AETNA BETTER HEALTH®
Clinical Policy Bulletin:
Tocilizumab (Actemra)

Number: 0799

Policy

Note: REQUIRES PRECERTIFICATION.*

I. Aetna considers intravenous or subcutaneous tocilizumab (Actemra) medically necessary for the treatment of individuals with moderate-to-severe active rheumatoid arthritis who have had an inadequate response to 1 or more disease-modifying anti-rheumatic drugs (DMARDs) (see Note).

II. Aetna considers intravenous tocilizumab medically necessary for the following indications:

A. Active systemic onset juvenile idiopathic arthritis, in persons who have not responded to a trial of a non-steroidal antiinflammatory drug (NSAID) alone, or whose initial symptoms include high fevers and painful polyarthritis (severe disease) (see note); or

B. Moderate to severely active polyarticular juvenile idiopathic arthritis, or juvenile rheumatoid arthritis) in persons 2 years of age and older (see note); or

C. Castleman’s disease (CD) when the following criteria are met:
   1. Second-line therapy as a single agent for relapsed or refractory unicentric CD for patients who are human immunodeficiency virus-negative and human herpesvirus-8-negative; or
   2. Subsequent therapy as a single agent for multicentric CD that has progressed following treatment of relapsed/refractory or progressive disease.
Tocilizumab (Actemra)

Aetna considers tocilizumab experimental and investigational for the following criteria:

- Use not approved by the FDA; AND
- The use is unapproved and not supported by the literature or evidence as an accepted off-label use

* Precertification of tocilizumab is required of all Aetna participating providers and members in applicable plan designs. For precertification of tocilizumab, call (866) 503-0857, or fax (866) 267-3277.

Note: There are several brands of targeted immune modulators on the market. There is a lack of reliable evidence that any one brand of targeted immune modulator is superior to other brands for medically necessary indications. Enbrel (etanercept), Humira (adalimumab), Remicade (infliximab), Simponi Aria (golimumab intravenous) and Stelara (ustekinumab) brands of targeted immune modulators ("least cost brands of targeted immune modulators") are less costly to Aetna. Consequently, because other brands (e.g., Actemra (tocilizumab), Cimzia (certolizumab), Cosentyx (secukinumab), Enblyso (vedolizumab), Kineret (anakinra), Ocrevus (abatacept), Otezla (apremilast), Rituxan (rituximab), Simponi (golimumab), and Xeljanz (tofacitinib)) of injectables are more costly than these least cost brands of targeted immune modulators, and least cost brands of targeted immune modulators are at least as likely to produce equivalent therapeutic results, no other brands of targeted immune modulator will be considered medically necessary unless the member has a contraindication, intolerance or incomplete response to at least 2 of the least cost brands of targeted immune modulator: Enbrel, Humira, Remicade, Simponi Aria, or Stelara, for the same medically necessary indication. If the least costly targeted immune modulator does not have the labeled indication (see appendix), then Aetna considers medically necessary another brand of targeted immune modulator that has the required labeling indication. For some Aetna plans, the use of other brands of intravenously infused targeted immune modulators (tocilizumab (Actemra), abatacept (Ocrevus), and rituximab (Rituxan)) will not be considered medically necessary unless the member has a contraindication, intolerance or incomplete response to the least cost brand of intravenously infused targeted immune modulator, infliximab (Remicade) for the same medically necessary indication.

See also CPB 0314 - Rituximab (Rituxan), CPB 0315 - Enbrel (Etanercept), CPB 0341 - Remicade (infliximab), CPB 0595 - Kineret (Anakinra), CPB 0655 - Adalimumab (Humira), CPB 0720 - Abatacept (Ocrevus), CPB 0761 - Certolizumab Pegol (Cimzia), and CPB 0790 - Golimumab (Simponi).

Background

Rheumatoid arthritis (RA) is a chronic, inflammatory, autoimmune disorder characterized by inflammation of synovial joints resulting in progressive erosion of cartilage and bone. The main objectives of treatment of RA are 3-fold: (i) to interfere with the disease process (i.e., inflammation and destruction of the joints), (ii) preserve physical function, and (iii) prevent long-term disability. The American College of Rheumatology (ACR)'s guidelines for the treatment of RA (1996) recommended that newly diagnosed patients with RA begin treatment with disease-modifying anti-rheumatic drugs (DMARDs) within 3 months of diagnosis. Methotrexate (MTX) remains the most commonly prescribed DMARD and is the standard by which recent new and emerging therapies are measured. In addition to traditional DMARDs, tumor necrosis factor (TNF) antagonists (e.g., adalimumab,
etanercept, and infliximab) are currently being used for the treatment of RA. However, only 60 to 70 % of RA patients respond to treatment with a TNF antagonist. Furthermore, the majority of patients show only a partial response according to ACR20 (20 % improvement) criteria (Voll and Kalden, 2005). Contraindications such as infection and cardiac failure also add to the number of patients who need alternative treatment.

A better understanding of the inflammatory pathway in RA has led to the development of a number of targeted biological therapies. Over-activity of the cytokine, interleukin-6 (IL-6), plays an important role in both the exudative as well as the proliferative phase of rheumatoid inflammation, joint destruction and osteoporosis. Thus, inhibition of IL-6 activity is a rational approach in the treatment of patients with RA. Tocilizumab, a humanized monoclonal antibody, blocks inflammatory responses by inhibiting both the soluble as well as the membrane-bound IL-6 receptor.

The effectiveness of tocilizumab in rheumatoid arthritis has been demonstrated in multicenter, randomized clinical studies. In a double-blind, randomized, placebo-controlled, parallel group phase III study, Smolen et al (2008) evaluated the therapeutic effects of tocilizumab in patients with RA. A total of 623 patients with moderate-to-severe active RA were randomly assigned to receive tocilizumab 8 mg/kg (n = 205), tocilizumab 4 mg/kg (n = 214), or placebo (n = 204) intravenously every 4 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 less than 20 % improvement in both swollen and tender joint counts. The primary endpoint was the proportion of patients with 20 % improvement in signs and symptoms of RA according to ACR20 response at week 24. The intention-to-treat analysis population consisted of 622 patients: 1 patient in the 4 mg/kg group did not receive study treatment and was thus excluded. At 24 weeks, ACR20 responses were seen in more patients receiving tocilizumab than in those receiving placebo (120 [59 %] patients in the 8 mg/kg group, 102 [48 %] in the 4 mg/kg group, 54 [26 %] in the placebo group; odds ratio 4·0 [95 % confidence interval (CI): 2.6 to 6.1], p < 0.0001 for 8 mg/kg versus placebo; and 2.6 [1.7 to 3.9], p < 0.0001 for 4 mg/kg versus placebo). More people receiving tocilizumab than those receiving placebo had at least one adverse event (143 [69 %] in the 8 mg/kg group; 151 [71 %] in the 4 mg/kg group; 129 [63 %] in the placebo group). The most common serious adverse events (SAE) were serious infections or infestations, reported by 6 patients in the 8 mg/kg group, 3 in the 4 mg/kg group, and 2 in the placebo group. The authors concluded that tocilizumab could be an effective therapeutic approach in patients with moderate-to-severe active RA.

