> The LITHE evaluated 1,196 patients with moderate to severe rheumatoid arthritis who had an inadequate response to MTX. Results have not been published to date, however a Roche media release announced that patients treated with tocilizumab had three times less progression of joint damage, measured by Total Sharp Score, when compared to patients treated with MTX alone. Significantly more patients treated with tocilizumab 8 mg/kg were also found to achieve remission at six months as compared to MTX (33% vs 4%), and these rates continued to increase over time to one year (47% vs 8%). These benefits were maintained or improved at two years.<sup>51</sup> 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. The findings showed that ACR 20 was seen in significantly more patients receiving tocilizumab than in those receiving placebo at week 24 ( $P<0.001$ ). Significantly more patients treated with tocilizumab achieved ACR 50 and ACR 70 responses at week 24 as well ( $P<0.001$ ). Greater improvements in physical function, as measured by the Health Assessment Questionnaire-Disability Index (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).<sup>52</sup> TOWARD 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 than 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).<sup>53</sup> RADIATE 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 mg/kg 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. This study found 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.<sup>54</sup> 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% 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.<sup>55</sup> 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 (95% CI, not reported), 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.<sup>56</sup> A second 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).<sup>9</sup> In a third Cochrane review etanercept was compared to MTX or placebo in adult patients with rheumatoid arthritis, and found that at six months 64% of individuals on etanercept 25 mg twice

weekly attained an ACR 20 vs 15% of patients on either MTX alone or placebo (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.<sup>57</sup> 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 placebo (RR, 1.87; 95% CI, 1.43 to 2.45). These effects were similar in with 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).<sup>58</sup> 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 treatment 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;  $P < 0.05$ ).<sup>59</sup>

Infliximab is the only immunomodulator indicated for the treatment of ulcerative colitis. Two trials, (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 the infliximab 5 mg/kg and 10 mg/kg treated patients 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.<sup>60</sup>

**Table 4. Clinical Trials**

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<b>Ankylosing Spondylitis</b>				
<p>van der Heijde et al<sup>16</sup></p> <p>Adalimumab 40 mg every other week</p> <p>vs</p> <p>placebo</p> <p>Patients were allowed to continue MTX, NSAIDs, prednisone or prednisone equivalent and SSZ.</p>	<p>DB, MC, RCT</p> <p>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</p>	<p>N=315</p> <p>24 weeks</p>	<p>Primary: ASAS 20 response at week 12</p> <p>Secondary: ASAS 20 response at week 24, measures of disease activity, spinal mobility and function, ASAS partial remission</p>	<p>Primary: An ASAS 20 response was attained in 58% of participants taking adalimumab vs 21% of participants taking placebo at week 12 (<math>P&lt;0.001</math>).</p> <p>Secondary: A significantly greater ASAS 20 response was also noted at week 24 with adalimumab vs placebo (52% vs 18%; <math>P&lt;0.001</math>).</p> <p>Adalimumab treatment, 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%; <math>P&lt;0.001</math>) which was sustained through week 24 (42% vs 15%; <math>P&lt;0.001</math>).</p> <p>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 (<math>P&lt;0.001</math>) and 45% vs 12% and 39% and 13% at week 24 (<math>P&lt;0.001</math>), respectively.</p> <p>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 (<math>P&lt;0.001</math>).</p>
<p>Gorman et al<sup>17</sup></p> <p>Etanercept 25 mg twice a week</p> <p>vs</p> <p>placebo</p> <p>Patients were allowed to continue stable doses of DMARDs, NSAIDs, and oral corticosteroids.</p>	<p>DB, RCT</p> <p>Patients ≥18 years of age with active inflammatory AS based on the modified New York criteria, despite accepted treatments</p>	<p>N=40</p> <p>4 months</p>	<p>Primary: Measures of morning stiffness, spinal pain, functioning, patient's global assessment of disease activity, joint swelling</p> <p>Secondary: Physician's global assessment of</p>	<p>Primary: A response to treatment was detected in 80% of individuals receiving adalimumab as opposed to 30% receiving placebo (<math>P=0.004</math>).</p> <p>Primary endpoints were reported as follows for the adalimumab and placebo groups, respectively: duration of morning stiffness, 25.0±78.9 minutes vs 60.0±65.0 minutes (<math>P&lt;0.001</math>); scores for nocturnal spinal pain (0=none to 100=most severe), 15.0±24.3 vs 38.0±27.8 (<math>P&lt;0.001</math>); mean swollen joint scores (0=none to 3=severe), 1.6±3.8 vs 3.7±7.6 (<math>P=0.17</math>); patient's global assessment of disease activity (0=none to 5=very severe), 2.0±0.6 vs 3.0±0.9 (<math>P&lt;0.001</math>); and the BASFI scores (0=none to 10=severe limitations), 2.2±2.1 vs 3.1±3.0 (<math>P&lt;0.001</math>).</p> <p>Secondary:</p>

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			disease activity, measures of spinal mobility, scores for enthesitis and peripheral-joint tenderness, ESR and CRP levels, adverse events	<p>Differences in a number of secondary outcomes did reach statistical significance among those taking etanercept compared to placebo including, physician's global assessment of disease activity (23.0±10.6; <math>P&lt;0.001</math>), chest expansion (3.5±1.9 cm vs 2.9±1.7 cm; <math>P=0.006</math>), Modified Newcastle Enthesis Index, which is a measure of 17 entheses on a 4 point pain scale (0.0±3.0 vs 1.5±8.0; <math>P=0.001</math>), ESR level (8.5±12.8 mm/hour vs 16.5±18.7 mm/hour; <math>P&lt;0.001</math>) and CRP level (0.7±1.1 mg/dL vs 2.0±2.8 mg/dL; <math>P=0.003</math>).</p> <p>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.</p>
<p>Calin et al<sup>18</sup></p> <p>Etanercept 25 mg twice a week</p> <p>vs</p> <p>placebo</p> <p>Patients were allowed to continue stable doses of DMARDs (HCQ, MTX, or SSZ) one NSAID, and oral corticosteroids (≤10 mg prednisone).</p>	<p>DB, MC, RCT</p> <p>Patients 18 to 70 years of age with active AS based on the modified New York criteria</p>	<p>N=84</p> <p>12 weeks</p>	<p>Primary: ASAS 20 response</p> <p>Secondary: ASAS 50 response, ASAS 70 response, individual components of ASAS, BASDAI, acute phase reactants, spinal mobility tests, safety</p>	<p>Primary: ASAS 20 response was found in 60.0% of etanercept patients compared to 23.1% of placebo patients at 12 weeks (<math>P&lt;0.001</math>).</p> <p>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 (<math>P&lt;0.001</math>). ASAS 70 was significantly different between groups up until week eight (28.9% with etanercept vs 7.7% with placebo; <math>P&lt;0.05</math>).</p> <p>The changes in the individual ASAS components were reported as follows for etanercept and placebo: spinal inflammation, 43.3% vs 15.9% (<math>P=0.003</math>); nocturnal and total pain, 43.1% vs 6.2% (<math>P=0.000</math>); patient's global assessment, 37.0% vs 12.6% (<math>P=0.11</math>); functional impairment (BASFI), 35.4% vs 3.4% (<math>P=0.000</math>); BASDAI composite score, 43.6% vs 13.6% (<math>P=0.001</math>); and BASDAI fatigue score, 42.6% vs -4.9% (<math>P=0.000</math>).</p> <p>Injection site reactions occurred more frequently with etanercept treatment compared to placebo (33% vs 15%; <math>P&lt;0.05</math>).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Davis et al<sup>19</sup></p> <p>Etanercept 25 mg twice weekly until week 72, then 50 mg once weekly</p> <p>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.</p>	<p>ES, OL</p> <p>Patients 18 to 70 years of age with active AS based on the modified New York criteria</p>	<p>N=257</p> <p>Up to 192 weeks</p>	<p>Primary: Safety (adverse events, serious adverse events, infections, serious infections, death) and efficacy (ASAS 20 response, ASAS 5/6 response, partial remission rates)</p> <p>Secondary: Not reported</p>	<p>Primary: After up to 192 weeks of treatment the most common adverse events were injection site reactions, headache and diarrhea; no deaths were reported.</p> <p>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.</p> <p>Injection site reactions were reported in 22.2% of patients which lead to the withdrawal of 0.4% of patients.</p> <p>A total of 71% of patients were considered ASAS 20 responders at week 96 and 81% were considered responders at week 192.</p> <p>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.</p> <p>Placebo patients who switched to etanercept in the OL extension showed similar rates of efficacy maintenance.</p> <p>Secondary: Not reported</p>
<p>Inman et al<sup>20</sup></p> <p>Golimumab 50 mg once every 4 weeks</p> <p>vs</p> <p>golimumab 100 mg once every 4 weeks</p> <p>vs</p>	<p>DB, MC, PC, RCT</p> <p>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</p>	<p>N=356</p> <p>24 weeks</p>	<p>Primary: ASAS 20 response at week 14</p> <p>Secondary: Not reported</p>	<p>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%; <math>P \leq 0.001</math>).</p> <p>All individual components of the ASAS response criteria were significantly improved in the golimumab 50 mg group vs the placebo group at week 14.</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>placebo</p> <p>Patients who were on stable doses of HCQ, MTX, NSAID, oral corticosteroid and/or SSZ were permitted in the study.</p>				
<p>Braun et al<sup>21</sup></p> <p>Infliximab 5 mg/kg at weeks 0, 2 and 6</p> <p>vs</p> <p>placebo</p> <p>Concurrent use of NSAIDs not to exceed the baseline dose was allowed.</p>	<p>DB, MC, PC, RCT</p> <p>Adult patients (mean age of 40) with AS based on the modified New York criteria with BASDAI score <math>\geq 4</math> and spinal pain score of <math>\geq 4</math></p>	<p>N=70</p> <p>12 weeks</p>	<p>Primary: Improvement from baseline in BASDAI by 50% at week 12</p> <p>Secondary: Improvement from baseline in spinal pain, BASFI, BASMI, SF-36, CRP, ESR</p>	<p>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 placebo (9%; 95% CI, 3 to 22). The difference between the groups was significant starting at week two and continuing through until 12 weeks (<math>P &lt; 0.0001</math>).</p> <p>Secondary: At week 12, the infliximab treated patients had significant mean improvement from baseline in spinal pain (<math>P &lt; 0.0001</math>), BASFI (<math>P &lt; 0.0023</math>), BASMI (<math>P &lt; 0.0001</math>), CRP (<math>P &lt; 0.0001</math>) and ESR (<math>P &lt; 0.0001</math>); while there was no significant 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 (<math>P &lt; 0.0001</math>); however, only the improvement in the physical component was significantly greater than placebo (<math>P &lt; 0.0001</math>).</p> <p>More patients reported infections in the infliximab group (51%) compared to placebo (35%; difference, 16%; 95% CI, -7 to 40; <math>P = 0.227</math>). More patients in the infliximab group experienced serious adverse events and were withdrawn from the study compared to placebo (3 vs 0; <math>P = 0.239</math>).</p>
<p>van der Heijde et al<sup>22</sup> (ASSERT)</p> <p>Infliximab 5 mg/kg at weeks 0, 2, 6, 12 and 18</p>	<p>MC, PC, RCT</p> <p>Adult patients (median age of 40) with AS based on the modified New</p>	<p>N=279</p> <p>24 weeks</p>	<p>Primary: Proportion of patients with ASAS 20 at week 24</p>	<p>Primary: After 24 weeks, significantly more patients were ASAS 20 responders in the infliximab group (61.2%) compared to placebo (19.2%; <math>P &lt; 0.001</math>). The difference was significant at week two and continued to week 24.</p> <p>Secondary:</p>

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vs placebo  Concurrent NSAIDs, acetaminophen or tramadol were allowed during the study.	York criteria for at least three months with a BASDAI score of $\geq 4$ , spinal pain assessment score of $\geq 4$ on a VAS and a normal chest radiograph within three months and negative tuberculosis screening		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) and quality of life (SF-36)	<p>Over the 24-week study period, there were significantly more ASAS 40 responders in the infliximab group compared to placebo (<math>P &lt; 0.001</math>). At 24 weeks 47% were ASAS 40 responders compared to 12% with placebo (<math>P &lt; 0.001</math>). There were significantly more infliximab treated patients with ASAS 5/6 (49%) compared to placebo (8%; <math>P &lt; 0.001</math>). There was a significantly greater proportion of patients that achieved a partial ASAS response in the infliximab group (22.4%) compared to placebo (1.3%; <math>P &lt; 0.001</math>).</p> <p>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 (<math>P &lt; 0.001</math>). The patients in the infliximab treated group had a significantly greater median improvement in BASFI compared to placebo (<math>P &lt; 0.001</math>). There was a significantly greater median improvement in BASMI in the infliximab group compared to placebo (<math>P = 0.019</math>). The infliximab treated patients had a significantly greater median improvement in swollen joint count compared to placebo (<math>P = 0.019</math>). There was a significantly greater improvement in the physical component of the SF-36 in the infliximab group compared to placebo (<math>P &lt; 0.001</math>); there was no significant difference in the mental component (<math>P = 0.547</math>).</p> <p>There were a higher proportion of patients experiencing at least one adverse event in the infliximab group compared to placebo (82.2% vs 72.0%). The number of patients reporting at least one infection was higher in the infliximab group compared to placebo (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 either group, pharyngitis, rhinitis, and increased liver enzymes were greater in the infliximab group.</p>
<b>Crohn's Disease</b>				
Ma et al <sup>23</sup>  Adalimumab	SR  OL and RCT cohort studies in patients	N=1,810 (15 trials)  8 weeks to 4	Primary: Short-term and long-term efficacy	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

