2011

Is Actemra (tocilizumab) in Combination with Methotrexate an Effective Treatment for Rheumatoid Arthritis in Patients who had an Inadequate Response to Methotrexate Alone?

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July 7, 2011

Abstract

OBJECTIVE: The objective of this systematic review is to determine whether or not Actemra (tocilizumab) in combination with methotrexate is an effective treatment for rheumatoid arthritis in patients who had an inadequate response to methotrexate alone. Previous studies have shown other biologic agents and disease modifying antirheumatic drugs (DMARDs) to have some efficacy in treating rheumatoid arthritis. However, tocilizumab is a newly approved FDA drug and therefore, its efficacy in treating RA has yet to be determined.

KEYWORDS: rheumatoid arthritis, tocilizumab, Actemra, and methotrexate.

INTRODUCTION

Rheumatoid arthritis (RA) is the most common inflammatory arthritis and currently affects 1% of the population.[1] It is predominantly a female condition, but it can also be seen in males. This autoimmune disease is characterized by progressive joint inflammation and damage that is symmetric in nature. Rheumatoid arthritis has a predilection for the small bones of the hands and feet including the metacarpal phalanx (MCP), proximal interphalanx (PIP), and metatarsal phalanx (MTP) but may also affect the wrists, elbows, knees, ankles, and cervical spine.[3] This disease spares the distal interphalanx (DIP) and the axial skeleton except the cervical spine. The articular signs and symptoms of rheumatoid arthritis include morning stiffness lasting greater than 1 hour, joint swelling and tenderness, and limitation of movement.[3] Deformities of the hand that are characteristic of RA include swan neck and boutonniere deformities. Extra-articular manifestations that may be seen are fever, fatigue, weight loss, anemia, lymphadenopathy, scleritis, episcleritis, pericarditis, vasculitis, amyloidosis, and osteoporosis.[3]

Aggressive treatment is required to treat the chronic and erosive nature of rheumatoid arthritis that can eventually lead to joint destruction. The exact etiology of rheumatoid arthritis is unknown, and it is mainly a clinical diagnosis with labs and radiographs used for confirmation. Therefore, physician assistants and other health care providers in various fields including family medicine, internal medicine, orthopedics, and rheumatology must be adept and prompt in diagnosing and treating this condition. Rheumatoid factor and anti-CCP are positive in 70-80% of patients.[3] Joint space narrowing and joint erosions may be present on radiographs with joint erosions indicating late disease and a worse prognosis.[3]

Treatment for rheumatoid arthritis has targeted the inflammatory system with disease modifying antirheumatic drugs (DMARDs) and biologic agents that target specific cytokines. The most common DMARD used is methotrexate, which is the first line therapy.[3] Examples of other DMARDs are sulfasalazine and leflunomide. The biologic agents include etanercept, infliximab, adalimumab, and abatacept. Corticosteroids and over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs) may be used as adjuvant therapy.

The current treatments for rheumatoid arthritis target specific cytokines, including tumor necrosis factor α (TNFα) and interleukin 1 (IL-1).[1] However, an estimated 20-40% of patients do not respond to these regimens even when combined with methotrexate.[1] It has become essential to search for other treatment regimens for rheumatoid arthritis. Tocilizumab (Actemra) is a recent FDA approved drug that targets the cytokine, interleukin 6 (IL-6), which has been shown to be increased in the synovial tissue in patients with RA.[4] This cytokine causes activation of monocytes, neutrophils, T cells, B cells, and osteoclasts, which are all substantially involved in the initiation and progression of rheumatoid arthritis[4]. Targeting interleukin 6 offers an alternative treatment regimen for those individuals whose rheumatoid arthritis has been resistant to the current treatment modalities.

OBJECTIVE

The objective of this systematic review is to determine whether or not Actemra (tocilizumab) in combination with methotrexate is an effective treatment for rheumatoid arthritis in patients who had an inadequate response to methotrexate alone. Previous studies have shown other biologic agents and disease modifying antirheumatic drugs (DMARDs) to have some efficacy in treating rheumatoid arthritis. However, tocilizumab is a newly approved FDA drug and therefore, its efficacy in treating RA has yet to be determined.

METHODS

The three studies that are included in this review are double-blind randomized controlled trials comparing tocilizumab plus methotrexate to a placebo plus methotrexate for the treatment of rheumatoid arthritis. Tocilizumab was given as 2, 4 or 8 mg/kg in the Maini study and as 4 or 8 mg/kg in the Smolen and Emery studies. The study population was adult patients with active rheumatoid arthritis who had an inadequate response to methotrexate. The reduction in the number of swollen and tender joints was the outcome measured using the ACR20 response rate as the primary efficacy endpoint and ACR50 and ACR70 response rates as secondary efficacy endpoints.

These studies were found by the author using Ovid, MEDLINE, and Cochrane databases. The key words rheumatoid arthritis, tocilizumab, Actemra, and methotrexate were used in the literature searches to find English articles published in peer-reviewed articles dated 2006 to the present. The articles were chosen if they were relevant, valid, and the outcomes of the studies mattered to the patients (Patient Oriented Evidence that Matters or POEMS). The selected studies were those that abided by the following set of criteria: POEM, randomized controlled trial, a diagnosis of rheumatoid arthritis according to the American College of Rheumatology revised criteria, active rheumatoid arthritis for 6 months or more, a swollen joint count of 6 or more, and a tender joint count of 8 or more. The studies that did not meet all of these requirements were excluded from this review. The statistics that are reported are p-values, numbers needed to treat (NNT), relative risk reduction (RRR), absolute risk reduction (ARR), control event rate (CER), and experimental event rate (EER). Table 1 shows the demographics of the three studies included in this review.