In a phase III clinical study, Emery and co-workers (2008) examined the safety and effectiveness of tocilizumab in patients with RA refractory to TNF antagonist therapy. A total of 499 patients with inadequate response to one or more TNF antagonists were randomly assigned to receive 8 mg/kg or 4 mg/kg tocilizumab or placebo (control) intravenously every 4 weeks with stable MTX for 24 weeks. ACR20 responses, secondary safety and effectiveness endpoints were assessed. ACR20 was achieved at 24 weeks by 50.0 %, 30.4 % and 10.1 % of patients in the 8 mg/kg, 4 mg/kg and control groups, respectively (less than p < 0.001 both tocilizumab groups versus control). At week 4, more patients achieved ACR20 in 8 mg/kg tocilizumab versus controls (less than p = 0.001). Patients responded regardless of most recently failed anti-TNF or the number of failed treatments. Disease activity score 28 (DAS28) remission (i.e., DAS28 less than 2.6) rates at week 24 were clearly dose-related, being achieved by 30.1 %, 7.6 % and 1.6 % of 8 mg/kg, 4 mg/kg and control groups (less than p = 0.001 for 8 mg/kg and p = 0.053 for 4 mg/kg versus control). Most AEs were mild or moderate with overall incidences of 84.0 %, 87.1 % and 80.6 %, respectively. The most common AEs with higher incidence in tocilizumab groups were infections, gastrointestinal symptoms, rash and headache. The incidence of SAE was higher in controls (11.3 %) than in the 8 mg/kg
(6.3 %) and 4 mg/kg (7.4 %) groups. The authors concluded that tocilizumab in combination with MTX is effective in achieving rapid and sustained improvements in signs and symptoms of RA in patients with inadequate response to TNF antagonists and has a manageable safety profile.

Genovese et al (2008) examined the safety and effectiveness of tocilizumab combined with conventional DMARDs in patients with active RA. A total of 1,220 patients were randomized (2:1 ratio) in the phase III, double-blind, placebo-controlled, multi-center TOWARD (Tocilizumab in Combination With Traditional DMARD Therapy) study. Patients remained on stable doses of DMARDs and received tocilizumab 8 mg/kg or placebo (control group) every 4 weeks for 24 weeks. At week 24, the proportion of patients achieving a response according to ACR20 was significantly greater in the tocilizumab plus DMARD group than in the control group (61 % versus 25 %; p < 0.0001). Secondary end points including ACR50/70, DAS28, DAS28 remission responses (DAS28 less than 2.6), European League Against Rheumatism (EULAR) responses, and systemic markers such as the C-reactive protein (CRP) and hemoglobin levels showed superiority of tocilizumab plus DMARDs over DMARDs alone. Seventy-three percent of patients in the tocilizumab group had greater than or equal to 1 AE, compared with 61 % of patients in the control group. Adverse events leading to withdrawal from the study were infrequent (4 % of patients in the tocilizumab group and 2 % of those in the control group); SAE occurred in 6.7 % and 4.3 % of patients in the tocilizumab and control groups, respectively, and serious infections occurred in 2.7 % and 1.9 %, respectively. Elevations in the alanine aminotransferase level, from normal at baseline to greater than 3-fold the upper limit of normal, occurred in 4 % of patients in the tocilizumab group and 1 % of those in the control group, and elevated total cholesterol levels were observed in 23 % and 6 % of patients, respectively. Sixteen patients started lipid-lowering therapy during the study. Grade 3 neutropenia occurred in 3.7 % of patients receiving tocilizumab and none of the patients in the control group, and no grade 4 neutropenia was reported. The authors concluded that tocilizumab combined with any of the DMARDs evaluated was safe and effective in reducing articular and systemic symptoms in patients with an inadequate response to these agents.

In an open-label, long-term extension trial following an initial 3-month randomized phase II trial, Nishimoto and colleagues (2009a) assessed the safety and effectiveness of 5-year, long-term tocilizumab monotherapy for patients with RA. A total of 143 out of the 163 patients who participated in the initial blinded study received tocilizumab monotherapy (8 mg/kg) every 4 weeks. Concomitant therapy with non-steroidal anti-inflammatory drugs and/or oral prednisolone (10 mg daily maximum) was permitted. All patients were evaluated with ACR improvement criteria, DAS28, and EULAR response, as well as for safety issues. A total of 94 (66 %) of the 143 patients had completed 5 years as of March 2007; 32 patients (22 %) withdrew from the study due to AEs and 1 patient (0.7 %) due to unsatisfactory response. Fourteen patients withdrew because of the patient's request or other reasons. The SAE rate was 27.5 events per 100 patient-years, with 5.7 serious infections per 100 patient-years, based on a total tocilizumab exposure of 612 patient-years. Of the 88 patients receiving corticosteroids at baseline, 78 (88.6 %) were able to decrease their corticosteroid dose, and 28 (31.8 %) discontinued corticosteroids. At 5 years, 79/94 (84.0 %), 65/94 (69.1 %) and 41/94 (43.6 %) of the patients achieved ACR20, ACR50, and ACR70 improvement criteria, respectively. Remission defined as DAS28 less than 2.6 was achieved in 52/94 (55.3 %) of the patients. The authors concluded that in this 5-year extension study, tocilizumab demonstrated sustained long-term effectiveness and a generally good safety profile.

In a multi-center, double-blind, randomized, controlled study, Nishimoto et al (2009b) examined the safety and effectiveness of tocilizumab monotherapy in active RA patients...
with an inadequate response to low dose MTX. A total of 125 patients were allocated to receive either tocilizumab 8 mg/kg every 4 weeks plus MTX placebo (tocilizumab group) or tocilizumab placebo plus MTX 8 mg/week (control group) for 24 weeks. The clinical responses were measured using the ACR criteria and the DAS in 28 joints. Serum vascular endothelial growth factor (VEGF) levels were also monitored. At week 24, 25.0 % in the control group and 80.3 % in the tocilizumab group achieved ACR20 response. The tocilizumab group showed superior ACR response criteria over control at all time points. Additionally, serum VEGF levels were significantly decreased by tocilizumab treatment. The overall incidences of AEs were 72 and 92 % (SAE: 4.7 and 6.6 %; serious infections: 1.6 and 3.3 %) in the control and the tocilizumab groups, respectively. All SAE improved by adequate treatment. The authors concluded that tocilizumab monotherapy was well-tolerated and provided an excellent clinical benefit in active RA patients with an inadequate response to low dose MTX.

Oldfield et al (2009) stated that intravenous tocilizumab 8 mg/kg (and no less than 4.8 mg), in combination with MTX, is approved in the European Union for the treatment of moderate-to-severe active RA in adult patients with inadequate response to, or who are intolerant of, prior DMARD or TNF antagonist therapy. It may also be administered as monotherapy in patients intolerant of MTX or in whom MTX therapy is inappropriate. Tocilizumab is also approved in Japan for the treatment of polyarticular-course juvenile idiopathic arthritis, systemic-onset juvenile idiopathic arthritis and Castleman's disease. Intravenous tocilizumab was effective and generally well-tolerated when administered either as monotherapy or in combination with conventional DMARDs in several well designed clinical studies in adult patients with moderate-to-severe RA. Tocilizumab-based therapy was consistently more effective than placebo, MTX or other DMARDs in reducing disease activity, and some trials also showed significant benefits with tocilizumab in terms of reducing structural joint damage and improving health-related quality of life. In particular, tocilizumab-based therapy was effective in patients with long-standing disease in whom anti-TNF therapy had previously failed. The authors noted that more data are needed to determine the comparative safety and effectiveness of tocilizumab versus other biological agents and to establish their relative cost effectiveness. However, the present data suggest that tocilizumab is an important emerging treatment option in adult patients with moderate-to-severe RA.