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	with Crohn's disease who had lost response and were intolerable or refractory to infliximab	years	Secondary: Adverse events	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.
Shao et al <sup>24</sup>  Certolizumab  vs  placebo	MA  DB, RCTs in patients with moderate to severe Crohn's disease	N=1,040 (3 trials)  12 to 26 weeks	Primary: Clinical response (a decrease of $\geq 100$ points from baseline in CDAI score) and clinical remission (CDAI score of $\leq 150$ points) at week four  Secondary: Safety	Primary: Certolizumab use 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%).
Targan et al <sup>25</sup>  Infliximab 5 mg/kg  vs  infliximab 10 mg/kg  vs  infliximab 20 mg/kg  vs  placebo	DB, MC, PC, RCT  Adult patients with Crohn's disease for six months with CDAI scores between 220 and 400 and previously receiving mesalamine (for $\geq 8$ weeks and a stable dose for four weeks), corticosteroids (maximum of 40 mg/day for $\geq 8$	N=108  12 weeks	Primary: Decrease from baseline in CDAI of $\geq 70$ 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 placebo ( $P<0.001$ ).  At week two, 61% of the infliximab treated patients had a response compared to 17% with placebo ( $P<0.001$ ). More patients were in remission (CDAI score $<150$ ) in the infliximab group at two weeks (27%) compared to placebo (4%; $P=0.06$ ). At week four, 33% of the infliximab treated patients were in remission compared to 4% with placebo ( $P<0.005$ ). The response rate remained significantly higher in the infliximab treated patients through the 12 weeks of the study (41%) compared to placebo (12%; $P=0.008$ ); however, the remission rate was not significantly different at 12 weeks (24% vs 8%; $P=0.31$ ).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	weeks and a stable dose for two weeks), mercaptopurine or azathioprine (for ≥6 months and stable dose for eight weeks)			
<p>Present et al<sup>26</sup>                      Infliximab 5 mg/kg at weeks 0, 2 and 6                      vs                      infliximab 10 mg/kg at weeks 0, 2 and 6                      vs                      placebo</p>	<p>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 Crohn's disease</p>	<p>N=94                      18 weeks</p>	<p>Primary:                      Reduction of ≥50% from baseline in number of draining fistulas at two or more consecutive study visits                      Secondary:                      Number of patients with a complete response (absence of any draining fistula at two consecutive visits), length of time to beginning of response and duration of response</p>	<p>Primary:                      There were significantly greater response rates in the infliximab 5 mg/kg (68%) and 10 mg/kg (56%) groups compared to placebo (26%; <math>P=0.002</math> and <math>P=0.02</math>, respectively). The response rates were not significantly different between the two infliximab groups.                      Secondary:                      More patients in the infliximab 5 mg/kg (55%) and 10 mg/kg groups had complete response compared to placebo (13%; <math>P=0.001</math> and <math>P=0.04</math>, respectively). In the infliximab group, the median time to the onset of response was two weeks compared to six weeks with placebo. The duration of response was approximately three months in patients that reached the primary endpoint.                      The most frequently reported adverse events in the infliximab group were headache, abscess, upper respiratory tract infection and fatigue.</p>
<p>Hyams et al<sup>27</sup>                      (REACH)                      Infliximab 5 mg/kg at weeks 0, 2 and 6; those</p>	<p>MC, OL, RCT                      Patients 6 to 17 years of age with a PCDAI &gt;30 at</p>	<p>N=112                      46 weeks</p>	<p>Primary:                      Clinical response at week 10 (decrease from baseline to week</p>	<p>Primary:                      At week 10, 88.4% of patients responded to the induction regimen (95% CI, 82.5 to 58.9).                      Secondary:</p>

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<p>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</p> <p>vs</p> <p>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</p>	<p>baseline and initiated immunomodulator therapy (azathioprine, mercaptopurine or MTX) <math>\geq 8</math> weeks before screening and at stable dose for two weeks</p>		<p>10 in PCDAI of <math>\geq 15</math> points and total PCDAI of no more than 30)</p> <p>Secondary: Maintenance of clinical response and remission (PCDAI <math>\leq 10</math>)</p>	<p>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 (<math>P=0.002</math> and <math>P&lt;0.001</math>, respectively). At week 10, there was a significant decrease in PCDAI score compared to baseline that continued at weeks 30 and 54 (all <math>P&lt;0.001</math>). There was a significant decrease in corticosteroid use at week 10 compared to baseline that continued at weeks 30 to 54 (all <math>P&lt;0.001</math>).</p> <p>Adverse events were similar between the two groups. Infection was the most common adverse event in both treatment groups.</p>
<p>Behm et al<sup>28</sup></p> <p>Adalimumab, certolizumab, or infliximab</p> <p>vs</p> <p>placebo</p>	<p>SR</p> <p>RCTs including patients <math>\geq 18</math> years of age with Crohn's disease who had a clinical response or clinical remission with a TNF-<math>\alpha</math> blocker, or patients with Crohn's disease in remission but unable to wean corticosteroids, who were then randomized to maintenance of remission with a TNF-<math>\alpha</math> blocker or placebo</p>	<p>N=3,586 (9 trials)</p> <p>Duration varied</p>	<p>Primary: Clinical remission, clinical response, steroid-sparing effects</p> <p>Secondary: Not reported</p>	<p>Primary: Adalimumab demonstrated the ability to maintain clinical remission and clinical response (RR, 2.69; 95% CI, 1.88 to 3.86; <math>P&lt;0.00001</math>), while also having a steroid-sparing effect (data specific to clinical remission and steroid-sparing effect not reported).</p> <p>Certolizumab was shown to maintain both clinical remission (RR, 1.68; 95% CI, 1.30 to 2.16; <math>P=0.000072</math>) and clinical response (RR, 1.74; 95% CI, 1.41 to 2.13; <math>P&lt;0.00001</math>) compared to placebo.</p> <p>Infliximab maintained fistula healing (RR, 1.87; 95% CI, 1.15 to 3.04; <math>P=0.012</math>) and clinical remission (RR, 2.50; 95% CI, 1.64 to 3.80; <math>P=0.000019</math>) and clinical response (RR, 1.66; 95% CI, 1.00 to 2.76; <math>P=0.0046</math>) and achieved a steroid sparing effect (RR, 3.13; 95% CI, 1.25 to 7.81; <math>P=0.014</math>) all compared to placebo.</p> <p>Secondary: Not reported</p>

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<b>Juvenile Idiopathic/Rheumatoid Arthritis</b>				
<p>Ruperto et al<sup>29</sup></p> <p>Abatacept 10 mg/kg every 28 days</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, RCT (OL lead in period)</p> <p>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</p>	<p>N=122 (RCT); 190 (OL lead in period)</p> <p>6 months (4-month OL lead in)</p>	<p>Primary: Time to flare</p> <p>Secondary: Proportion of patients with a disease flare, changes in baseline in each of six core response variables and assessment of safety and tolerability</p>	<p>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 (<math>P=0.0002</math>).</p> <p>Secondary: There was a significantly greater proportion of patients that experienced a flare in the placebo group compared to abatacept (53% vs 12%; <math>P=0.0003</math>). The HR for patients in the abatacept to experience a flare compared to placebo was 0.31 (95% CI, 0.16 to 0.59).</p> <p>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 (<math>P=0.1712</math>), 77% of the abatacept group and 52% of the placebo group improved by ≥50% as measured by ACR (<math>P=0.0071</math>), 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% with placebo (<math>P=0.0195</math>).</p> <p>Adverse events were similar between the groups.</p>
<p>Lovell et al<sup>30</sup></p> <p>Adalimumab 24 mg/m<sup>2</sup> (maximum of 40 mg) every other week with or without MTX</p> <p>vs</p> <p>placebo</p> <p>Patients were stratified according to MTX use and</p>	<p>DB, MC, OL, RCT</p> <p>Patients 4 to 17 years of age with active JRA who had previously received treatment with NSAIDs</p>	<p>N=171</p> <p>48 weeks</p>	<p>Primary: Rate of disease flare in patients not receiving MTX</p> <p>Secondary: ACR Pedi 30, 50, 70, and 90 responses at week 48, and safety</p>	<p>Primary: Among those not receiving MTX, flares occurred in 43% receiving adalimumab and 71% receiving placebo (<math>P=0.03</math>). In the patients receiving MTX, flares occurred in 37% and 65% of participants in the adalimumab and placebo groups, respectively (<math>P=0.02</math>).</p> <p>Secondary: In patients receiving MTX, ACR Pedi 30, 50, 70, and 90 responses were reported in 63% vs 38% (<math>P=0.03</math>), 63% vs 35% (<math>P=0.03</math>), 63% vs 27% (<math>P=0.002</math>) and 42% vs 27% (<math>P=0.17</math>), respectively.</p> <p>For those participants not taking MTX therapy, ACR Pedi 30, 50, 70, and 90 responses were detected in 57% vs 32% (<math>P=0.06</math>), 53% vs 32%</p>

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<p>received OL adalimumab 24 mg/m<sup>2</sup> (maximum of 40 mg) every other week for 16 weeks.</p> <p>The patients with an ACR Pedi 30 response at week 16 were then randomly assigned to receive adalimumab or placebo.</p>				<p>(<i>P</i>=0.10), 47% vs 29% (<i>P</i>=0.16) and 30% vs 18% (<i>P</i>=0.28), respectively.</p> <p>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.</p>
<p>Lovell et al<sup>31</sup></p> <p>Etanercept 0.4 mg/kg twice weekly</p> <p>vs</p> <p>placebo</p> <p>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 assigned to either etanercept or placebo.</p> <p>Concurrent analgesics, NSAIDs, or oral corticosteroids (≤10 mg/day of prednisone or equivalent) were allowed.</p>	<p>DB, MC, OL, RCT</p> <p>Patients 4 to 17 years of age with active polyarticular JRA despite treatment with NSAIDs and MTX ≥10 mg/m<sup>2</sup>/week</p>	<p>N=69</p> <p>7 months</p>	<p>Primary: Rate of disease flare</p> <p>Secondary: Median time to flare, safety</p>	<p>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 etanercept (81% vs 28%; <i>P</i>=0.003).</p> <p>Secondary: The median time to flare was reported as 116 days in the active treatment arm compared to 28 days with placebo (<i>P</i>&lt;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.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Lovell et al<sup>32</sup></p> <p>Etanercept 0.4 mg/kg (maximum of 25 mg) twice weekly</p> <p>Intraarticular and soft-tissue injections of corticosteroids were permitted after 12 continuous weeks of etanercept.</p> <p>MTX could be added to treatment after one year.</p> <p>Concurrent analgesics, NSAIDs, or oral corticosteroids (<math>\leq 10</math> mg/day of prednisone or equivalent) were allowed.</p>	<p>Ongoing ES, MC, OL by Lovell et al<sup>22</sup> (updated efficacy and safety results from the study)</p>	<p>N=58</p> <p>Median of 4 years</p>	<p>Primary: JRA 30% DOI</p> <p>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</p>	<p>Primary: Thirty-two patients were available for efficacy analysis after four years with 94% meeting the JRA 30% DOI.</p> <p>Secondary: Approximately 94 and 78% of participants met the JRA 50% DOI and JRA 70% DOI, respectively.</p> <p>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 18.0 from 88.0 at baseline and the median patient's assessment of pain score was lowered to 0.9 from 3.6 at baseline.</p> <p>Duration of morning stiffness was only assessed through one year and was reported as 5.0 minutes at month 12 (from 53.0 minutes at baseline).</p> <p>After four years, there were five reports of serious adverse events and 0.03 serious infections (requiring intravenous antibiotics or hospitalizations)/patient year.</p>
<p>Horneff et al<sup>33</sup></p> <p>Etanercept 0.4 mg/kg twice weekly</p> <p>Combination treatment with MTX or oral corticosteroids was permitted</p>	<p>MC, OL</p> <p>Patients 4-17 years of age with active idiopathic juvenile arthritis despite treatment with MTX</p>	<p>N=322</p> <p>Up to 48 months, median of 12 months</p>	<p>Primary: Change in indices of disease activity, 30%, 50% and 70% improvement in idiopathic juvenile arthritis</p> <p>Secondary: Safety</p>	<p>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 7.0 (SD, 23.0) minutes from 45.0 (SD, 65.0) 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). Patient's and physician's global assessment scores (on a scale of 0=best to 100=worst) were reduced to 16.0 (SD, 18.0) and 20.0 (SD, 23.0) from 56.0 (SD, 27.0) and 67.0 (SD, 25.0), 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>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p><math>P &lt; 0.0001</math> with the exception of swollen joint count at 30 months; <math>P &lt; 0.0005</math> and duration of morning stiffness; <math>P &lt; 0.001</math>).</p> <p>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.</p>
<b>Psoriasis</b>				
<p>Leonardi et al<sup>35</sup> (PHOENIX-2)</p> <p>Ustekinumab 45 mg vs ustekinumab 90 mg vs placebo</p> <p>Each group received a subcutaneous injection at week 0, 4, and then every 12 weeks thereafter.</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients <math>\geq 18</math> years of age with a diagnosis of plaque psoriasis for <math>\geq 6</math> months, candidates for phototherapy or systemic therapy, had a baseline PASI score of 12 or higher, and had <math>\geq 10\%</math> BSA involvement</p>	<p>N=766  <math>\leq 76</math> weeks</p>	<p>Primary: Proportion of patients achieving PASI 75 at week 12</p> <p>Secondary: Not reported</p>	<p>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 (63.9%; 95% CI, 57.8 to 70.1; <math>P &lt; 0.0001</math> and 63.3%; 95% CI, 57.1 to 69.4; <math>P &lt; 0.0001</math> for the 45 and 90 mg vs placebo, respectively).</p> <p>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 (<math>P = 0.0008</math> for the 45 mg group and <math>P = 0.0005</math> for the 90 mg group vs placebo) and PASI 75 by week four (<math>P &lt; 0.0001</math> for each comparison vs placebo).</p> <p>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).</p> <p>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 (<math>P &lt; 0.0001</math>), The median percentage improvement in PASI remained stable to at least week 76.</p> <p>Secondary: Not reported</p>
<p>Papp et al<sup>27</sup> (PHOENIX-2)</p> <p>Ustekinumab 45 mg</p>	<p>DB, MC, PC, RCT</p> <p>Patients <math>\geq 18</math> years of age, with a diagnosis of plaque</p>	<p>N=1,230  <math>\leq 52</math> weeks</p>	<p>Primary: Proportion of PASI 75 responders at week 12</p>	<p>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; <math>P &lt; 0.0001</math> and 72.0%; 95% CI, 67.5 to 76.5; <math>P &lt; 0.0001</math> for 45 and 90 mg vs placebo, respectively).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>vs ustekinumab 90 mg vs placebo</p> <p>Each group received an injection at week 0, 4, and then every 12 weeks thereafter.</p> <p>Partial responders at week 28 were re-randomized to continue dosing every 12 weeks or escalate to dosing every 8 weeks.</p>	<p>psoriasis for ≥6 months, were candidates for phototherapy or systemic therapy, had a baseline PASI score of 12 or higher, and had ≥10% BSA involvement</p>		<p>Secondary: Proportion of 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</p>	<p>Secondary: A greater proportion of patients in each ustekinumab group achieved a 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; <math>P&lt;0.0001</math> for the 45 mg vs placebo and 68.6%; 95% CI, 63.9 to 73.4; <math>P&lt;0.0001</math> for the 90 mg vs placebo).</p> <p>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; <math>P&lt;0.0001</math> for the 45 mg group and -9.0; 95% CI, -9.0 to -8.0; <math>P&lt;0.0001</math> for the 90 mg group vs placebo).</p> <p>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 with 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.</p> <p>Among the re-randomized partial responders, dosing intensification did not result in greater efficacy compared with 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; <math>P=0.468</math>).</p> <p>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 visits vs 1.54 visits; <math>P=0.210</math>), 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 visits vs 1.58 visits; <math>P=0.014</math>) 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; <math>P=0.004</math>).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Griffiths et al<sup>36</sup></p> <p>Etanercept 50 mg twice weekly</p> <p>vs</p> <p>ustekinumab 45 mg at weeks 0 and 4</p> <p>vs</p> <p>ustekinumab 90 mg at weeks 0 and 4</p> <p>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.</p>	<p>MC, PG, RCT</p> <p>Patients ≥18 years of age, with a diagnosis of plaque psoriasis for ≥6 months, were candidates for phototherapy or systemic therapy, had a baseline PASI score of ≥12, had a score of ≥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</p>	<p>N=903</p> <p>12 weeks</p>	<p>Primary: PASI 75 at week 12</p> <p>Secondary: Physician's global assessment score of 0 or 1, PASI 90, difference between PASI at week 12 and 12 weeks after retreatment</p>	<p>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 with etanercept (56.8%; <i>P</i>=0.01 vs ustekinumab 45 mg; <i>P</i>&lt;0.001 vs ustekinumab 90 mg).</p> <p>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 (65.1% on ustekinumab 45 mg and 70.6% on ustekinumab 90 mg vs 49.0% on etanercept; <i>P</i>&lt;0.001 for each comparison vs etanercept).</p> <p>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 (<i>P</i>&lt;0.001, for each comparison vs etanercept).</p> <p>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.</p> <p>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.</p>
<p>Schmitt et al<sup>37</sup></p> <p>Adalimumab, cyclosporine, efalizumab*, etanercept, or infliximab</p>	<p>MA</p> <p>RCTs in patients with moderate to severe psoriasis</p>	<p>16 trials</p> <p>Duration varied</p>	<p>Primary: PASI 75</p> <p>Secondary: Tolerability</p>	<p>Primary: Compared with placebo a greater proportion of patients receiving adalimumab (RD, 64%; 95% CI, 61 to 68; <i>P</i>&lt;0.00001), cyclosporine (RD, 33%; 95% CI, 13 to 52; <i>P</i>&lt;0.0009), efalizumab (RD, 24%; 95% CI, 19 to 30; <i>P</i>&lt;0.00001), etanercept 50 mg twice weekly (RD, 44%; 95% CI, 40 to 48; <i>P</i>&lt;0.00001) and etanercept 25 mg twice weekly (RD, 30%; 95% CI, 25 to</p>

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vs placebo				<p>35; <math>P&lt;0.00001</math>) achieved PASI 75 response. The infliximab group had the greatest response (RD, 77%; 95% CI, 72 to 81; <math>P&lt;0.00001</math>).</p> <p>Secondary: Average monthly rates of serious adverse events were 0.5% with 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.</p> <p>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.</p>
<b>Psoriatic Arthritis</b>				
<p>Genovese et al<sup>38</sup></p> <p>Adalimumab 40 mg every other week</p> <p>vs</p> <p>placebo</p> <p>Patients who completed a 12 week blinded phase could elect to receive OL therapy.</p>	<p>DB, MC, RCT</p> <p>Patients with moderately to severely active PsA with an inadequate response to DMARD therapy</p>	<p>N=100</p> <p>24 weeks</p>	<p>Primary: ACR 20 response at week 12</p> <p>Secondary: ACR 50 response, ACR 70 response, PsARC scores, assessments of disability, psoriatic lesions, quality of life</p>	<p>Primary: At week 12, an ACR 20 response was achieved by 39% of adalimumab patients vs 16% of placebo patients (<math>P=0.012</math>).</p> <p>Secondary: ACR 50 and ACR 70 responses were also achieved by significantly more patients on adalimumab (25% and 14%, respectively) compared to placebo at week 12 (2% and 0%, respectively; <math>P=0.001</math> for ACR 50 and <math>P=0.013</math> for ACR 70).</p> <p>A PsARC response was achieved by 51% of adalimumab patients vs 24% of placebo patients (<math>P=0.007</math>).</p> <p>At Week 12, measures of skin lesions (-3.7 units with adalimumab vs -0.3 units with placebo; <math>P\leq 0.001</math>) and disability were statistically significantly improved with adalimumab.</p> <p>Adalimumab use was associated with significant mean improvements from baseline in components of quality of life assessments such as physical functioning (<math>P=0.027</math>), bodily pain (<math>P=0.007</math>), general health (<math>P=0.017</math>) and</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>mental health (<math>P=0.009</math>).</p> <p>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.</p> <p>Serious adverse events occurred at a similar frequency during therapy with placebo (4.1%), blinded adalimumab (2.0%), and OL adalimumab (3.1%).</p> <p>Adalimumab use was not associated with serious infections.</p>
<p>Mease et al<sup>39</sup></p> <p>Adalimumab 40 mg every other week</p> <p>vs</p> <p>placebo</p> <p>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.</p>	<p>DB, MC, PG, RCT</p> <p>Patients <math>\geq 18</math> 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</p>	<p>N=315</p> <p>24 weeks</p>	<p>Primary: ACR 20 response at 12 weeks, change in mTSS at week 24</p> <p>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</p>	<p>Primary: At week 12, 58% of the adalimumab treated patients achieved an ACR 20 response, compared with 14% of the placebo-treated patients (<math>P&lt;0.001</math>).</p> <p>The mean change in the mTSS of radiographic structural damage was -0.2 in patients receiving adalimumab and 1.0 in those receiving placebo (<math>P&lt;0.001</math>).</p> <p>Secondary: ACR 20 response at 24 weeks was 57% with adalimumab and 15% with placebo (<math>P&lt;0.001</math>).</p> <p>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 (<math>P&lt;0.001</math> for both outcomes).</p> <p>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 (<math>P&lt;0.001</math>).</p> <p>PsARC response was achieved with adalimumab in 62% at 12 weeks and 60% at 24 weeks compared to 26% and 23% on placebo, respectively (<math>P</math> value not reported).</p> <p>Among the 69 adalimumab treated patients evaluated with the PASI, 59%</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>achieved a PASI 75 improvement response at 24 weeks, compared with 1% of placebo-treated patients (<math>P&lt;0.001</math>).</p> <p>Disability and quality of life measures were also significantly improved with adalimumab treatment compared with placebo (<math>P&lt;0.001</math> 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 groups at both week 12 (<math>P=0.708</math>) and week 24 (<math>P=0.288</math>).</p> <p>The rates of overall and serious adverse events were similar among groups.</p>
<p>Mease et al<sup>40</sup></p> <p>Etanercept 25 mg twice weekly</p> <p>vs</p> <p>placebo</p> <p>Patients on stable doses of corticosteroids (equal to <math>\leq 10</math> mg/day of prednisone) or MTX were permitted to continue therapy.</p>	<p>DB, RCT</p> <p>Patients 18 to 70 years of age with active PsA despite NSAID therapy</p>	<p>N=60</p> <p>12 weeks</p>	<p>Primary: PsARC, PASI 75 at 12 weeks</p> <p>Secondary: ACR 20 response, ACR 50 response, ACR 70 response, PASI 75, improvement in target psoriasis lesions</p>	<p>Primary: Eighty-seven percent of etanercept treated patients met the PsARC, compared with 23% of placebo-controlled patients (<math>P&lt;0.0001</math>).</p> <p>PASI 75 improvement was detected in 26% of etanercept-treated patients vs none of placebo treated patients (<math>P=0.0154</math>).</p> <p>Secondary: The ACR 20 was achieved by 73% of etanercept-treated patients compared with 13% of placebo-treated patients (<math>P&lt;0.0001</math>), while approximately 48% and 5% achieved an ACR 50 response and 12% and 0% achieved an ACR 70 response, respectively (<math>P=0.0001</math> for ACR 50; <math>P</math> value not reported for ACR 70).</p> <p>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 with none of the placebo-treated patients (<math>P=0.0154</math>).</p> <p>Median target lesion improvements were 50% and 0%, for etanercept and placebo, respectively (<math>P=0.0004</math>).</p> <p>There were no significant differences detected in the rate of adverse events between groups.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Mease et al<sup>41</sup></p> <p>Etanercept 25 mg twice weekly</p> <p>vs</p> <p>placebo</p> <p>Patients who completed a 24 week blinded phase could elect to receive OL therapy in a 48 week extension.</p> <p>Patients on stable doses of corticosteroids (equal to ≤10 mg/day of prednisone) or MTX were permitted to continue therapy.</p>	<p>DB, MC, RCT</p> <p>Patients 18 to 70 years of age with active PsA despite NSAID therapy</p>	<p>N=205</p> <p>72 weeks</p>	<p>Primary: ACR 20 response</p> <p>Secondary: ACR 50 response, ACR 70 response, change in mTSS, PsARC, PASI 75, SF-36 Health Survey, HAQ, safety</p>	<p>Primary: At 12 weeks, 59% of etanercept patients met the ACR 20 improvement criteria for joint response, compared with 15% of placebo patients (<math>P&lt;0.0001</math>), and results were sustained at 24 and 48 weeks.</p> <p>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 (<math>P</math> values not reported).</p> <p>The mean annualized rate of change in the mTSS with etanercept was -0.03 unit, compared with 1.00 unit in the placebo group (<math>P&lt;0.0001</math>).</p> <p>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 (<math>P</math> values not reported).</p> <p>At 24 weeks, 23% of etanercept patients eligible for psoriasis evaluation achieved at least 75% improvement in the PASI, compared with 3% of placebo patients (<math>P=0.001</math>).</p> <p>SF-36 PCS scores improved more often with etanercept compared to placebo, but SF-36 MCS scores did not differ significantly between groups.</p> <p>HAQ scores at 24 weeks were significantly improved with etanercept (54%) over placebo (6%; <math>P&lt;0.0001</math>).</p> <p>Injection site reactions occurred at a greater rate with etanercept than placebo (36% vs 9%; <math>P&lt;0.001</math>).</p>
<p>Kavanaugh et al<sup>42</sup></p> <p>Golimumab 50 mg once every 4 weeks</p> <p>vs</p>	<p>MC, PC, RCT</p> <p>Patients ≥18 years of age with a diagnosis of PsA and active PsA</p>	<p>N=405</p> <p>24 weeks</p>	<p>Primary: ACR 20 response at week 14</p> <p>Secondary:</p>	<p>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%; <math>P&lt;0.001</math>).</p> <p>Similar ACR 20 responses at week 14 were observed in patients with</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>golimumab 100 mg once every 4 weeks</p> <p>vs</p> <p>placebo</p> <p>Patients who had used or were currently using MTX, an NSAID, an oral corticosteroid, or a systemic or topical psoriasis treatment were enrolled.</p>	<p>despite current or previous DMARD or NSAID therapy and no evidence of active TB and/or no evidence of latent TB on screening</p>		<p>Not reported</p>	<p>different PsA subtypes.</p> <p>ACR responses observed in the golimumab treated groups were similar in patients receiving and not receiving concomitant MTX.</p> <p>Secondary: Not reported</p>
<p>Antoni et al<sup>43</sup></p> <p>Infliximab 5 mg/kg at weeks 0, 2, 6, 14 and 22</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, PG, RCT</p> <p>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 rheumatoid factor</p>	<p>N=200</p> <p>24 weeks</p>	<p>Primary: ACR 20 response at week 14</p> <p>Secondary: PsARC, PASI 75, duration of morning stiffness, dactylitis in hands and feet, presence or absence of enthesopathy in the feet and SF-36</p>	<p>Primary: At week 14, there was significantly more patients in the infliximab treated group that achieved an ACR 20 response (58%) compared to placebo (11%; <math>P&lt;0.001</math>). This difference continued through week 24 (54% vs 16%; <math>P&lt;0.001</math>).</p> <p>Secondary: A significantly greater percentage of patients in the infliximab treated group had improvement in PsARC (77%) compared to placebo (27%; <math>P&lt;0.001</math>) at week 14 and continued through week 24 (70% vs 32%; <math>P&lt;0.001</math>).</p> <p>At weeks 14 and 24, fewer patients in the infliximab group had digits with dactylitis (18% and 12%) compared to placebo (30% and 34%; <math>P=0.025</math> and <math>P&lt;0.001</math>, respectively).</p> <p>Fewer patients in the infliximab group had enthesopathy compared to placebo at week 14 (22% vs 34%; <math>P=0.016</math>) and week 24 (20% vs 37%; <math>P=0.002</math>).</p> <p>A significantly higher proportion of patients achieved PASI 75 in the</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>infliximab group compared to placebo at weeks 14 and 24 (64% vs 2%; <math>P&lt;0.001</math> and 60% vs 1%; <math>P&lt;0.001</math>, respectively).</p> <p>At week 14, the physical and mental components of the SF-36 were significantly improved in the infliximab group compared to placebo (both <math>P&lt;0.001</math>). There was also significant improvement at week 24 in the physical and mental components of the SF-36 in the infliximab group compared to placebo (<math>P&lt;0.001</math> and <math>P=0.047</math>, respectively).</p> <p>Adverse events were similar between the groups. There were a higher proportion of patients who discontinued treatment due to adverse events in the infliximab group compared to placebo (4% vs 1%). There were a greater number of patients in the infliximab group that had increased ALT compared to placebo (1% vs 6%).</p>
<b>Rheumatoid Arthritis</b>				
<p>Keystone et al<sup>44</sup> (RAPID 1)</p> <p>Certolizumab 400 mg at weeks 0, 2, and 4 then 200 mg every 2 weeks plus MTX (CZP 200 mg)</p> <p>vs</p> <p>certolizumab 400 mg at weeks 0, 2, and 4 then 400 mg every 2 weeks plus MTX (CZP 400 mg)</p> <p>vs</p> <p>placebo plus MTX</p> <p>Patients were randomized</p>	<p>DB, MC, PG, RCT</p> <p>Patients <math>\geq 18</math> years of age with a diagnosis of RA (defined by ACR 1987 criteria), for <math>\geq 6</math> months and up to 15 years with active disease despite treatment with MTX</p>	<p>N=982</p> <p>52 weeks</p>	<p>Primary: ACR 20 at 24 weeks, mean change from baseline in mTSS at 52 weeks</p> <p>Secondary: Mean change from baseline in mTSS at 24 weeks, HAQ-DI, ACR 20 at 52 weeks, ACR 50 and ACR 70 at 24 weeks</p>	<p>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 placebo (13.6%; <math>P&lt;0.001</math>). There was no significant difference detected between the two CZP regimens.</p> <p>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; <math>P&lt;0.001</math>).</p> <p>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 units for placebo; <math>P&lt;0.001</math>).</p> <p>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 (<math>P&lt;0.001</math>).</p> <p>ACR 20 response remained significantly higher with CZP 200 mg over 52 weeks (<math>P&lt;0.001</math> vs placebo). A significantly greater proportion of individuals achieved ACR 50 and ACR 70 with CZP 200 mg (37.1% and</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>2:2:1.</p> <p>Concurrent analgesics, NSAIDs/COX2 inhibitors, or oral corticosteroids (<math>\leq 10</math> mg/day of prednisone or equivalent) were allowed.</p>				<p>21.4%) and CZP 400 mg (39.9% and 20.6%) compared to placebo (7.6% and 3.0%; <math>P &lt; 0.001</math>) at week 24.</p> <p>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.</p>
<p>Smolen et al<sup>45</sup> (RAPID 2)</p> <p>Certolizumab 400 mg at weeks 0, 2, and 4 then 200 mg every 2 weeks plus MTX (CZP 200 mg)</p> <p>vs</p> <p>certolizumab 400 mg at weeks 0, 2, and 4 then 400 mg every 2 weeks plus MTX (CZP 400 mg)</p> <p>vs</p> <p>placebo plus MTX</p> <p>Patients were randomized 2:2:1.</p> <p>Concurrent analgesics, NSAIDs/COX2 inhibitors, or oral corticosteroids (<math>\leq 10</math> mg/day of prednisone or equivalent) were allowed.</p>	<p>DB, MC, RCT</p> <p>Patients <math>\geq 18</math> years of age with a diagnosis of RA (defined by ACR 1987 criteria) for <math>\geq 6</math> months and up to 15 years with active disease despite treatment with MTX</p>	<p>N=619</p> <p>24 weeks</p>	<p>Primary: ACR 20 at 24 weeks</p> <p>Secondary: ACR 50, ACR 70, mTSS, SF-36 Health Survey and individual ACR core set variables, safety</p>	<p>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%; <math>P \leq 0.001</math>).</p> <p>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; <math>P \leq 0.01</math>).</p> <p>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; <math>P \leq 0.01</math> compared to CZP 200 mg; <math>P \leq 0.001</math> compared to CZP 400 mg).</p> <p>Active treatment resulted in greater improvements in SF-36 scores vs placebo (<math>P &lt; 0.001</math>) and ACR core components vs placebo (<math>P &lt; 0.001</math>).</p> <p>Serious infection was reported in 3.2% of CZP 200 mg patients, 2.4% of CZP 400 mg patients and 0% on placebo.</p> <p>Tuberculosis was reported in five patients receiving certolizumab.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Fleischmann et al<sup>46</sup> (FAST4WARD)</p> <p>Certolizumab 400 mg every 4 weeks</p> <p>vs</p> <p>placebo</p> <p>Concurrent analgesics, NSAIDs, or oral corticosteroids (<math>\leq 10</math> mg/day of prednisone or equivalent) were allowed.</p>	<p>DB, MC, RCT</p> <p>Patients 18 to 75 years of age with adult onset RA (defined by ACR 1987 criteria) for <math>\geq 6</math> months, with active disease and failed at least one prior DMARD</p>	<p>N=220</p> <p>24 weeks</p>	<p>Primary: ACR 20 at 24 weeks</p> <p>Secondary: ACR 50, ACR 70, ACR component scores, DAS 28, patient reported outcomes, safety</p>	<p>Primary: ACR 20 achievement at 24 weeks was significantly higher with certolizumab (45.5%) than placebo (9.3%; <math>P &lt; 0.001</math>).</p> <p>Secondary: A significantly greater proportion of ACR 50 and ACR 70 responders were found in the active treatment group vs placebo (22.7% vs 3.7%; <math>P &lt; 0.001</math> and 5.5% vs 0%; <math>P \leq 0.05</math>, respectively). A significant improvement in all ACR components was also detected among patients on certolizumab vs placebo (<math>P \leq 0.05</math>).</p> <p>A significantly greater change in DAS 28 was also reported with active treatment (-1.5 vs -0.6 for placebo; <math>P &lt; 0.001</math>).</p> <p>Patients reported significant improvements in physical function with certolizumab as measured by HAQ-DI (<math>P &lt; 0.001</math>), arthritis pain (<math>P \leq 0.05</math>), HRQoL (<math>P &lt; 0.001</math>) and fatigue (<math>P &lt; 0.001</math>).</p> <p>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.</p>
<p>Emery et al<sup>47</sup></p> <p>Golimumab 100 mg once every 4 weeks and placebo</p> <p>vs</p> <p>golimumab 50 mg once every 4 weeks and MTX</p> <p>vs</p> <p>golimumab 100 mg once</p>	<p>DB, PC, RCT</p> <p>MTX naïve patients <math>\geq 18</math> years of age with a diagnosis of active RA for <math>\geq 3</math> months and not previously treated with a TNF-blocker</p>	<p>N=637</p> <p>24 weeks</p>	<p>Primary: ACR 50 response at week 24</p> <p>Secondary: ACR 20, 70, 90 responses at week 24</p>	<p>Primary: The golimumab monotherapy group was not statistically different from the MTX monotherapy group in ACR response (<math>P = 0.053</math>). 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 (<math>P = 0.049</math>).</p> <p>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 (<math>P = 0.028</math> for both groups).</p> <p>ACR 70 response was not significant and ACR 90 response was significant for the golimumab 50 mg and MTX groups.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
every 4 weeks and MTX vs placebo and MTX				
Keystone et al <sup>48</sup> 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 been 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 <sup>49</sup> Golimumab 50 mg once every 4 weeks vs	DB, PC, RCT Patients ≥18 years of age with a diagnosis of active RA for ≥3 months	N=461 24 weeks	Primary: ACR 20 response at week 14 Secondary: ACR 50 response	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