On January 8, 2010, the FDA approved tocilizumab (Actemra) for the treatment of adults with moderate-to-severe RA who have not adequately responded to or can not tolerate other approved drug classes for RA. Actemra can be used alone or with methotrexate and DMARDs and after the use and failure of at least one TNF antagonist. Actemra recommended use is limited to patients who have failed other approved therapies because of serious safety concerns that were noted in clinical studies. These safety concerns include elevated liver enzymes, elevated low-density lipoprotein (LDL), hypertension, and gastrointestinal perforations. The FDA is requiring the manufacturer to perform a post-marketing clinical trial to further assess the long-term safety of Actemra. Specifically, the FDA wants to evaluate the impact of elevated LDL cholesterol and blood pressure observed in some patients in shorter-term trials on the cardiovascular health of patients treated with Actemra. Furthermore, a Risk Evaluation and Mitigation Strategy (REMS) will require the drug sponsor to implement a communication plan for physicians informing them how to appropriately monitor their patients for liver and/or gastrointestinal side effects. The REMS will include a medication guide to ensure that patients are informed of the benefits and risks of Actemra.

Juvenile idiopathic arthritis (JIA), commonly referred to as juvenile RA, is the most common chronic rheumatic disease in children with onset before age 16. Typical symptoms include stiffness when awakening, limping, and joint swelling. Any joint can be
affected and inflammation may limit the mobility of the affected joints. About half of JIA cases involve fewer than 5 joints (pauciarticular forms) and often include uveitis. Polyarticular forms of JIA affect 5 or more joints, usually in a symmetrical fashion. It can be rheumatoid factor positive or negative. Overall, JIA affects more girls than boys, however late-onset pauciarticular JIA is more common in boys. While it was once believed that most children eventually outgrow JIA, it is now known that between 25 and 70% of children with JIA will still have active disease into adulthood.

Gartlehner and colleagues (2008) noted that biologics are an important therapeutic option for treating patients with JIA. In adults, they are associated with rare but SAE such as serious infections and malignancies. The authors reviewed systematically the evidence on the safety and effectiveness of biologics for the treatment of JIA. They limited evidence to prospective studies for efficacy but included retrospective observational evidence for safety. Outcomes of interest were clinical response, radiographical progression, quality of life, and AEs. One randomized controlled trial (RCT) and 11 uncontrolled prospective studies provided data on efficacy; 3 additional studies assessed safety. The only RCT and 6 uncontrolled trials support the general efficacy of etanercept for the treatment of JIA. Internal and external validity of these studies are limited. The evidence on other biologic agents such as adalimumab, abatacept, anakinra, infliximab, rituximab, and tocilizumab is sparse or entirely missing. Because of the lack of sound long-term safety data, evidence is insufficient to draw firm conclusions about the balance of risks and benefits of any biologics for the treatment of JIA. Clinicians have to be aware of the lack of evidence supporting a long-term net benefit when considering biologics for patients with JIA.

Herlin (2008) stated that in recent years the treatment of JIA has undergone marked changes. There is substantial evidence that inhibitors of TNF-alpha (e.g., etanercept, infliximab and adalimumab) show significant effectiveness when standard therapy fails, and long-term tolerability is fairly good. Patients with systemic JIA do not respond well to treatment with TNF inhibitors, but they may benefit from treatment with IL-1 and IL-6 receptor antagonists. Moreover, the author noted that "our knowledge is still limited regarding which patients respond to a specific biological therapy".

Ilowite (2008) summarized the recent data on biologic therapies in the treatment of JIA. New data from large prospective randomized trials have demonstrated efficacy of anti-TNF agents and a co-stimulator signal inhibitor. The results of a pivotal trial of infliximab in polyarticular JIA suggested efficacy, but the primary outcome was not significantly different from placebo. Important information regarding dosing in children was obtained, however. A pivotal trial of adalimumab did prove efficacy, and resulted in U.S. Food and Drug Administration (FDA) approval. The monoclonal antibodies to TNF appear to be more effective in treating chronic uveitis associated with JIA than etanercept. Anti-IL-1 and anti-IL-6 therapy, particularly for systemic disease patients, looks very promising, as well. The co-stimulation modifier abatacept was shown to be effective and relatively well-tolerated in the short-term, also resulting in FDA approval. Continued experience with these agents and appropriate systems-based methods such as formal registries, to complement existing FDA procedures for monitoring safety, will improve the ability to identify short-term and long-term toxicities of these new agents. The author concluded that as experience is gained, and longer-term safety is shown, it is likely that biologics will be introduced as therapy earlier in the course of patients who inadequately respond to conventional DMARDs.

Systemic juvenile idiopathic arthritis (sJIA) is characterized by inflammatory arthritis with intermittent fever, rash, anemia, hepatosplenomegaly, pleuritis, and pericarditis. The peak age of onset of sJIA is between 18 months and 2 years, although persistence of the disease into adulthood occurs. It has a poorer long-term prognosis than other subtypes of
juvenile arthritis, accounting for almost 2/3 of all deaths in children with arthritis, and an overall mortality rate between 2 and 4 %. There are currently no FDA approved therapies of sJIA. Current treatment consists of high-dose corticosteroids. Interleukin-6 is thought to contribute to the major features of sJIA including chronic synovial inflammation, articular cartilage damage, fever, anemia, growth impairment, and osteoporosis.

A phase 3 study found that the IL-6 inhibitor tocilizumab was significantly more effective than placebo in the short-term (12-week) treatment of patients with sJIA (de Bendetti et al, 2010). Children and adolescents (aged 2 to 17 years) with active sJIA, with disease duration of 6 or more months, and inadequate response to non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, were randomized (2:1) to receive tocilizumab every 2 weeks (at a dose of 8 mg/kg for patients 30 kg or more body weight, and a dose of 12 mg/kg for patients less than 30 kg) or placebo. Stable doses of NSAIDs and methotrexate were continued. Tapering of corticosteroids was allowed starting at week 6. Patients who met rescue criteria received standard of care and were offered open-label tocilizumab and considered non-responders. The primary end point was the proportion of patients with JIA ACR30 response plus absence of fever at week 12 for tocilizumab patient versus control (intention-to-treat analysis). These investigators enrolled 112 patients (75 subjects treated with tocilizumab and 30 control subjects) with a mean age of 9.6 years. The authors reported that baseline characteristics were similar across groups. By week 12, 1 control patient and 2 tocilizumab patients withdrew from the study, and more control subjects than tocilizumab subjects required rescue therapy (54 % versus 1 %). These investigators found that significantly more tocilizumab patients than control patients achieved JIA ACR30 response plus absence of fever at week 12 (85 % versus 24 %, p < 0.0001). In addition, 70 % of patients on tocilizumab achieved a JIA ACR70 and 37 % achieved a JIA ACR90, compared to 8 % and 5 % of control patients, respectively. Nearly 2/3 of patients in the study were free of rash after 3 months. No control patients and 3 tocilizumab patients experienced significant adverse events (angioedema and urticaria in 1 patient, varicella, and bacterial arthritis), all of which resolved without sequelae, according to investigators.

Doggrell (2008) stated that some patients with RA and systemic-onset JIA are resistant to inhibitors of IL-1 and TNF. Increased levels of IL-6 are associated with both these conditions. Tocilizumab has recently been used in phase III trials in RA and systemic-onset JIA. The author carried out a study to assess findings of phase III clinical trials with tocilizumab. In the study of the Tocilizumab Pivotal Trial in Methotrexate Inadequate Responders, the primary efficacy end-point was the proportion of subjects with a 20 % improvement in their RA signs and symptoms according to the ACR criteria and, at 24 weeks, this value was 26 % with placebo and was increased to 48 and 59 % with tocilizumab at 4 and 8 mg respectively. In the trial of tocilizumab in systemic-onset JIA, the primary end-point in the open-label lead-in was the proportion of subjects achieving an ACR Pedi 30 response and 91 % of subjects had achieved this at 6 weeks. This response was maintained by the majority of subjects being treated with tocilizumab during a 12-week double-blind trial and 48 weeks of open trial follow-up. Small numbers of subjects developed infections in both studies. The author concluded that if long-term safety can be established, tocilizumab will probably become part of the treatment for RA and may become a major breakthrough for the treatment of systemic-onset JIA.

Yokota and associates (2008) examined the safety and effectiveness of tocilizumab in children with JIA. A total of 56 children (aged 2 to 19 years) with disease refractory to conventional treatment were given 3 doses of tocilizumab 8 mg/kg every 2 weeks during a 6-week open-label lead-in phase. Patients achieving an American College of Rheumatology Pediatric (ACR Pedi) 30 response and a CRP concentration of less than 5 mg/L were randomly assigned to receive placebo or to continue tocilizumab treatment for
12 weeks or until withdrawal for rescue medication in a double-blind phase. The primary endpoint of the double-blind phase was an ACR Pedi 30 response and CRP concentration of less than 15 mg/L. Patients responding to tocilizumab and needing further treatment were enrolled in an open-label extension phase for at least 48 weeks. At the end of the open-label lead-in phase, ACR Pedi 30, 50, and 70 responses were achieved by 51 (91%), 48 (86%), and 38 (68%) patients, respectively. A total of 43 patients continued to the double-blind phase and were included in the efficacy analysis. Four (17%) of 23 patients in the placebo group maintained an ACR Pedi 30 response and a CRP concentration of less than 15 mg/L compared with 16 (80%) of 20 in the tocilizumab group (p < 0.0001). By week 48 of the open-label extension phase, ACR Pedi 30, 50, and 70 responses were achieved by 47 (98%), 45 (94%), and 43 (90%) of 48 patients, respectively. Serious side effects were anaphylactic reaction, gastrointestinal hemorrhage, bronchitis, and gastroenteritis. The authors concluded that tocilizumab is effective in children with systemic-onset JIA. It might therefore be a suitable treatment in the control of this disorder, which has so far been difficult to manage.

On April 15, 2011, the FDA approved tocilizumab, given alone or in combination with methotrexate, for the treatment of active sJIA in children aged 2 years or older.

Tocilizumab has been approved by the FDA for the treatment of polyarticular juvenile idiopathic arthritis in persons 2 years of age and older (Genentech, 2013). FDA approval of Actemra was based on the CHERISH study, a three-part study including an open-label extension in children 2 to 17 years of age with active polyarticular juvenile idiopathic arthritis, who had an inadequate response to methotrexate or inability to tolerate methotrexate. Part I consisted of a 16-week active tocilizumab treatment lead-in period (n = 188) followed by Part II, a 24-week randomized double-blind placebo-controlled withdrawal period, followed by Part III, a 64-week open-label period. Patients had at least 6 months of active disease (mean disease duration of 4.2 ± 3.7 years), with at least five joints with active arthritis (swollen or limitation of movement accompanied by pain and/or tenderness) and/or at least 3 active joints having limitation of motion (mean, 20 ± 14 active joints).

At the conclusion of the open-label Part I, 91% of patients taking background methotrexate in addition to tocilizumab and 83% of patients on tocilizumab monotherapy achieved an ACR 30 response at week 16 compared to baseline and entered the blinded withdrawal period (Part II) of the study (Genentech, 2013). The proportions of patients with JIA ACR 50/70 responses in Part I were 84.0%, and 64%, respectively for patients taking background methotrexate in addition to tocilizumab and 80% and 55% respectively for patients on tocilizumab monotherapy. In Part II, patients (ITT, n=163) were randomized to tocilizumab (same dose received in Part I) or placebo in a 1:1 ratio that was stratified by concurrent methotrexate use and concurrent corticosteroid use. Each patient continued in Part II of the study until Week 40 or until the patient satisfied JIA ACR 30 flare criteria (relative to Week 16) and qualified for escape.

The primary endpoint was the proportion of patients with a JIA ACR 30 flare at week 40 relative to week 16 (Genentech, 2013). JIA ACR 30 flare was defined as 3 or more of the 6 core outcome variables worsening by at least 30% with no more than 1 of the remaining variables improving by more than 30% relative to Week 16. Tocilizumab treated patients experienced significantly fewer disease flares compared to placebo-treated patients (26% [21/82] versus 48% [39/81]; adjusted difference in proportions -21%, 95% CI: -35%, -8%). During the withdrawal phase (Part II), more patients treated with tocilizumab showed JIA ACR 30/50/70 responses at Week 40 compared to patients withdrawn to placebo. The most common serious adverse events were serious infections.
On October 12, 2012, the FDA expanded the approved indication for tocilizumab (Actemra) for the treatment of adults with moderately to severely active RA who have had an inadequate response to 1 or more DMARDs. Actemra can be used both alone as a single-agent therapy and in combination with MTX or other DMARDs.

Tocilizumab is being studied in the treatment of other diseases/disorders including autoimmune diseases. Venkiteshwaran (2009) stated that tocilizumab has also been studied for potential use in the treatment of other IL-6 related disorders including Crohn disease.

Fautrel (2008) noted that adult-onset Still disease (AOSD) is an inflammatory condition of unknown origin typically characterized by 4 main symptoms: (i) spiking fever greater than or equal to 39 degrees C, (ii) arthralgia or arthritis, (iii) skin rash, and (iv) hyperleucocytosis (greater than or equal to 10,000 cells/mm3) with neutrophils greater than or equal to 80 %. The disease evolution of AOSD can be monocyclic, polycyclic, or chronic. In chronic disease, joint involvement is often predominant and erosions are noted in 1/3 of patients. No prognostic factors have been identified to date. Therapeutic strategies are from observational data. Corticosteroids are usually the first-line treatment. With inadequate response to corticosteroids, MTX appears the best choice to control disease activity and allow for tapering of steroid use. For refractory disease, biological therapy with agents blocking IL-1 (anakinra) and then those blocking IL-6 (tocilizumab) seem the most promising.