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<p>golimumab 100 mg once every 4 weeks</p> <p>vs</p> <p>placebo</p> <p>Patients were allowed to continue stable doses of concomitant HCQ, MTX, or SSZ during the trial.</p>	<p>previously treated with ≥1 dose of a TNF-blocker without a serious adverse reaction</p>		<p>at week 14, DAS 28 response at week 14, ACR 20 response at week 24, improvement from baseline in HAQ scores at week 24</p>	<p>100 mg groups, respectively, compared with 17.7% of patients in the placebo group (<math>P=0.006</math>, golimumab 50 mg vs placebo; <math>P&lt;0.001</math>, golimumab 100 mg vs placebo).</p> <p>Secondary: ACR 50 response at week 14 was significant for the golimumab-treated groups compared to placebo.</p> <p>DAS 28 response was significant for golimumab 50 and 100 mg groups compared to placebo (56.2% and 59.5% vs 30.3%, respectively; <math>P&lt;0.001</math>).</p> <p>ACR 20 response at week 24 was significant for the golimumab-treated groups compared to placebo.</p> <p>At week 24, golimumab improved physical function and fatigue according to HAQ and FACIT-F scores, respectively.</p>
<p>Jones et al<sup>50</sup> (AMBITION)</p> <p>Tocilizumab 8 mg/kg every 4 weeks</p> <p>vs</p> <p>MTX 7.5 to 20 mg every week</p> <p>or</p> <p>placebo for 8 weeks followed by tocilizumab 8 mg/kg from week nine on</p>	<p>DB, DD, PG, RCT</p> <p>Patients ≥18 years of age, with moderate to severe RA for ≥3 months, oral glucocorticoids (up to 10 mg/day prednisone or equivalent) and NSAIDs were permitted if the dose was stable for ≥6 weeks</p>	<p>N=673</p> <p>24 weeks</p>	<p>Primary: Proportion of patients achieving ACR 20 response at week 24</p> <p>Secondary: Proportion of patients with 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</p>	<p>Primary: At week 24, 70.6% of tocilizumab patients as compared to 52.1% of MTX patients achieved an ACR 20 response (<math>P&lt;0.001</math>). 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).</p> <p>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 MTX (<math>P&lt;0.001</math>).</p> <p>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 (<math>P&lt;0.001</math>). 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).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			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	<p>A greater improvement in physical function was seen by a higher mean change in HAQ-DI with tocilizumab when compared to that of MTX.</p> <p>There was no statistically significant difference with regards to the number of adverse events experienced in the tocilizumab group when compared to MTX (79.9% vs 77.5%; <i>P</i>=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%; <i>P</i> value not reported).</p>
<p>Smolen et al<sup>52</sup> (OPTION)</p> <p>Tocilizumab 8 mg/kg every 4 weeks plus MTX (stable, 10 to 25 mg weekly)</p> <p>vs</p> <p>tocilizumab 4 mg/kg every 4 weeks plus MTX (stable, 10 to 25 mg weekly)</p> <p>vs</p> <p>placebo every 4 weeks plus MTX (stable, 10 to 25</p>	<p>DB, PC, PG, RCT</p> <p>Patients ≥18 years of age, with moderate to severe RA &gt;6 months duration, who had an inadequate response to MTX; all other DMARDs were discontinued before the start of the study, oral glucocorticoids (≤10 mg/day prednisone or equivalent) and NSAIDs were</p>	<p>N=622</p> <p>24 weeks</p>	<p>Primary: ACR 20 response at week 24</p> <p>Secondary: ACR 50/70, DAS 28, and EULAR responses at week 24, difference in HAQ-DI, SF-36, and FACIT-F, scores from baseline, and adverse events</p>	<p>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; <i>P</i>&lt;0.0001 for both).</p> <p>Secondary: Significantly more patients in both tocilizumab groups achieved ACR 50 (31% vs 44% vs 11%; <i>P</i>&lt;0.0001) and ACR 70 at week 24 (12% vs 22% vs 2%; <i>P</i>&lt;0.0001) compared to placebo.</p> <p>Disease activity was found to be reduced as measured by a DAS 28 score &lt;2.6 in significantly more patients in both tocilizumab groups when compared to placebo (13.0% vs 27.0% vs 0.8%; <i>P</i>&lt;0.0002 for 4 mg/kg and <i>P</i>&lt;0.0001 for 8 mg/kg).</p> <p>EULAR response was also found to be significantly decreased in both tocilizumab groups (21% vs 38% vs 3%; <i>P</i>&lt;0.0001 for both).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg weekly)	permitted if doses were stable for six weeks or more			<p>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; <math>P&lt;0.0296</math> for 4 mg/kg and <math>P&lt;0.0082</math> for 8 mg/kg).</p> <p>Significant differences were seen with regards to changes in the SF-36 physical score in both tocilizumab groups (9.7 vs 9.5 vs 5.0; <math>P&lt;0.0001</math> for both) and in the SF-36 mental score (5.7 vs 7.3 vs 2.7; <math>P&lt;0.0394</math> for 4 mg/kg and <math>P&lt;0.0012</math> for 8 mg/kg).</p> <p>The mean change in FACIT-F score from baseline showed significant improvements in both tocilizumab groups (7.3 vs 8.6 vs 4.0; <math>P&lt;0.0063</math> for 4 mg/kg and <math>P&lt;0.0001</math> for 8 mg/kg).</p> <p>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.</p>
<p>Genovese et al<sup>53</sup> (TOWARD)</p> <p>Tocilizumab 8 mg/kg plus DMARD every 4 weeks</p> <p>vs</p> <p>placebo plus DMARD every 4 weeks</p>	<p>DB, MC, PC, RCT</p> <p>Patients <math>\geq 18</math> years of age, with moderate to severe RA, who received stable doses of permitted DMARDs (MTX, chloroquine, HCQ, parenteral gold, SSZ, azathioprine, and leflunomide) for <math>\geq 8</math> weeks prior to study entry and oral glucocorticoids (<math>\leq 10</math> mg/day prednisone</p>	<p>N=1,220</p> <p>24 weeks</p>	<p>Primary: ACR 20 responses at week 24</p> <p>Secondary: ACR 50/70 responses at week 24, number of swollen and tender joints, DAS 28, EULAR response, HAQ, FACIT-F score, and SF-36, and adverse events</p>	<p>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%; <math>P&lt;0.0001</math>). No obvious differences were seen in ACR 20 response with regards to patients who received two or more DMARDs.</p> <p>Secondary: At week 24, significantly more patients in the tocilizumab group achieved ACR 50 and ACR 70 responses when compared to the placebo group (ACR50, 30% vs 9%; ACR70, 21% vs 3%; <math>P&lt;0.0001</math> for both).</p> <p>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; <math>P&lt;0.0001</math>).</p> <p>Mean DAS 28 improved incrementally over time with greater changes in the</p>

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	<p>or equivalent) and NSAIDs/COX2 inhibitors if the doses were stable for <math>\geq 6</math> weeks</p>			<p>tocilizumab group seen by week 24 (-3.17 and -1.16 respectively; <math>P &lt; 0.0001</math>). Remission rates at week 24 were also higher in the tocilizumab group when compared to placebo (30% vs 3%; <math>P &lt; 0.0001</math>).</p> <p>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 (<math>P &lt; 0.0001</math>).</p> <p>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 of <math>\geq 0.3</math>). Mean changes from baseline were also significantly higher in the tocilizumab group when compared to placebo for the disability index of the HAQ (-0.5 vs -0.2; <math>P &lt; 0.0001</math>) and FACIT-F scores (8.0 vs 3.6; <math>P &lt; 0.0001</math>).</p> <p>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; <math>P &lt; 0.0001</math> for both).</p> <p>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% 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%).</p>
<p>Emery et al<sup>54</sup> (RADIATE)</p> <p>Tocilizumab 8 mg/kg plus MTX (stable, 10 to 25 mg weekly) for 4 weeks</p> <p>vs</p>	<p>DB, PC, PG</p> <p>Patients <math>\geq 18</math> years of age with moderate to severe active RA with failure to respond to one or more TNF</p>	<p>N=499</p> <p>24 weeks</p>	<p>Primary: ACR 20 responses</p> <p>Secondary: DAS 28, number of patients requiring rescue</p>	<p>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 (<math>P &lt; 0.001</math>). At week four, more patients achieved ACR 20 in the 8 mg/kg tocilizumab group than those in the control group (<math>P &lt; 0.001</math>).</p> <p>Patients responded, as measured by ACR 20 response, regardless of the most recently failed TNF antagonist or the number of failed treatments.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>tocilizumab 4 mg/kg plus MTX (stable, 10 to 25 mg weekly) for 4 weeks</p> <p>vs</p> <p>placebo plus MTX (stable, 10 to 25 mg weekly) for 4 weeks</p>	<p>antagonists within the past year; patients must have discontinued TNF agents (Enbrel<sup>®</sup>, Humira<sup>®</sup>, Remicade<sup>®</sup>) or DMARDs (other than MTX) before enrolling</p>		<p>therapy, and adverse events</p>	<p>Secondary:</p> <p>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 (<math>P&lt;0.001</math> for 8 mg/kg; <math>P=0.053</math> for 4 mg/kg vs control).</p> <p>Rescue therapy with 8 mg/kg of tocilizumab plus MTX was offered at week 16 in all cases of treatment failure (&lt;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 with 11% of patients in the 8 mg/kg group.</p> <p>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.</p>
<p>Maxwell et al<sup>55</sup></p> <p>Abatacept 2 to 10 mg/kg alone or in combination with DMARDs or biologics</p> <p>vs</p> <p>placebo or DMARDs or biologics</p>	<p>SR</p> <p>RCTs of patients ≥16 years of age with RA meeting the ACR 1987 revised criteria</p>	<p>N=2,908 (7 trials)</p> <p>≥3 months</p>	<p>Primary: ACR 50 response and safety</p> <p>Secondary: ACR 20, ACR 70, components of ACR radiographic progression, DAS, EULAR response criteria, changes in HAQ and SF-36</p>	<p>Primary:</p> <p>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 treated patients compared to controls (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).</p> <p>The RR for adverse events in abatacept compared to controls was 1.05 (95% CI, 1.01 to 1.08). There was a greater number of serious adverse infections in the abatacept treated patients 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).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>Secondary: 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).</p> <p>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 100.2).</p> <p>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).</p> <p>The abatacept treated patients were significantly more likely to reach low DAS (DAS 28&lt;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&lt;2.6) with RR of 12.74 (95% CI, 4.76 to 34.15).</p> <p>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&gt;0.3 of 5 (95% CI, 4 to 7).</p> <p>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).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Navarro-Sarabia et al<sup>56</sup></p> <p>Adalimumab 20, 40, 80 mg every week to every other week, alone or in combination with DMARDs</p> <p>vs</p> <p>placebo or placebo plus DMARDs</p>	<p>SR</p> <p>RCTs in patients with confirmed RA (defined by ACR 1987 criteria), who had active disease and who either failed MTX or other DMARDs therapy, or DMARD naive</p>	<p>N=2,381 (6 trials)</p> <p>12 to 52 weeks</p>	<p>Primary: ACR, EULAR responses, DAS 28, components of ACR responses, radiographic data</p> <p>Secondary: Safety</p>	<p>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.</p> <p>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).</p> <p>The RR to achieve an ACR 70 response was reported as 5.14 (95% CI, 3.14 to 8.41) and a NNT of 7.0 (95% CI, 5.0 to 13.0).</p> <p>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.</p> <p>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.</p> <p>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 5.0 (95% CI, 3.0 to 9.0), 7.0 (95% CI, 4.0 to 20.0) and 9.0 (95% CI, 3.0 to 38.0), respectively at 24 weeks.</p> <p>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).</p>
<p>Mertens et al<sup>9</sup></p> <p>Anakinra 50 to 150 mg daily</p> <p>vs</p>	<p>SR</p> <p>RCTs in patients &gt;18 years of age with RA</p>	<p>N=2,876 (5 trials)</p> <p>24 weeks</p>	<p>Primary: Patients achieving ACR 20</p> <p>Secondary: Patients</p>	<p>Primary: ACR 20 achievement was noted in significantly more participants taking anakinra (38%) compared to 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.</p> <p>Secondary:</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo			achieving ACR 50 and ACR 70, safety	<p>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, Larsen radiographic scores and change in ESR compared to placebo.</p> <p>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%).</p>
<p>Blumenauer et al<sup>57</sup></p> <p>Etanercept 10 or 25 mg twice weekly alone or in combination with MTX</p> <p>vs</p> <p>MTX or placebo</p>	<p>SR</p> <p>RCTs in 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 &gt;30 minutes, acute phase reactants such as Westergren ESR or CRP</p>	<p>N=949 (3 trials)</p> <p>≥6 months</p>	<p>Primary: ACR 20, ACR 50, ACR 70 responses, erosion scores</p> <p>Secondary: Safety</p>	<p>Primary:</p> <p>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).</p> <p>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). 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).</p> <p>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).</p> <p>Seventy-two percent of patients receiving etanercept had no increase in Sharp erosion score vs 60% of MTX patients. The Sharp erosion scores and joint space narrowing 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).</p> <p>Secondary:</p> <p>Injection site reactions were reported in 34% of patients on etanercept 10</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>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).</p> <p>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.</p>
<p>Wiens et al<sup>58</sup></p> <p>Infliximab 3 mg/kg at weeks 0, 2 and 6 then every 8 weeks plus MTX</p> <p>vs</p> <p>placebo plus MTX</p>	<p>MA</p> <p>RCTs in adult patients with RA</p>	<p>N=2,129 (7 trials)</p> <p>≥14 weeks</p>	<p>Primary: ACR 20, ACR 50, ACR 70 response</p> <p>Secondary: Safety and discontinuation of therapy</p>	<p>Primary:</p> <p>Through 30 weeks, the proportion of patients achieving an ACR 20 was 59% in the infliximab group compared to controls (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 controls groups achieving an ACR 70, respectively.</p> <p>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 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 controls achieved an ACR 70.</p> <p>Secondary:</p> <p>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 placebo (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 controls (4% vs 12%; RR, 0.41; 95% CI, 0.18 to 0.95).</p>
<p>Nixon et al<sup>59</sup></p> <p>Adalimumab, anakinra, etanercept, or infliximab with or without MTX</p>	<p>MA</p> <p>RCTs in patients with a clinical diagnosis of RA</p>	<p>N=6,694 (13 trials)</p> <p>≥6 months</p>	<p>Primary: ACR 20 response and ACR 50 response</p>	<p>Primary:</p> <p>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.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs MTX or placebo			Secondary: Not reported	<p>The OR to achieve an ACR 50 response with adalimumab treatment 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.</p> <p>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 OR, 3.20 and OR, 8.53 vs OR, 4.56, respectively).</p> <p>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 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; <math>P&lt;0.05</math>).</p> <p>Secondary: Not reported</p>
<b>Ulcerative Colitis</b>				
Rutgeerts et al <sup>60</sup> (ACT 1 and ACT2)  Infliximab 5 to 10 mg/kg at weeks 0, 2, 6 and then every 8 weeks	DB, MC, PC, RCT  Adult patients with endoscopy confirmed active ulcerative colitis (Mayo score 6 to 12)	N=364 (ACT 1) N=364 (ACT 2)  30 weeks (ACT 2)	Primary: Clinical response at week eight  Secondary: Clinical response or clinical	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 placebo (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 placebo (29.3%; $P<0.001$ for both).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	and moderate to severe active disease on sigmoidoscopy despite concurrent treatment with corticosteroids alone or in combination with azathioprine or mercaptopurine (ACT 1) or despite concurrent treatment with corticosteroids alone or mercaptopurine and medications containing 5-aminosalicylates (ACT 2)	54 weeks (ACT1)	remission with discontinuation of corticosteroids at week 30 (ACT 1 and ACT 2) and week 54 (ACT 1), clinical remission and mucosal 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	<p>Secondary:</p> <p>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 placebo (29.8%; <math>P&lt;0.001</math> and <math>P=0.002</math>, 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 placebo (26.0%; <math>P&lt;0.001</math> for 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 placebo (45.5% and 44.3% vs 19.8%; <math>P&lt;0.001</math> for both).</p> <p>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 placebo (14.9%; <math>P&lt;0.001</math> and <math>P=0.002</math>, 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 placebo (5.7%; <math>P&lt;0.001</math> 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 placebo (15.7%; <math>P=0.001</math> and <math>P&lt;0.001</math>, 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 placebo (10.6%; <math>P=0.003</math> and <math>P&lt;0.001</math>, 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 placebo (34.7% and 34.4% vs 16.5%; <math>P=0.001</math> for both).</p> <p>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 placebo (77.4% and 67.7% vs 35.3%; <math>P&lt;0.001</math> and <math>P=0.010</math>, respectively). In ACT 2 at week eight when compared to placebo (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%; <math>P=0.011</math>), but not infliximab 5 mg/kg group</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>(63.3%; <math>P=0.053</math>).</p> <p>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 placebo (33.9%; <math>P&lt;0.001</math> for both). In ACT 2 at week 8, 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 placebo (30.9%; <math>P&lt;0.001</math> for both). In ACT 1, the proportion of patients with mucosal healing at week 30 was significantly higher in the infliximab 5 and 10 mg/kg groups (50.4% and 49.2%) compared to placebo (24.8%; <math>P&lt;0.001</math> 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 placebo (30.1%; <math>P=0.009</math> and <math>P&lt;0.001</math>, 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 placebo (45.5% and 46.7% vs 18.2%; <math>P=0.001</math> for both).</p>

\* 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, AS=ankylosing spondylitis, ASAS=assessment of spondyloarthritis international society criteria; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index, BASFI=Bath Ankylosing Spondylitis Functional Index, BASMI=Bath Ankylosing Spondylitis Metrology Index, BSA=body surface area, CDAI=Crohn's disease activity index, CHAQ=Childhood Health Assessment Questionnaire, COX=cyclooxygenase, CRP=C-reactive protein, DAS 28=Disease Activity Score in 28 joints, DMARD=disease-modifying antirheumatic drug, DOI=definition of improvement, 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, HCQ=hydroxychloroquine, JRA=juvenile rheumatoid arthritis, mTSS=modified Total Sharp Scores, MTX=methotrexate, NSAIDs=nonsteroidal anti-inflammatory drugs, PASI=psoriasis area and severity index, PCDAI=pediatric Crohn's disease activity index, PsA=psoriatic arthritis, PsARC=psoriatic arthritis response criteria, RA=rheumatic arthritis, SF-36=short form-36, SF-36 MCS=short form-36-mental component, SF-36 PCS=short form-36-physical component, SSZ=sulfasalazine, TB=tuberculosis, TNF=tumor necrosis factor, VAS=visual analog scale

**Special Populations****Table 5. Special Populations**<sup>3-8,10-12</sup>

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.  Approved for use in children $\geq 6$ years of age for the treatment of juvenile rheumatoid arthritis.	Safety and efficacy in patients with renal dysfunction have not been established.	Safety and efficacy in patients with hepatic dysfunction have not been established.	C	Unknown; importance of drug administration to mother should be determined.
Adalimumab	Use caution; no dose adjustment required in elderly.  Approved for use in children $\geq 4$ years of age for the treatment of juvenile rheumatoid arthritis.	Safety and efficacy in patients with renal dysfunction have not been established.	Safety and efficacy in patients with hepatic dysfunction have not been established.	B	Unknown; importance of drug administration to mother should be determined.
Anakinra	Use caution; no dose adjustment required in elderly.  Safety and efficacy in the pediatric population have not been established.	Dosage adjustment may be required in patients with severe renal impairment or end stage renal disease (creatinine clearance $< 30$ mL/minute).	Safety and efficacy in patients with hepatic dysfunction have not been established.	B	Unknown; caution should be used when administered to nursing women.
Certolizumab	Use caution; no dose adjustment required in elderly.  Safety and efficacy in the pediatric population have not been established.	Safety and efficacy in patients with renal dysfunction have not been established.	Not reported	B	Unknown; importance of drug administration to mother should be determined.
Etanercept	Use caution; no dose adjustment required in elderly.  Approved for use in children $\geq 2$ years of age for the treatment of	Safety and efficacy in patients with renal dysfunction have not been	Safety and efficacy in patients with hepatic dysfunction have not been	B	Unknown; importance of drug administration to mother should be determined.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	juvenile rheumatoid arthritis.	established.	established.		
Golimumab	Use caution; no dose adjustment required in elderly.  Safety and efficacy in the pediatric population have not been established.	Safety and efficacy in patients with renal dysfunction have not been established.	Safety and efficacy in patients with hepatic dysfunction have not been established.	B	Unknown; importance of drug administration to mother should be determined.
Infliximab	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients for the treatment of rheumatoid arthritis and psoriasis.  Safety and efficacy in elderly patients have not been established for the treatment of Crohn's disease, ulcerative colitis, ankylosing spondylitis or psoriatic arthritis.  Approved for use in children ≥6 years of age for the treatment of Crohn's disease.  Safety and efficacy in the pediatric population have not been established for the treatment of ulcerative colitis and plaque psoriasis.	Safety and efficacy in patients with renal dysfunction have not been established.	Safety and efficacy in patients with hepatic dysfunction have not been established.	B	Unknown; importance of drug administration to mother should be determined.
Tocilizumab	Use caution; no dose adjustment required in elderly.  Safety and efficacy in the pediatric population have not been established.	No dosage adjustment required in mild renal impairment.  Safety and efficacy in patients with moderate to severe renal dysfunction have not	Safety and efficacy in patients with hepatic dysfunction have not been established.	C	Unknown; importance of drug administration to mother should be determined.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
		been established.			
Ustekinumab	No dose adjustment required in elderly.  Safety and efficacy in the pediatric population have not been established.	Safety and efficacy in patients with renal dysfunction have not been established.	Safety and efficacy in patients with hepatic dysfunction have not been established.	B	Unknown; importance of drug administration to mother should be determined.