Puechal and colleagues (2011) reported the first series of patients with AOSD treated with tocilizumab. All AOSD patients treated with tocilizumab in France between July 2006 and July 2009 after failure to all available therapies were included in this cohort study. The main outcome measures were the EULAR improvement criteria and resolution of systemic symptoms at the 3- and 6-month follow-up periods. A total of 14 patients with refractory AOSD were included. At the start of tocilizumab treatment, despite a mean prednisone dosage of 23.3 mg/day, based on a 28-joint count, mean tender joints were 10.5, mean swollen joints were 7.9, and the mean DAS in 28 joints was 5.61. Recurrent systemic involvement, including fever and rash, was present in 7 patients. Tocilizumab was administered at 5 to 8 mg/kg every 2 or 4 weeks (8 mg/kg/month, n = 9). Eleven patients successfully completed the 6-month study; 1 withdrew due to necrotizing angiodermatitis, another due to chest pain at each tocilizumab infusion, and a third due to systemic flare. A good EULAR response was observed in 64 % of patients (9 of 14) at 3 months and EULAR remission was observed in 57 % (8 of 14) at 6 months. Systemic symptoms were resolved in 86 % of patients (6 of 7). Moreover, corticosteroid dose was reduced by 56 %. No other severe adverse effects occurred. The authors concluded that tocilizumab is a promising new treatment for AOSD. The limitations of this study were its observational nature and the lack of a control group. Well-designed studies (i.e., multi-center randomized controlled trials) are needed to ascertain the potential of tocilizumab for the treatment of adult Still’s disease.

de Boysson et al (2013) reviewed the safety and effectiveness of tocilizumab in the treatment of patients with AOSD. These investigators reported on 2 patients with AOSD who were successfully treated with tocilizumab. All published information on the use of tocilizumab in this disease was also retrieved through a systematic review of the English-language literature. Including the authors’ cases, a total of 35 patients were given tocilizumab for AOSD (8 mg/kg/month in 22 patients). The main clinical manifestations were arthritis in all 35 patients and systemic symptoms such as fever or skin rash in 28 (80 %). Thirty-three (94 %) patients had unsuccessfully tried other immunosuppressive agents such as MTX, TNF-α blockers, or anakinra. Most of the patients achieved a response with tocilizumab, such as a prompt articular improvement in 30/35 (86 %)
patients and a disappearance of systemic symptoms in 27/28 (96 %). Twenty-eight (80 
%) patients tapered their steroid intakes, including 7 (20 %) who were able to discontinue 
them. Four (11 %) patients relapsed, and 2 were successfully retreated with tocilizumab. 
Regarding safety, tocilizumab is a well-tolerated treatment, but severe side effects such 
as macrophage activation syndrome or cytomegalovirus reactivation are possible and 
require ongoing vigilance. The authors concluded that these findings suggested that 
tocilizumab should probably be proposed in refractory AOSD, as it allows for remission to 
be induced and the dose of steroid intakes to be reduced. It is a well-tolerated treatment 
that can be administered according to the therapeutic sequence of RA. Moreover, they 
stated that further prospective studies are needed to assess the better use of this 
treatment (dosage and duration) and its place among other conventional treatments.

Nishimoto et al (2008) noted that Takayasu arteritis (TA) is a chronic inflammatory disease 
that involves the aorta and its major branches. Since over-production of IL-6 appears to 
play a pathogenic role in TA, these researchers reported the use of tocilizumab in 
the treatment a 20-year-old woman with refractory active TA complicated by ulcerative 
colitis (UC). Treatment with tocilizumab improved the clinical manifestations of TA and the 
arbitrary laboratory findings in this patient and ameliorated the activity of UC. These 
results indicated that IL-6 receptor inhibition with tocilizumab might be a future treatment 
option for TA.

Keser et al (2014) stated that since there is no completed, placebo-controlled, RCT, the 
level of evidence for management of TA is low, generally reflecting the results of open 
study, case series and expert opinion. The most commonly used agents include 
corticosteroids and conventional immunosuppressive agents such as azathioprine, 
leflunomide, MTX, and mycophenolate mofetil. In patients who remain resistant and/or 
intolerant to these agents, biologic drugs including TNF inhibitors, rituximab and 
tocilizumab seem to be promising. Anti-platelet treatment may also lower the frequency of 
ischemic events in TA. In the presence of short-segment, critical arterial stenosis, balloon 
angioplasty or stent graft replacement may be useful. On the other hand, long-segment 
stenosis with extensive peri-arterial fibrosis or occlusion requires surgical bypass of the 
affected segment, which is clearly associated with superior results compared with 
endovascular intervention. As a general rule, both endovascular intervention and surgical 
procedures should be avoided during the active phase of the disease. Earlier diagnosis, 
better assessment of disease activity and future clinical trials will obviously improve the 
management of TA.

In an open-label, phase I, dosage-escalation study Illei et al (2010) evaluated the safety of 
tocilizumab and collected preliminary data on the clinical and immunologic efficacy of 
tocilizumab in patients with systemic lupus erythematosus (SLE). A total of 16 patients 
with mild-to-moderate disease activity were assigned to receive 1 of 3 doses of 
tocilizumab given intravenously every other week for 12 weeks (total of 7 infusions): 2 
mg/kg in 4 patients, 4 mg/kg in 6 patients, or 8 mg/kg in 6 patients. Patients were then 
monitored for an additional 8 weeks. The infusions were well-tolerated. Tocilizumab 
treatment led to dosage-related decreases in the absolute neutrophil count, with a median 
decrease of 38 % in the 4 mg/kg dosage group and 56 % in the 8 mg/kg dosage group. 
Neutrophil counts returned to normal after cessation of treatment. One patient was 
withdrawn from the study because of neutropenia. Infections occurred in 11 patients; 
none was associated with neutropenia. Disease activity showed significant improvement, 
with a decrease of greater than or equal to 4 points in the modified Safety of Estrogens in 
Lupus Erythematosus National Assessment version of the Systemic Lupus Erythematosus 
Disease Activity Index score in 8 of the 15 evaluable patients. Arthritis improved in all 7 
patients who had arthritis at baseline and resolved in 4 of them. Levels of anti-double-
stranded DNA antibodies decreased by a median of 47 % in patients in the 4 mg/kg and 8
mg/kg dosage groups, with a 7.8 % decrease in their IgG levels. These changes, together with a significant decrease in the frequency of circulating plasma cells, suggest a specific effect of tocilizumab on autoantibody-producing cells. The authors concluded that although neutropenia may limit the maximum dosage of tocilizumab in patients with SLE, the observed clinical and serologic responses are promising and warrant further studies to establish the optimal dosing regimen and efficacy.

Tumor nerosis factor receptor associated periodic syndrome (TRAPS), also known as familial Hibernian fever, is a periodic fever syndrome associated with mutations in a receptor for TNF that is inheritable in an autosomal dominant manner. Individuals with TRAPS exhibit episodic symptoms such as abdominal pain, rash, recurrent high fever, as well as joint/muscle aches and puffy eyes. Since IL-6 levels are elevated in TRAPS, it has been hypothesized that tocilizumab might be effective in treating this disorder.

Vaitla and colleagues (2011) described treatment outcomes in the first case of a patient with TRAPS treated with tocilizumab. The patient, a 52-year-old man with lifelong TRAPS in whom treatment with etanercept and anakinra had failed, was administered tocilizumab for 6 months, and the therapeutic response was assessed by measurement of monocyte CD16 expression and cytokine levels. Following treatment, the evolving acute attack was aborted and further attacks of TRAPS were prevented. The patient did not require corticosteroids and showed significant clinical improvement in scores for pain, stiffness, and well-being. Moreover, the acute-phase response diminished significantly with treatment. Monocyte CD16 expression was reduced and the numbers of circulating CD14+CD16+ and CD14++CD16- monocytes were transiently decreased. However, cytokine levels were not reduced. The authors concluded that this case supported the notion of a prominent role for IL-6 in mediating the inflammatory attacks in TRAPS, but blockade of IL-6 did not affect the underlying pathogenesis. They stated that these preliminary findings require confirmation.

Kemta et al (2012) evaluated the safety and effectiveness of biologics in patients with active relapsing polychondritis (RP). A systematic review of the literature using PubMed was performed through December 2010. MeSH terms and keywords were used relating to RP and biologics. All papers reporting the safety and/or effectiveness of biologics in RP were selected. Reference lists of included papers were also searched. All publications related to case-series or isolated case-reports. No RCT has been performed; a total of 30 papers that included 62 patients were published. These patients were treated with TNF-alpha blockers (n = 43), rituximab (n = 11), anakinra (n = 5), tocilizumab (n = 2), and abatacept (n = 1). The end point of treatment differed from 1 publication to the other and therefore made the comparison of effectiveness among the various biologics difficult. Biologics were effective in 27 patients, partially effective in 5 patients, and ineffective in 29 patients. Safety appeared to be good. However, 4 deaths were recorded (2 sepsis, 1 post-operatively after aortic aneurysm surgery, and 1 after accidental dislocation of the tracheostomy device). The authors concluded that the experience with biologics in RP is very limited and their effectiveness and indications need to be better defined. They stated that RCTs, although difficult to perform because of the rarity of RP, are needed to determine the place of biologics in the treatment strategy of this orphan disease.

Tocilizumab is usually administered in an hour-long intravenous infusion at a dose of 4 to 8 mg/kg body weight once every 4 weeks. It is generally well-tolerated. The SAE reported in Actemra global clinical studies included serious infections and hyper-sensitivity (allergic) reactions including a few cases of anaphylaxis. The most common side effects were upper respiratory tract infection, nasopharyngitis, headache, hypertension. Increases in liver function tests (alanine transaminase and aspartate transferase, also known as serum glutamic-oxaloacetic transaminase) were seen in some patients. These
increases were generally mild and reversible, with no hepatic injuries or any observed impact on liver function.

Hingorani and Casas (2012) stated that a high circulating concentration of IL-6 is associated with increased risk of coronary heart disease (CHD). Blockade of the IL-6 receptor (IL6R) with tocilizumab licensed for treatment of RA reduces systemic and articular inflammation. However, whether IL6R blockade also reduces risk of CHD is unknown. Applying the Mendelian randomization principle, these researchers used single nucleotide polymorphisms (SNPs) in the gene IL6R to evaluate the likely safety and effectiveness of IL6R inhibition for primary prevention of CHD. These investigators compared genetic findings with the effects of tocilizumab reported in randomized trials in patients with RA. In 40 studies including up to 133,449 individuals, an IL6R SNP (rs7529229) marking a non-synonymous IL6R variant (rs8192284; p.Asp358Ala) was associated with increased circulating log IL-6 concentration (increase per allele 9.45 %, 95 % CI: 8.34 to 10.57) as well as reduced CRP (decrease per allele 8.35 %, 95 % CI: 7.31 to 9.38) and fibrinogen concentrations (decrease per allele 0.85 %, 95 % CI: 0.60 to 1.10). This pattern of effects was consistent with IL6R blockade from infusions of tocilizumab (4 to 8 mg/kg every 4 weeks) in patients with RA studied in randomized trials. In 25,458 CHD cases and 100,740 controls, the IL6R rs7529229 SNP was associated with a decreased odds of CHD events (per allele odds ratio 0.95, 95 % CI: 0.93 to 0.97, p = 1.53 × 10(-5)). The authors concluded that on the basis of genetic evidence in human beings, IL6R signaling seems to have a causal role in development of CHD. Blockade of IL6R could provide a novel therapeutic approach to prevention of CHD that warrants testing in suitably powered randomized trials. Genetic studies in populations could be used more widely to help to validate and prioritize novel drug targets or to re-purpose existing agents and targets for new therapeutic uses.

Kiltz et al (2012) noted that axial spondyloarthritis (SpA) -- including ankylosing spondylitis (AS) -- is a frequent chronic inflammatory disease that affects mainly the axial skeleton. There is evidence that NSAIDs and TNF-α blockers are effectives, but not all patients achieve remission or a major clinical response. A variety of new drug classes have been investigated during the last years for the treatment of patients with AS in whom TNF blockers have failed or are contraindicated. Data for abatacept, anakinra, apremilast, bisphosphonates, rituximab, secukinumab, sulfasalazine, thalidomide and tocilizumab (TCZ) were found. All studies had problems with design and methodology. The authors concluded that although some trends for effectiveness were seen, there is at present insufficient evidence to support a recommendation for any of these compounds. So far, none of these new drugs has been shown to reach response rates compared to TNF-blockers.

Sieper and associates (2014) noted that clinical trials BUILDER-1 and BUILDER-2 were aimed to evaluate the safety and effectiveness of TCZ in patients with AS. BUILDER-1 was a 2-part, phase II/III parallel-group trial in patients with AS naive to anti-TNF (aTNF) treatment. Patients in part 1 received TCZ 8 mg/kg or placebo for 12 weeks. In part 2 (beginning after part 1 enrolment ended), newly enrolled patients received TCZ 4 or 8 mg/kg or placebo for 24 weeks. The same treatment arms were used in BUILDER-2, a phase III study in aTNF-inadequate responders. The primary end-point for both studies was the proportion of patients achieving 20 % improvement in the Assessments in Axial SpondyloArthritis international Society (ASAS). Secondary and exploratory end-points included ASAS40 response rates, Bath Ankylosing Spondylitis Disease Activity Index improvement, changes in joint counts, enthesitis score and CRP. A total of 102 patients were randomized in BUILDER-1 part 1; 99 (48 TCZ, 51 placebo) completed 12 weeks. Week 12 ASAS20 response rates were 37.3 % and 27.5 % in the TCZ and placebo arms, respectively (p = 0.2823). Secondary and exploratory end-points did not differ between
treatment arms. Levels of CRP declined with TCZ treatment, suggesting adequate IL-6 receptor blockade. As a result, BUILDER-1 part 2 and BUILDER-2 were terminated. The authors stated that TCZ safety results were consistent with previous observations in RA, except for a cluster of anaphylactic and hypersensitivity events at Bulgarian study sites. No apparent explanation for this clustering could be found. They concluded that BUILDER-1 failed to demonstrate TCZ efficacy in treating aTNF-naive patients with AS.

Macchioni and colleagues (2013) stated that glucocorticoids (GCs) are the mainstay of treatment of polymyalgia rheumatica (PMR). However GCs-related adverse events occur frequently, particularly in patients with relapsing disease. Several studies have demonstrated that IL-6 is a key player in the pathogenesis of PMR. These investigators reported 2 patients with PMR treated with TCZ and reviewed the published evidence on the safety and effectiveness of TCZ in patients with PMR. These researchers treated 2 GCs-naive patients with newly diagnosed pure PMR with monthly TCZ infusions (8 mg/kg body weight) for 6 months. Disease activity and drug tolerability were assessed clinically, by laboratory tests, and bilateral shoulder ultrasonography before starting the treatment and subsequently every month during TCZ therapy. They performed a systematic literature search (PubMed until July 2012) using the terms "tocilizumab", "anti-IL-6-receptor", "polymyalgia rheumatica", "giant cell arteritis", and "large-vessel vasculitis" to identify published reports of patients with PMR treated with TCZ. One of the 2 patients responded well to TCZ, while the other patient required GCs therapy after the 2nd TCZ infusion because of lack of appreciable clinical response. Both patients tolerated TCZ well. The review of the literature revealed 4 reports with a total of 9 patients who received TCZ for PMR. In 7 of these 9 patients, PMR was associated with giant cell arteritis. Including the 2 patients in this study, 5 patients received TCZ alone and 6 TCZ plus GCs. A good response to TCZ treatment was observed in all patients reported in the literature without any major adverse events. The authors concluded that TCZ both as monotherapy and in association with GCs appears to be mostly effective and safe to treat patients with PMR. Moreover, they stated that larger controlled studies are needed to confirm these favorable data.