**Adverse Drug Events**

The anti tumor necrosis factor- $\alpha$  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  $\geq 5\%$  of study populations.

**Table 6. Adverse Drug Events (%)<sup>3-8,10-12</sup>**

Adverse Event	Abatacept	Adalimumab	Anakinra	Certolizumab	Etanercept	Golimumab*	Infliximab	Tocilizumab	Ustekinumab
<b>Gastrointestinal</b>									
Abdominal pain	-	7	5	-	5 to 10	-	12	-	-
Diarrhea	-	-	7	-	-	-	12	-	-
Dyspepsia	6	-	-	-	4 to 11	-	10	-	-
Nausea	$\geq 10$	9	8	-	9 to 15	-	21	-	-
Vomiting	-	-	-	-	3 to 5	-	-	-	-
<b>Laboratory Tests</b>									
Abnormal test	-	8	-	-	-	-	-	3 to 6	-
Alkaline phosphatase increased	-	5	-	-	-	-	-	-	-
Hematuria	-	5	-	-	-	-	-	-	-
Hypercholesterolemia	-	6	-	-	-	-	-	-	-
Hyperlipidemia	-	7	-	-	-	-	-	-	-
<b>Respiratory</b>									
Bronchitis	5 to 13	-	-	-	-	-	10	-	-
Coughing	8	-	-	-	5 to 6	-	12	-	-
Flu syndrome	-	7	-	-	-	-	14	-	-
Nasopharyngitis	12	-	-	5	-	-	-	4 to 7	7 to 8
Non-upper respiratory infection	-	-	-	-	38 to 51	-	-	-	-
Pharyngitis	-	-	-	-	6 to 7	6	-	-	-
Respiratory disorder	-	-	-	-	5	-	-	-	-
Rhinitis	-	-	-	-	12 to 16	-	-	-	-
Sinusitis	5 to 13	11	7	-	3 to 5	-	14	-	-
Upper respiratory infection	$\geq 10$	17	14	6	29 to 31	7	32	6 to 8	4 to 5
<b>Skin</b>									
Pruritus	-	-	-	-	-	-	7	-	-
Rash	-	12	-	-	5 to 14	-	10	-	-
<b>Other</b>									
Accidental injury	-	10	-	-	-	-	-	-	-

Adverse Event	Abatacept	Adalimumab	Anakinra	Certolizumab	Etanercept	Golimumab*	Infliximab	Tocilizumab	Ustekinumab
Alopecia	-	-	-	-	1 to 6	-	-	-	-
Arthralgia	-	-	6	-	-	-	-	-	-
Asthenia	-	-	-	-	5 to 11	-	-	-	-
Back pain	7	6	-	-	-	-	8	-	-
Body pain	-	-	-	-	-	-	8	-	-
Dizziness	9	-	-	-	7 to 8	-	-	-	-
Fatigue	-	-	-	-	-	-	9	-	-
Fever	-	-	-	-	-	-	7	-	-
Flu like symptoms	-	-	6	-	-	-	-	-	-
Headache	18	12	12	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	71	-	34 to 37	-	-	-	-
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.

**Contraindications/Precautions**<sup>3-8,10-12</sup>

The immunomodulators are contraindicated in patients with a known hypersensitivity to any of the agents or to any component of the individual products. Additionally, anakinra is contraindicated in patients with a known hypersensitivity to *Escherichia coli*-derived proteins. Some of the immunomodulators are associated with boxed warnings which are outlined below.

Numerous precautions are associated with the anti-tumor necrosis factor (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).

Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents including tocilizumab for rheumatoid arthritis. The most common serious infections included pneumonia, urinary tract infection, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis. Opportunistic infections reported with tocilizumab include tuberculosis, cryptococcus, aspergillosis, candidiasis, and pneumocystosis. 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.

**Black Box Warning for Infliximab**<sup>7</sup>

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 Remicade <sup>®</sup> . These cases have had a very aggressive disease course and have been fatal. All reported Remicade <sup>®</sup> 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 Remicade <sup>®</sup> at or prior to diagnosis.

**Black Box Warning for Tocilizumab<sup>10</sup>**

**WARNING**

**Serious Infections**

Patients treated with Actemra<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup> use and during therapy. Treatment for latent infection should be initiated prior to Actemra<sup>®</sup> 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<sup>®</sup> 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<sup>®</sup>, 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<sup>4-6,43</sup>**

**WARNING**

**Serious Infection**

Patients treated with Cimzia<sup>®</sup>, Enbrel<sup>®</sup>, Humira<sup>®</sup>, Remicade<sup>®</sup> or Simponi<sup>®</sup> 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<sup>®</sup>, Enbrel<sup>®</sup>, Humira<sup>®</sup>, Remicade<sup>®</sup> and Simponi<sup>®</sup> should be discontinued if a patient develops a serious infection or sepsis.

Reported infections include:

- 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<sup>®</sup>, Enbrel<sup>®</sup>, Remicade<sup>®</sup>, or Simponi<sup>®</sup> use and during therapy. Treatment for latent infection should be initiated prior to Cimzia<sup>®</sup>, Enbrel<sup>®</sup>, Humira<sup>®</sup>, Remicade<sup>®</sup>, or Simponi<sup>®</sup> 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.

The risks and benefits of treatment with Cimzia<sup>®</sup>, Enbrel<sup>®</sup>, Humira<sup>®</sup>, Remicade<sup>®</sup>, or Simponi<sup>®</sup> 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<sup>®</sup>, Enbrel<sup>®</sup>, Humira<sup>®</sup>, Remicade<sup>®</sup> or Simponi<sup>®</sup>, 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<sup>®</sup>, Enbrel<sup>®</sup>, Humira<sup>®</sup>, Remicade<sup>®</sup> or Simponi<sup>®</sup> 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.<sup>10</sup>

**Table 7. Drug Interactions**<sup>10,15</sup>

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, anakinra, etanercept, infliximab	Riloncept	Concurrent use may increase the risk of serious infections and neutropenia.
Etanercept	Cyclophosphamide	Concurrent administration may result in a higher incidence of developing non-cutaneous solid malignancies.

**Dosage and Administration****Table 8. Dosing and Administration**<sup>3-8,10-12</sup>

Generic Name	Adult Dose	Pediatric Dose	Availability
Abatacept	<u>Rheumatoid arthritis:</u> Initial (<60 kg), 500 mg IV over 30 minutes at weeks 0, 2 and 4; (60 to 100 kg), 750 mg IV over 30 minutes at weeks 0, 2 and 4; (>100 kg), 1,000 mg IV over 30 minutes at weeks 0, 2 and 4; maintenance (<60 kg), 500 mg IV over 30 minutes every 4 weeks; (60 to 100 kg), 750 mg IV over 30 minutes every 4 weeks; (>100 kg) 1,000 mg IV over 30 minutes every 4 weeks	<u>Juvenile idiopathic arthritis (6 to 17 years):</u> Initial, (<75 kg), 10 mg/kg IV over 30 minutes at weeks 0, 2 and 4; (≥75 kg), follow adult dosing not to exceed 1,000 mg/dose; maintenance (<75 kg), 10 mg/kg IV over 30 minutes every 4 weeks; (≥75 kg), follow adult dosing not to exceed 1,000 mg/dose	Single use vial: 250 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
Adalimumab	<p><u>Ankylosing spondylitis:</u> 40 mg SC every other week</p> <p><u>Crohn's disease:</u> 160 mg SC at week 0 (may administer as four injections in 1 day or two injections daily for 2 consecutive days), followed by 80 mg SC during week 2 (day 15), then 40 mg SC every other week starting at week 4 (day 29)</p> <p><u>Plaque psoriasis:</u> Initial, 80 mg SC followed by 40 mg SC every other week starting 1 week after the initial dose</p> <p><u>Psoriatic arthritis:</u> 40 mg SC every other week</p> <p><u>Rheumatoid arthritis:</u> 40 mg SC every other week; may increase to 40 mg SC every week in patients not receiving concomitant methotrexate</p>	<p><u>Juvenile idiopathic arthritis (4 to 17 years):</u> 15 to &lt;30 kg, 20 mg SC every other week; ≥30 kg, 40 mg SC every other week</p> <p>There is limited data in pediatric patients with a weight &lt;15 kg.</p>	<p>Prefilled pen: 40 mg/0.8 mL</p> <p>Prefilled syringe: 20 mg/0.4 mL 40 mg/0.8 mL</p>
Anakinra	<p><u>Rheumatoid arthritis:</u> 100 mg SC daily</p>	<p>Safety and efficacy in the pediatric population have not been established.</p>	<p>Prefilled syringe: 100 mg/0.67 mL</p>
Certolizumab	<p><u>Crohn's disease:</u> Initial, 400 mg SC (as two SC injections of 200 mg) once, repeat at weeks 2 and 4; maintenance, 400 mg SC (as two SC injections of 200 mg) once every 4 weeks</p> <p><u>Rheumatoid arthritis:</u> Initial, 400 mg SC (as two SC injections of 200 mg) once and then repeat at weeks 2 and 4; maintenance, 200 mg SC once every other week or 400 mg (as two SC injections of 200 mg) every 4 weeks</p>	<p>Safety and efficacy in the pediatric population have not been established.</p>	<p>Prefilled syringe: 200 mg/mL</p> <p>Vial (powder for injection): 200 mg</p>
Etanercept	<p><u>Ankylosing spondylitis:</u> 50 mg SC weekly (given as one 50 mg injection or two 25 mg injections in one day, or one 25 mg injection given 3 to 4 days apart)</p> <p><u>Plaque psoriasis:</u> Initial, 50 mg SC twice weekly, given 3 to 4 days apart for 3 months; maintenance, 50 mg SC weekly</p> <p><u>Psoriatic arthritis:</u> 50 mg SC weekly (given as one 50 mg injection or two 25 mg injections in one day, or one 25 mg injection given 3 to 4 days apart)</p>	<p><u>Juvenile idiopathic arthritis; 2 to 17 years):</u> 0.8 mg/kg/week up to a maximum of 50 mg/week SC</p>	<p>Prefilled "SureClick" autoinjector: 50 mg/mL</p> <p>Prefilled syringes: 25 mg/0.5 mL 50 mg/mL</p> <p>Vial (powder for injection): 25 mg</p>

Generic Name	Adult Dose	Pediatric Dose	Availability
	<u>Rheumatoid arthritis:</u> 50 mg SC weekly (given as one 50 mg injection or two 25 mg injections in one day, or one 25 mg injection given 3 to 4 days apart)		
Golimumab	<u>Ankylosing spondylitis:</u> 50 mg SC once monthly  <u>Psoriatic arthritis:</u> 50 mg SC once monthly  <u>Rheumatoid arthritis:</u> 50 mg SC once monthly in combination with methotrexate	Safety and efficacy in the pediatric population have not been established.	Prefilled "SmartJect" autoinjector: 50 mg/0.5 mL  Prefilled syringe: 50 mg/0.5 mL
Infliximab	<u>Ankylosing Spondylitis:</u> Induction, 5 mg/kg IV over 2 hours at weeks 0, 2, and 6; maintenance, 5 mg/kg IV over 2 hours every 6 weeks  <u>Crohn's disease:</u> Induction, 5 mg/kg IV over 2 hours at weeks 0, 2, and 6; maintenance, 5 mg/kg IV over 2 hours every 8 weeks; may be increased to 10 mg/kg in patients that respond then lose response  <u>Plaque psoriasis:</u> Induction, 5 mg/kg IV over 2 hours at weeks 0, 2, and 6; maintenance, 5 mg/kg IV over 2 hours every 8 weeks  <u>Psoriatic arthritis:</u> Induction, 5 mg/kg IV over 2 hours at weeks 0, 2, and 6; maintenance, 5 mg/kg IV over 2 hours every 8 weeks; with or without methotrexate  <u>Rheumatoid arthritis:</u> Induction, 3 mg/kg IV over 2 hours at weeks 0, 2, and 6; maintenance, 3 mg/kg IV over 2 hours every 8 weeks; may be increased to 10 mg/kg IV over 2 hours every 8 weeks or 3 mg/kg IV over 2 hours every 4 weeks if incomplete response; all in combination with methotrexate  <u>Ulcerative colitis:</u> Induction, 5 mg/kg IV over 2 hours at weeks 0, 2, and 6; maintenance, 5 mg/kg IV over 2 hours every 8 weeks	<u>Crohn's Disease (&gt;6 years old):</u> Induction, 5 mg/kg IV over 2 hours at weeks 0, 2 and 6; maintenance, 5 mg/kg IV over 2 hours every 8 weeks	Single use vial: 100 mg
Tocilizumab	<u>Rheumatoid arthritis:</u> Initial/maintenance, 4 mg/kg IV every 4 weeks as a 60 minute infusion; dose may be increased to 8 mg/kg every 4 weeks; maximum, 800 mg/infusion	Safety and efficacy in the pediatric population have not been established.	Single use vials: 80 mg/4 mL 200 mg/10 mL 400 mg/20 mL

Generic Name	Adult Dose	Pediatric Dose	Availability
Ustekinumab	<u>Plaque psoriasis:</u> Initial ( $\leq 100$ kg), 45 mg SC followed by 45 mg 4 weeks later; ( $> 100$ kg), 90 mg SC followed by 90 mg 4 weeks later; maintenance ( $\leq 100$ kg), 45 mg every 12 weeks; ( $> 100$ kg), 90 mg every 12 weeks	Safety and efficacy in the pediatric population have not been established.	Single use vials: 45 mg/0.5 mL 90 mg/mL

IV-intravenous, SC=subcutaneous.