Al Rashidi et al (2013) noted that despite their disadvantages, GCs remain a mainstay of therapy for PMR. Second-line anti-rheumatic and immune-modulatory drugs are not infrequently required because of disease relapses during GCs tapering and GCs adverse effects. Therapy with MTX or with an anti-TNF drug showed modest efficacy in this situation. Tocilizumab is an anti-IL-6 receptor antibody that is being recently studied in the treatment of PMR patients who are intolerant or refractory to GCs, especially after failure of a second-line agent. These researchers reported a case of PMR in which GCs were stopped because of adverse effects despite good response. The condition responded to neither MTX nor etanercept. Treatment with TCZ has led to significant improvement of the patient's clinical and biochemical PMR activity parameters, and the patient was kept in a solid remission for 1 year without any TCZ-related adverse effects. The authors concluded that tocilizumab is a promising drug in the management of PMR. Moreover, they stated that further studies are needed to clearly define the indications and duration of TCZ therapy in the management of PMR.

In an observational study, Elhai and co-workers (2013) evaluated the safety and effectiveness of tocilizumab and abatacept in systemic sclerosis (SSc)-associated polyarthritis or SSc-associated myopathy. A total of 20 patients with SSc with refractory polyarthritis and 7 with refractory myopathy from the EUSTAR (EULAR Scleroderma Trials and Research) network were included: 15 patients received tocilizumab and 12 patients abatacept. All patients with SSc-myopathy received abatacept. Clinical and biological assessments were made at the start of treatment and at the last infusion. After 5 months, tocilizumab induced a significant improvement in the 28-joint count Disease Activity Score
and its components, with 10/15 patients achieving a EULAR good response. Treatment was stopped in 2 patients because of inefficacy. After 11 months' treatment of patients with abatacept, joint parameters improved significantly, with 6/11 patients fulfilling EULAR good-response criteria. Abatacept did not improve muscle outcome measures in SSc-myopathy. No significant change was seen for skin or lung fibrosis in the different groups. Both treatments were well-tolerated. The authors concluded that tocilizumab and abatacept appeared to be safe and effective on joints, in patients with refractory SSC. No trend for any change of fibrotic lesions was seen but this may relate to the exposure time and inclusion criteria. They stated that larger studies with longer follow-up are needed to further determine the safety and effectiveness of these drugs in SSC.

Silva-Fernandez et al (2014) analyzed the current evidence on the therapeutic use of biological agents for systemic vasculitis (SV). Medline, Embase, the Cochrane Database of Systematic Reviews, and the Cochrane Central Register of Controlled Trials were searched up to the end of April 2013. Systematic reviews and meta-analysis, clinical trials, cohort studies, and case series with more than 3 patients were included. Independent article review and study quality assessment was done by 2 investigators with consensus resolution of discrepancies. Of 3,447 citations, abstracts, and hand-searched studies screened, 90 were included. Most of the studies included ANCA-associated vasculitis (AAV) patients and only a few included large vessel vasculitis (LVV) patients. Rituximab was the most used agent, having demonstrated efficacy for remission induction in patients with AAV. A number of studies used different anti-TNFα agents with contrasting results. A few uncontrolled studies on the use of abatacept, alemtuzumab, mepolizumab, and tocilizumab were found. The authors concluded that current evidence on the use of biological therapies for SV is mainly based on uncontrolled, observational data. Rituximab is not inferior to cyclophosphamide for remission induction in AAV and might be superior in relapsing disease. Infliximab and adalimumab are effective as steroid-sparing agents. Etanercept is not effective to maintain remission in patients with granulomatosis with polyangiitis, and serious adverse events have been reported. For LVV, both infliximab and etanercept had a role as steroid-sparing agents, and tocilizumab might be effective also for remission induction in LVV.

Abisror et al (2013) analyzed the efficacy and tolerance of tocilizumab in patients with TA. These researchers retrospectively studied patients with TA (ACR and/or Ishikawa's criteria): 5 French multi-center cases and 39 from the literature. Clinical, biological, radiological disease activity and treatment were analyzed before tocilizumab, during the follow-up and at the last available visit. A total of 44 patients (median age of 26 years [3 to 65]) were included in the present study: 5 patients from the 3 French university hospitals and 39 cases from the literature review. Median follow-up after initiation of tocilizumab was 15 months [8 to 33]. Clinical and biological activities significantly decreased within 3 months, similarly to steroid amount (from 15 mg/day [5 to 75] at baseline to 10 mg/day [2 to 30] at 6 months; p < 0.05) and steroid-dependence rate. Even radiological activity did not significantly decrease at 6 months, significant decrease of arterial FDG uptake was noted at 6 months. Median duration of tocilizumab treatment was 9 months [3 to 180]. At the last visit, tocilizumab was continued in 17/32 patients (53 %), and was discontinued in the 15 remaining cases because of the remission (n = 5), relapse (n = 3), persistent radiological activity (n = 3), cutaneous rash (n = 2), severe infection (n = 1) and lacking of care welfare system (n = 1). No death related to tocilizumab treatment was noted. The authors concluded that this study showed the efficacy of tocilizumab in terms of clinical, biological and radiological response, as well as steroid-sparing agent. Moreover, they stated that only well-designed studies could definitely address the efficacy of tocilizumab in TA.
Elkayam et al (2014) described the Israeli experience of treating AOSD with TCZ. Israeli rheumatologists who treated AOSD with TCZ filled in questionnaires on symptoms, number of tender and swollen joints, erythrocyte sedimentation rate (ESR), CRP, and dosage of prednisone at initial TCZ administration, after 6 months, and at the end of follow-up. A total of 9 males and 6 females patients, aged 33 ± 12 years, mean disease duration 9 years (range of 1 to 25) were identified. They had used a mean of 3.6 disease-modifying drugs, including 10 patients with TNF blockers. Intravenous TCZ 8 mg/kg was administered every 4 weeks (12 patients) or every 2 weeks (3 patients). All patients completed at least 6 months of treatment. The mean follow-up period was 15.7 ± 9 months. At the onset of therapy, despite the use of prednisone (27.6 ± 26.3 mg/d), all patients reported joint pain. Fever was reported in 9 patients, rash in 7, pleuritis in 3, and hepatitis in 2 before TCZ use, with mean ESR and CRP levels of 60 ± 28 mm/h and 11.6 ± 15 mg/dL, respectively. After 6 months of treatment and at the end of follow-up, the number of tender and swollen joints, the ESR and CRP levels, and the prednisone dosage decreased significantly. Only 2 patients still complained of mild arthralgias, and none reported systemic symptoms at the end of follow-up. The authors concluded that TCZ 8 mg/kg was extremely effective in treating adult patients with refractory Still's disease. Both TCZ and IL-1 blockade should be considered in the treatment algorithm of AOSD. Moreover, they stated that RCTs are needed to validate these findings.