**Clinical Guidelines**

**Table 9. Clinical Guidelines**

Clinical Guideline	Recommendations
<p>Assessment in Ankylosing Spondylitis/European League Against Rheumatism: <b>Recommendations for the Management of Ankylosing Spondylitis (2006)</b><sup>62</sup></p>	<p>Treatment of ankylosing spondylitis (AS) should be tailored according to:</p> <ul style="list-style-type: none"> <li>○ Current manifestations of the disease (axial, peripheral, enthesal, extra-articular symptoms and signs).</li> <li>○ Level of current symptoms, clinical findings, and prognostic indicators (disease activity/inflammation, pain, function [disability, handicap], structural damage [hip involvement, spinal deformities]).</li> <li>○ General clinical status (age, sex, comorbidity, concomitant drugs).</li> <li>○ Wishes and expectations of the patient.</li> </ul> <ul style="list-style-type: none"> <li>● 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 in Ankylosing Spondylitis core set. The frequency of monitoring should be decided on an individual basis depending on symptoms, severity, and drug treatment.</li> <li>● Optimal management of AS requires a combination of non-pharmacological and pharmacological treatments.</li> <li>● Non-pharmacological treatment of AS should include patient education and regular exercise. Individual and group physical therapy should be considered. Patient associations and self help groups may be useful.</li> <li>● Non-steroidal anti-inflammatory drugs (NSAIDs) are recommended as first line drug treatment for patients with AS with pain and stiffness. In those with increased gastrointestinal risk, non-selective NSAIDs plus a gastroprotective agent, or a selective cyclooxygenase (COX)-2 inhibitor could be used.</li> <li>● Analgesics, such as opioids and paracetamol, might be considered for pain control in patients in whom NSAIDs are insufficient, contraindicated, and/or poorly tolerated.</li> <li>● 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.</li> <li>● There is no evidence for the efficacy of disease modifying antirheumatic agents (DMARDs), including methotrexate and sulfasalazine, for the treatment of axial disease. Sulfasalazine may be considered in patients with peripheral arthritis.</li> <li>● Anti-tumor necrosis factor (TNF) treatment should be given to patients with persistently high disease activity despite conventional treatments according to the Assessment in Ankylosing Spondylitis</li> </ul>

Clinical Guideline	Recommendations
	<p>recommendations. There is no evidence to support the obligatory use of DMARDs before, or concomitant with, anti-TNF treatment in patients with axial disease.</p> <ul style="list-style-type: none"> <li>• Total hip arthroplasty should be considered in patients with refractory pain or disability and radiographic evidence of structural damage, independent of age. Spinal surgery, corrective osteotomy and stabilization procedures, may be of value in selected patients.</li> </ul>
<p>Assessment in Ankylosing Spondylitis: <b>Consensus Statement for the Use of Anti-Tumor Necrosis Factor Agents in Patients with Ankylosing Spondylitis (2006)</b><sup>63</sup></p>	<ul style="list-style-type: none"> <li>• All patients should have had adequate therapeutic trials of at least two NSAIDs. An adequate therapeutic trial is defined as:               <ul style="list-style-type: none"> <li>○ Treatment for at least three months at maximum recommended or tolerated anti-inflammatory dose unless contraindicated.</li> <li>○ Treatment for &lt;3 months where treatment was withdrawn because of intolerance, toxicity, or contraindications.</li> </ul> </li> <li>• Patients with pure axial manifestations do not have to take DMARDs before anti-TNF treatment can be started.</li> <li>• Patients with symptomatic peripheral arthritis should have an insufficient response to at least one local corticosteroid injection if appropriate.</li> <li>• Patients with persistent peripheral arthritis must have had a therapeutic trial of sulfasalazine.</li> <li>• Patients with symptomatic enthesitis must have failed appropriate local treatment.</li> <li>• Etanercept and infliximab are both recommended as options for the treatment of patients with active AS who are not satisfactorily treated conventionally with NSAIDs. It is expected that adalimumab may be effective but data are limited and it has not been registered for the use in AS to date (please note that the publication of these guidelines was before Food and Drug Administration (FDA) approval of golimumab).</li> <li>• It is recommended and strongly encouraged that all clinicians prescribing these agents should preferably register patients on TNF-blocker treatment in a national register to collect information on outcome and toxicity of anti-TNF agents.</li> <li>• At present there is limited evidence to support long term treatment beyond two or more years. For infliximab there is evidence of efficacy and safety for up to three years, and for etanercept up to two years. Data for longer term treatment are expected but are not yet available. Withdrawal of anti-TNF treatment after years of continuous treatment often leads to clinical relapse.</li> <li>• The evidence for consecutive use of the different agents is limited. As with rheumatoid arthritis, switching from one anti-TNF agent to another has been done but there is limited experience. Early reports on limited patient numbers suggest that the switch is possible and partly successful (unpublished observations).</li> </ul>
<p>National Institute for Health and Clinical Excellence: <b>Adalimumab, Etanercept and Infliximab for Ankylosing Spondylitis (2008)</b><sup>64</sup></p>	<ul style="list-style-type: none"> <li>• Adalimumab or etanercept are recommended as treatment options for adults with severe active AS only if all of the following criteria are fulfilled:               <ul style="list-style-type: none"> <li>○ The patient's disease satisfies the modified New York criteria for diagnosis of AS.</li> <li>○ There is confirmation of sustained active spinal disease, demonstrated by: a score of at least four units on the Bath Ankylosing Spondylitis 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</li> </ul> </li> </ul>

Clinical Guideline	Recommendations
	<p>weeks apart without any change of treatment).</p> <ul style="list-style-type: none"> <li>○ Conventional treatment with two or more NSAIDs taken sequentially at maximum tolerated or recommended dosage for four weeks has failed to control symptoms.</li> <li>● 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.</li> <li>● 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.</li> <li>● Golimumab was not incorporated into the guidelines at last publication due to the recent FDA approval (April 24, 2009).</li> </ul>
<p>American College of Gastroenterology: <b>Management of Crohn's Disease in Adults(2009)</b><sup>65</sup></p>	<p><u>Mild to moderate active disease</u></p> <ul style="list-style-type: none"> <li>● Ileal, ileocolonic, or colonic disease has commonly been treated in clinical practice with oral mesalamine 3.2 to 4.0 g daily or sulfasalazine for ileocolonic or colonic disease as 3 to 6 g daily in divided doses.</li> <li>● Despite the use of oral mesalamine treatment in the past, new evidence suggests that this approach is minimally effective as compared with placebo and less effective than budesonide or conventional corticosteroids.</li> <li>● Alternatively, metronidazole at a dose of 10 to 20 mg/kg/day has been used in a proportion of patients not responding to sulfasalazine.</li> <li>● Controlled ileal release budesonide (9 mg/day) is effective when active disease is confined to the ileum and/or right colon.</li> <li>● Anti-tuberculous therapy has not been effective for either induction of remission or maintenance of remission in patients with Crohn's disease.</li> </ul> <p><u>Moderate to severe disease</u></p> <ul style="list-style-type: none"> <li>● 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 7 to 28 days).</li> <li>● Infection or abscess requires appropriate antibiotic therapy or drainage (percutaneous or surgical).</li> <li>● Elemental diets are less effective than corticosteroids, but can avoid corticosteroid-induced toxicities.</li> <li>● 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.</li> <li>● The anti-TNF monoclonal antibodies, 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.</li> <li>● 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.</li> <li>● Adalimumab, certolizumab, and infliximab may be used as alternatives to steroid therapy in selected patients in whom corticosteroids are</li> </ul>

Clinical Guideline	Recommendations
	<p>contraindicated or not desired.</p> <ul style="list-style-type: none"> <li>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 anti-TNF monoclonal antibody therapy.</li> </ul> <p><u>Severe/fulminant disease</u></p> <ul style="list-style-type: none"> <li>As a consequence 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.</li> <li>Patients with persistence of Crohn's related symptoms despite introduction of conventional oral steroids or an anti-TNF (adalimumab or infliximab), or those presenting with high fever, frequent vomiting, evidence of intestinal obstruction, rebound tenderness, cachexia, or evidence of an abscess should be hospitalized.</li> <li>Surgical evaluation is warranted for patients with intestinal obstruction or who have a tender abdominal mass.</li> <li>An abdominal mass should be evaluated through transabdominal ultrasound, magnetic resonance imaging scan.</li> <li>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.</li> <li>There is no specific role for total parenteral nutrition in addition to steroids. Nutritional support through elemental feeding or parenteral hyperalimentation is indicated, after 5 to 7 days, for patients who are unable to maintain adequate nutritional requirements.</li> </ul> <p><u>Perianal and fistulizing disease</u></p> <ul style="list-style-type: none"> <li>Acute suppuration is an indication for surgical drainage with or without placement of non-cutting setons.</li> <li>Nonsuppurative, chronic fistulization, or perianal fissuring is treated medically with antibiotics, immunosuppressives or infliximab.</li> </ul> <p><u>Maintenance therapy</u></p> <ul style="list-style-type: none"> <li>Mesalamine and sulfasalazine have not had consistent maintenance benefits after medical inductive therapy.</li> <li>Conventional corticosteroids should not be used as long-term agents to prevent relapse of Crohn's disease.</li> <li>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.</li> <li>Azathioprine/6-mercaptopurine and methotrexate have demonstrable maintenance benefits after inductive therapy with corticosteroids.</li> <li>Azathioprine can maintain remissions induced by infliximab in steroid-naive patients.</li> <li>Maintenance therapy with adalimumab, certolizumab, and infliximab is effective.</li> <li>Infliximab monotherapy and infliximab combined with azathioprine are more effective than azathioprine for maintenance of patients with</li> </ul>

Clinical Guideline	Recommendations
	<p>moderate to severe Crohn's disease who have failed to respond to first-line therapy with mesalamine and/or corticosteroids.</p> <ul style="list-style-type: none"> <li>• Maintenance therapy with natalizumab is effective.</li> <li>• 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.</li> </ul>
<p>National Institute for Health and Clinical Excellence: <b>Etanercept for the Treatment of Juvenile Idiopathic Arthritis (2002)</b><sup>66</sup></p>	<ul style="list-style-type: none"> <li>• Etanercept is recommended for children aged 4 to 17 years who have active juvenile idiopathic arthritis in at least five joints and whose condition has not responded adequately to methotrexate or who have been unable to tolerate treatment with methotrexate.</li> <li>• Adalimumab was approved on 02/21/2008 for the treatment of juvenile idiopathic arthritis and as such is not included in this guideline.</li> </ul>
<p>American Academy of Dermatology: <b>Guidelines of Care for the Management of Psoriasis and Psoriatic Arthritis, Sections 2, 3 and 4 (2008-2009)</b><sup>67-69</sup></p>	<p><u>Topical therapies</u></p> <ul style="list-style-type: none"> <li>• Approximately 80% of patients are affected with mild to moderate psoriasis with the majority of cases being able to be successfully treated with topical agents.</li> <li>• Topical agents are also used adjunctively to either ultraviolet light or systemic medications for resistant lesions in patients with more severe disease.</li> <li>• 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.</li> <li>• Topical corticosteroids are the cornerstone of treatment for the majority of patients with psoriasis.</li> <li>• Other topical agents include anthralin, coal tar, nonmedicated topical moisturizers, pimecrolimus, salicylic acid, tacrolimus, tazarotene, vitamin D analogues, and combination products.</li> <li>• Salicylic acid is a topical keratolytic agent that has been used for many years and has no specific FDA indication.</li> <li>• 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.</li> </ul> <p><u>Systemic therapies</u></p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• 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.</li> <li>• 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.</li> <li>• 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</li> </ul>

Clinical Guideline	Recommendations
	<p>immunosuppression; effects are dose-dependent and response is observed after three to six months.</p> <ul style="list-style-type: none"> <li>• 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.</li> </ul> <p><u>Biologics</u></p> <ul style="list-style-type: none"> <li>• Three TNF-blockers 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).</li> <li>• 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.</li> <li>• NSAIDs and/or intra-articular injections of corticosteroids may be appropriate treatment options in patients with milder, localized disease.</li> <li>• 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-blockers, or both. These treatment options are considered the standard of care.</li> <li>• 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.</li> <li>• 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 expectancy.</li> <li>• Because the clinical trial efficacy data (primary end point of American College of Rheumatology 20% improvement) with all three FDA approved TNF-blockers 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.</li> <li>• 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.</li> </ul>
<p>American College of Rheumatology: <b>Recommendations for the Use of Nonbiologic and Biologic Disease-Modifying Antirheumatic Drugs in Rheumatoid Arthritis (June 2008)</b><sup>70</sup></p>	<p><u>Recommendations for the use of biologic DMARDs</u></p> <ul style="list-style-type: none"> <li>• Rheumatoid arthritis &lt;6 months, TNF-blockers recommended in the following: <ul style="list-style-type: none"> <li>○ Low or moderate disease activity &lt;6 months - biologics not recommended.</li> <li>○ High disease activity for &lt;3 months - recommended in patients with methotrexate who had never received DMARDs and have poor prognosis.</li> <li>○ High disease activity for 3 to 6 months - recommended in patients with methotrexate who had never received DMARDs.</li> </ul> </li> <li>• Rheumatoid arthritis ≥6 months, TNF-blockers recommended in the</li> </ul>