Multicentric Castleman disease (MCD) is an atypical lympho-proliferative disorder characterized by systemic lymphadenopathy and constitutional inflammatory symptoms. Dysregulated over-production of IL-6 is responsible for the clinical abnormalities. In a multi-center prospective study, Nishimoto et al (2005) evaluated the safety and effectiveness of a humanized anti-human IL-6 receptor monoclonal antibody (MRA) in patients with MCD. These researchers reported results of the first 60 weeks of the study enrolling 28 patients. The initial dosing period consisted of 8 infusions of 8 mg/kg MRA administered bi-weekly. Adjustments in the dose and treatment interval were allowed for each patient in an extension phase after 16 weeks. Within 16 weeks, treatment with MRA consistently alleviated lymphadenopathy and all the inflammatory parameters. Hemoglobin, albumin, and total cholesterol levels, high-density lipoprotein cholesterol values, and body mass index all increased significantly. In addition, fatigue diminished. Chronic inflammatory symptoms were successfully managed over 60 weeks. In 8 (28.6 %) patients, the MRA dose was decreased or the treatment interval was extended without exacerbation. Eleven (73.3 %) of 15 patients who had received oral corticosteroids before study entry were able to do well on a reduced corticosteroid dose. Most adverse events were mild to moderate in severity. The authors concluded that MRA was well-tolerated and significantly alleviated chronic inflammatory symptoms and wasting in patients with MCD. These preliminary findings need to be validated by well-designed studies.

An UpToDate review on “Multicentric Castleman’s disease” (Aster et al, 2014) states that “Monoclonal antibodies targeted against IL-6 (siltuximab) or the IL-6 receptor (tocilizumab, also called atlizumab or MRA) have demonstrated clinical efficacy in HIV/HHV-8 negative MCD, resulting in symptom resolution. Tocilizumab has been approved for use in Japan since 2005, but not in Europe or the United States. Siltuximab is approved in the United States for the treatment of patients with MCD who are HIV/HHV-8 negative, and it is under review by regulatory agencies in Europe. Data about combining other modalities with anti-IL-6-directed treatment are limited”.

Guidelines on non-Hodgkin’s lymphoma from the National Comprehensive Cancer Network (NCCN, 2015) recommend the use of tocilizumab in Castleman’s diseases (CD): 1) as second-line therapy as a single agent for relapsed or refractory unicentric CD for patients who are human immunodeficiency virus-negative and human herpesvirus-8-
negative; or 2) as subsequent therapy as a single agent for multicentric CD that has progressed following treatment of relapsed/refractory or progressive disease.

In a pilot study, Araki et al (2014) evaluated the safety and effectiveness of TCZ in patients with neuromyelitis optica (NMO). A total of 7 patients with anti-aquaporin-4 antibody (AQP4-Ab)-positive NMO or NMO spectrum disorders were recruited on the basis of their limited responsiveness to their current treatment. They were given a monthly injection of TCZ (8 mg/kg) with their current therapy for a year. These researchers evaluated the annualized relapse rate, the Expanded Disability Status Scale score, and numerical rating scales for neurogenic pain and fatigue. Serum levels of anti-AQP4-Ab were measured with AQP4-transfected cells; 6 females and 1 male with NMO were enrolled. After a year of TCZ treatment, the annualized relapse rate decreased from 2.9 ± 1.1 to 0.4 ± 0.8 (p < 0.005). The Expanded Disability Status Scale score, neuropathic pain, and general fatigue also declined significantly. The ameliorating effects on intractable pain exceeded expectations. The authors concluded that IL-6 receptor blockade is a promising therapeutic option for NMO.

In a review on “The future of uveitis treatment”, Lin and colleagues (2014) provided examples of some promising targets for immunomodulation in systemic and ocular diseases, which are currently in pre-clinical and early clinical (phase I/II) testing. These investigators noted that several case reports showed efficacy of tocilizumab in uveitis.

Furthermore, an UpToDate review on “Uveitis: Treatment” (Rosenbaum, 2014) does not mention tocilizumab as a therapeutic option.

Appendix

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<tr>
<th>Brand Name</th>
<th>Generic Name</th>
<th>FDA Labeled Indications</th>
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<td>Actemra</td>
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**Other CPT codes related to the CPB:**

- 96360  Intravenous infusion, hydration; initial, 31 minutes to 1 hour
- 96361   each additional hour (List separately in addition to code for primary procedure)
- 96365  Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
- 96366   each additional hour (List separately in addition to code for primary procedure)
- 96367   additional sequential infusion, up to 1 hour (List separately in addition to code for primary procedure)
- 96368   concurrent infusion (List separately in addition to code for primary procedure)
- 96372  Therapeutic, prophylactic or diagnostic injection (specify substance or drug); subcutaneous or intramuscular
- 96379  Unlisted therapeutic, prophylactic, or diagnostic intravenous or intra-arterial injection or infusion
- 96401  Chemotherapy administration, subcutaneous or intramuscular; non-hormonal anti-neoplastic

**HCPCS codes covered if selection criteria are met:**

- J3262  Injection, Tocilizumab (Actemra), 1 mg

**Other HCPCS codes related to the CPB:**

- J0135  Injection, adalimumab, 20 mg
- J1438  Injection, etanercept, 25 mg
- J1745  Injection, infliximab, 10 mg

**ICD-9 codes covered if selection criteria are met:**

- 714.0 - 714.31  Rheumatoid arthritis [as a first-line biologic for persons with rheumatoid arthritis who have had an inadequate response to 1 or more disease-modifying anti-rheumatic drugs (DMARDs)] [if the member has a contraindication, intolerance or incomplete response to at least 2 of the least cost brands of targeted immune modulators]
ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):

- **341.0** Neuromyelitis optica
- **359.6** Symptomatic inflammatory myopathy in diseases classified elsewhere [sclerosis associated myopathy/polyarthritis]
- **364.00 - 364.3** Iridocyclitis
- **446.0 - 446.7** Polyarteritis nodosa and allied conditions [systemic vasculitis, Takayasu's arteritis]
- **447.0 - 447.6** Other disorders of arteries and arterioles [systemic vasculitis]
- **555.0 - 555.9** Regional Enteritis [Crohn's disease]
- **696.0** Psoriatic arthropathy
- **710.0** Systemic lupus erythematosus
- **710.1** Systemic sclerosis [associated with myopathy/polyarthritis]
- **713.8** Arthropathy associated with other conditions classifiable elsewhere [sclerosis associated myopathy/polyarthritis]
- **714.32 - 714.33** Pauciarticular and monoarticular juvenile rheumatoid arthritis
- **720.0** Ankylosing spondylitis
- **725** Polymyalgia rheumatica
- **733.99** Other disorders of bone and cartilage [relapsing polychondritis]
- **785.6** Enlargement of lymph nodes [Castleman's disease]

The above policy is based on the following references:

24. Canadian Agency for Drugs and Technologies in Health (CADTH). Tocilizumab (Actemra – Hoffmann-La Roche Limited). Indication: Rheumatoid arthritis. CEDAC


50. Rosenbaum JT. Uveitis: Treatment. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed June 2014.