Clinical Guideline	Recommendations
	<p>following:</p> <ul style="list-style-type: none"> <li>○ Patients where methotrexate monotherapy led to an inadequate response, with moderate disease activity and features of a poor prognosis, and for patients with high disease activity, irrespective of prognostic features.</li> <li>○ Patients where prior methotrexate therapy was used in combination, or if sequential administration of other nonbiological DMARDs led to an inadequate response with at least moderate disease activity irrespective of prognostic features.</li> </ul> <ul style="list-style-type: none"> <li>● Abatacept is recommended in patients that had inadequate response with methotrexate in combination with DMARDs or sequential administration of other nonbiologic DMARDs and have at least moderate disease activity and features of poor prognosis.</li> <li>● Rituximab is recommended in patients that had inadequate response with methotrexate in combination with DMARDs or sequential administration of other nonbiologic DMARDs and have high disease activity and features of poor prognosis.</li> <li>● Anakinra was not addressed in the guidelines because it is not recommended for patients who were to start or resume treatment with DMARDs and its low utilization.</li> <li>● Certolizumab, golimumab, tocilizumab and ustekinumab had not been FDA approved for rheumatoid arthritis at the time of this publication.</li> </ul>
<p>National Institute for Health and Clinical Excellence:  <b>Rheumatoid Arthritis National Clinical Guideline for Management and Treatment in Adults (2009)</b><sup>13</sup></p>	<ul style="list-style-type: none"> <li>● 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.</li> <li>● 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.</li> <li>● In people with newly diagnosed rheumatoid arthritis for whom 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.</li> <li>● 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.</li> <li>● 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.</li> <li>● 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.</li> <li>● Consider offering short-term treatment with glucocorticoids (oral, intramuscular or intraarticular) to rapidly improve symptoms in people with newly diagnosed rheumatoid arthritis if they are not already receiving glucocorticoids as part of DMARD combination therapy.</li> <li>● Offer short-term treatment with glucocorticoids for managing flares in people with recent onset or established disease, to rapidly decrease</li> </ul>

Clinical Guideline	Recommendations
	<p>inflammation.</p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• 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.</li> <li>• 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.</li> <li>• Do not offer the combination of TNF-<math>\alpha</math> inhibitor therapy and anakinra for rheumatoid arthritis.</li> <li>• Oral NSAIDs/Cox-2 inhibitors should be used at the lowest effective dose for the shortest possible period of time.</li> <li>• When offering treatment with an oral NSAID/Cox-2 inhibitor, the first choice should be either a standard NSAID or a COX-2 inhibitor. In either case, these should be coprescribed with a proton pump inhibitor, choosing the one with the lowest acquisition cost.</li> <li>• All oral NSAIDs/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.</li> <li>• 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.</li> <li>• If NSAIDs or COX-2 inhibitors are not providing satisfactory symptom control, review the disease-modifying or biological drug regimen.</li> <li>• The TNF-alpha inhibitors adalimumab, etanercept and infliximab are recommended as options for the treatment of adults who have both of the following characteristics: <ul style="list-style-type: none"> <li>○ Active rheumatoid arthritis as measured by disease activity score (DAS 28) &gt;5.1 confirmed on at least two occasions, one month apart.</li> <li>○ 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.</li> </ul> </li> <li>• TNF-<math>\alpha</math> 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, adalimumab and etanercept may be given as monotherapy.</li> <li>• Treatment with TNF-<math>\alpha</math> 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.</li> </ul>

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> <li>• 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.</li> <li>• An alternative TNF-<math>\alpha</math> 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.</li> <li>• Escalation of dose of the TNF-<math>\alpha</math> inhibitors above their licensed starting dose is not recommended.</li> <li>• 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.</li> <li>• Use of the TNF-<math>\alpha</math> inhibitors for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate or other DMARDs is not recommended.</li> <li>• Initiation of TNF-<math>\alpha</math> 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.</li> </ul>
<p>National Institute for Health and Clinical Excellence:  <b>Adalimumab, Etanercept, Infliximab, Rituximab and Abatacept for the Treatment of Rheumatoid Arthritis After the Failure of a Tumor Necrosis Factor Inhibitor</b><sup>71</sup></p>	<ul style="list-style-type: none"> <li>• 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 inhibitor.</li> <li>• Treatment with rituximab should be given no more frequently than every six months and should be continued only if an adequate response is maintained at this dosing interval.</li> <li>• 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 inhibitor and cannot receive rituximab because of a contraindication to or adverse event with rituximab.</li> <li>• 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 inhibitor and cannot receive rituximab because of a contraindication to or adverse event with methotrexate.</li> <li>• Treatment with abatacept, adalimumab, etanercept and infliximab should be continued only if there is an adequate response six months after therapy.</li> <li>• 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.</li> </ul>
<p>American College of Gastroenterology, Practice Parameters Committee:  <b>Ulcerative Colitis Practice Guidelines in Adults (2010)</b><sup>72</sup></p>	<p><u>Management of mild-moderate distal colitis</u></p> <ul style="list-style-type: none"> <li>• Topical mesalamine agents are “superior” to topical steroids or oral aminosalicylates.</li> <li>• The combination of oral and topical agents is “superior” to each agent used alone.</li> <li>• 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</li> </ul>

Clinical Guideline	Recommendations
	<p>aminosalicylates in achieving clinical improvement in patients with mild-moderate distal colitis.</p> <ul style="list-style-type: none"> <li>• 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 0, 2 and 6.</li> <li>• Oral therapy effective for achieving and maintaining remission include: aminosalicylates, balsalazide, mesalamine, olsalazine and sulfasalazine.</li> </ul> <p><u>Maintenance of remission in distal disease</u></p> <ul style="list-style-type: none"> <li>• Balsalazide, mesalamine and sulfasalazine are effective in maintaining remission; combination oral and topical mesalamine is more effective than oral mesalamine alone.</li> <li>• Mesalamine suppositories are effective for maintenance of remission in patients with proctitis and mesalamine enemas are effective in patients with distal colitis.</li> <li>• Topical corticosteroids, including budesonide, have not been proven to be effective at maintaining remission.</li> <li>• When patients fail to maintain remission with the above therapies, thiopurines (6-mercaptopurine or azathioprine) and infliximab may be effective.</li> </ul> <p><u>Management of mild-moderate extensive colitis: active disease</u></p> <ul style="list-style-type: none"> <li>• Oral sulfasalazine is considered first line.</li> <li>• Reserve oral steroids for patients refractory to oral aminosalicylates or patients who require rapid improvement.</li> <li>• 6-mercaptopurine or azathioprine can be used for patients refractory to oral prednisone and are acutely ill, requiring intravenous therapy.</li> <li>• 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.</li> </ul> <p><u>Maintenance of remission for mild-moderate extensive colitis</u></p> <ul style="list-style-type: none"> <li>• Balsalazide, mesalamine, olsalazine and sulfasalazine are effective in reducing the number of relapses.</li> <li>• 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.</li> <li>• Infliximab effectively maintains remission in patient who responded to the infliximab induction regimen.</li> </ul> <p><u>Management of severe colitis</u></p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• Patients that show signs of toxicity should be hospitalized to receive intravenous steroids.</li> <li>• Failure to significantly improve within three to five days indicates need for intravenous cyclosporine (or colectomy - weaker evidence).</li> <li>• Infliximab may also be used to avoid colectomy in patients failing intravenous steroids; however, long-term efficacy in this setting is unknown.</li> </ul>

### 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.<sup>3-8,10-12</sup> There is 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). Additionally, current clinical guidelines do not distinguish among the different agents for any indication. The adverse event profiles are similar across the class. Of note, adalimumab and infliximab have the most FDA approved indications.

### Appendix I: Other Insurance Coverage

Managed Care Organization	Current Coverage
MassHealth (Massachusetts Medicaid)	PA required (all)
New Hampshire Medicaid	PA required (all); Enbrel & Humira preferred
New York Medicaid	Enbrel & Humira preferred; PA required (others)
MVP Healthcare	PA required (all); Enbrel & Humira preferred/Tier 2
Cigna Healthcare	PA required (all); Remicade, Enbrel & Humira preferred
Blue Cross Blue Shield of Vermont	PA required (all); QLs (Cimzia, Humira, Enbrel, Kineret, Extavia, Amevive)

### Appendix II: Utilization Within this Drug Class for DVHA: October 1, 2010 to March 31, 2011

Medication	Unique Utilizers	# of Claims	% Marketshare	Amount Paid	Avg Cost/Claim
Enbrel	71	281	47.79%	\$524,483.74	\$1,866.49
Humira	66	250	42.52%	\$432,465.62	\$1,729.86
Cimzia	12	34	5.78%	\$68,842.22	\$2,024.77
Stelara	4	10	1.70%	\$66,153.80	\$6,615.38
Simponi	2	9	1.53%	\$16,356.03	\$1,817.34
Kineret	1	4	0.68%	\$6,319.85	\$1,579.96
<b>Class Total:</b>	<b>NA</b>	<b>588</b>	<b>100%</b>	<b>\$1,114,621.26</b>	<b>\$1,895.61</b>

### Recommendations

In recognition of the established efficacy and safety of the immunomodulators for their Food and Drug Administration (FDA) approved indications, the recent addition of the juvenile rheumatoid arthritis indication for Actemra<sup>®</sup>, the limited head-to-head trials comparing the agents in this class, the potential risk for adverse effects including infections, the number of approved indications with published clinical evidence for Enbrel<sup>®</sup> and Humira<sup>®</sup>, and intravenous administration with Remicade<sup>®</sup>, the following changes are recommended to the Actemra<sup>®</sup> approval criteria (see below in red). For a summary of the clinical data for Actemra<sup>®</sup> in JRA, please refer to a separate new indication overview document.

#### Actemra<sup>®</sup>:

- Patient has a diagnosis of RA or juvenile RA (JRA) and has already been stabilized on Actemra<sup>®</sup>
- OR**
- Diagnosis is RA or juvenile RA (JRA) and patient has documentation of an inadequate response, adverse reaction or allergic response to methotrexate, or if methotrexate is contraindicated, at least 1 other DMARD.\*
- AND**
- The prescriber must provide a clinically valid reason why either Humira<sup>®</sup> or Enbrel<sup>®</sup> cannot be used.

The following changes are recommended to the Cimzia® approval criteria. (in red):

**Cimzia®:**

- Patient has a diagnosis of RA or Crohn's disease and has already been stabilized on Cimzia®

**OR**

- Patient age  $\geq$  18 years

**AND**

- Diagnosis is moderate to severe Crohn's disease and at least 2 of the following drug classes resulted in an adverse effect, allergic reaction, inadequate response, or treatment failure (i.e. resistant or intolerant to steroids or immunosuppressants): aminosaliclates, antibiotics, corticosteroids, and immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate.

**AND**

- **The prescriber must provide a clinically valid reason why Humira® cannot be used.**

**OR**

Diagnosis is RA and patient has documentation of an inadequate response, adverse reaction or allergic response to methotrexate, or if methotrexate is contraindicated, at least 1 DMARD (other DMARDs include leflunomide, sulfasalazine, gold, antimalarials, minocycline, D-penicillamine, azathioprine, cyclophosphamide and cyclosporine)

**AND**

- The prescriber must provide a clinically valid reason why either Humira® or Enbrel® cannot be used.

In addition, the current approval criteria for Orenzia® do not address its FDA-approved indication for the treatment of juvenile rheumatoid arthritis. Consequently, the following changes are recommended (in red):

**Orenzia®**

- Patient has a diagnosis of RA **or juvenile RA (JRA)** and has already been stabilized on Orenzia®

**OR**

Diagnosis is RA **or juvenile RA (JRA)** and methotrexate therapy resulted in an adverse effect, allergic reaction, inadequate response, or treatment failure. If methotrexate is contraindicated, another DMARD should be tried prior to approving Orenzia®. \* **Note:** Orenzia® may be used as monotherapy or concomitantly with DMARDs, other than TNF antagonists. Orenzia® should not be administered concomitantly with TNF antagonists (i.e. Enbrel®, Humira®, or Remicade®) and is not recommended for use with Kineret®.

**AND**

- The prescriber must provide a clinically valid reason why either Humira® or Enbrel® cannot be used.

**\* Patients with systemic juvenile arthritis (SJRA/SJIA) and fever are not required to have a trial of a DMARD, including methotrexate. Patients with systemic juvenile arthritis without fever should have a trial of methotrexate, but a trial of another DMARD in case of a contraindication to methotrexate, is not required before Enbrel®, Humira®, Actemra®, or Orenzia® is approved.**

At this time, DVHA has the following quantity limit restrictions in place:

- Actemra® (tocilizumab): Quantity limit = 4 vials/28 days (80 mg vial), 3 vials/28 days (200 mg vial) or 2 vials/28 days (400 mg vial)
- Cimzia® (certolizumab pegol): Quantity limit = 1 kit/28 days
- Simponi® (golimumab): Quantity limit = 1 syringe/month

- Stelara<sup>®</sup> (ustekinumab): Quantity limit = 45 mg (0.5 ml) or 90 mg (1 ml) per dose; 90 mg dose only permitted for pt weight > 100 kg

It is recommended that the following quantity limits be added for Humira<sup>®</sup>, Enbrel<sup>®</sup> and Kineret<sup>®</sup>:

- Kineret<sup>®</sup> (anakinra): Quantity limit = 1 syringe/day
- Humira<sup>®</sup> (adalimumab): Quantity limit = 6 syringes/28 days for the first month; 4 syringes/28 days subsequently
- Enbrel<sup>®</sup> (etanercept): Quantity limit = 8 syringes/28 days for the first 3 months; 4 syringes/28 days subsequently

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