Table 1. Demographics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	WD	Interventions
Emery, 2008 (1)	Double blind RCT	499	≥18	Active RA ≥6 months, swollen joint count ≥6, tender joint count ≥8, CRP >1 or ESR ≥28, treated with MTX for ≥12 weeks	Uncontrolled medical conditions, other inflammatory disease, malignancy, infection, immunodeficiency, Hgb <8.5, leucopenia, thrombocytopenia, neutropenia, abnormal LFTs, triglycerides >10, active TB, hepatitis B, hepatitis C	568	Tocilizumab 4 or 8 mg/kg IV q 4 weeks plus methotrexate once weekly
Maini, 2006 (2)	Double blind RCT	200	≥18	Active RA ≥6 months, swollen joint count ≥6, tender joint count ≥6, CRP >1 or ESR ≥28, showed inadequate response to MTX during a minimum of 6 months of therapy	Leucopenia, neutropenia, thrombocytopenia, abnormal LFTs, received DMARD other than MTX within 4 weeks prior to study, received anti-TNF agents within 12 weeks or leflunomide within 6 months of infusion of study medication	29	Tocilizumab 2, 4, or 8 mg/kg IV q 4 weeks plus methotrexate once weekly
Smolen, 2008 (3)	Double blind RCT	623	≥18	Swollen joint count ≥6, tender joint count ≥8, CRP >10 or ESR ≥28, received MTX for ≥12 weeks	Autoimmune diseases, significant systemic involvement secondary to RA, previous infection, hepatitis B, hepatitis C, recurrent herpes, abnormal chest x-ray, previous unsuccessful treatment with anti-TNF agents	57	Tocilizumab 4 or 8 mg/kg IV q 4 weeks plus methotrexate once weekly

OUTCOMES MEASURED

The primary outcome measured in all three studies was the ACR20 response. This is a scale established by the American College of Rheumatology. An ACR20 response requires a patient to have a 20% reduction in the number of swollen and tender joints. In addition, a 20% reduction must be seen in 3 out of 5 other parameters including physician global assessment of disease, patient global assessment of disease, patient assessment of pain, C-reactive protein or erythrocyte sedimentation rate, and degree of disability in Health Assessment Questionnaire (HAQ) score. The parameter that will be the focus of this review is the number of swollen and tender joints. Secondary endpoints that were measured include the ACR50 and ACR70 response rates which require a 50% and 70% reduction in the number of tender and swollen joints, respectively. The two studies by Smolen and Emery measured these outcomes at week 24 where as Maini measured the same outcomes at week 16.

RESULTS

All three double-blind randomized controlled trials used the ACR20 response as the primary efficacy endpoint. This endpoint was analyzed by intention to treat. In the Maini study, participants received tocilizumab at 2, 4, or 8 mg/kg plus methotrexate or a placebo plus methotrexate. In both the Smolen and Emery studies, participants received tocilizumab at 4 or 8 mg/kg plus methotrexate or a placebo plus methotrexate. All participants received tocilizumab or a placebo every 4 weeks and methotrexate every week. In addition, folic acid was administered weekly to each participant to minimize methotrexate-related toxicity. In order to be included in each of these studies, participants were required to have moderate to severe active RA for at least 6 months (defined as $\geq$ 6 tender joints and $\geq$ 6 swollen joints, an ESR $\geq$ 28 mm/hr, and/or an CRP $\geq$ 1 mg/dl) and to have had an inadequate response to methotrexate or

another DMARD. The Smolen study had the largest number of participants with 623 enrolled and 566 completing the study. 499 participants were enrolled in the Emery study with 418 completing the study. Lastly, the Maini study had 200 participants enrolled with 171 completing the study.

The ACR20 response was used as the primary efficacy endpoint, which is defined by the American College of Rheumatology as the number of participants with a 20% reduction in the signs and symptoms of rheumatoid arthritis. Smolen and Emery measured the ACR20 response at 24 weeks, where as Maini measured it at week 16.

Table 2. Percentage of participants who achieved an ACR20 response

Study	Placebo + MTX (control group)	Tocilizumab 2 mg/kg + MTX	Tocilizumab 4 mg/kg + MTX	Tocilizumab 8 mg/kg + MTX
Smolen	26%	---	48%	59%
Emery	10.1%	---	30.4%	50%
Maini	41%	64%	63%	74%

MTX = Methotrexate, NR = Not Reported

Table 2 shows the percentage of participants who achieved an ACR20 response at week 24 in the Smolen and Emery studies and at week 16 in the Maini study. In all three studies, significantly more participants receiving tocilizumab 8 mg/kg had achieved an ACR20 response compared to other doses of tocilizumab as well as to a placebo with p-values < 0.001. Additionally, those receiving 2 mg/kg or 4 mg/kg of tocilizumab achieved an ACR20 response that was significantly more than those receiving a placebo. The p-values for the 4 mg/kg groups in the Smolen, Emery, and Maini studies were < 0.001, <0.001, and <0.05 respectively. The p-value for the 2 mg/kg group in the Maini study was <0.05.

Since all of the results were presented as dichotomous data, they were left in this form to be analyzed. First, the control event rate (CER) and the experimental event rate were calculated.

The CER is the percentage of participants who responded to the placebo plus methotrexate and the EER is the percentage of participants who responded to the intervention (tocilizumab plus methotrexate). The CER and EER could then be used to calculate the absolute benefit increase (ABI) and the relative benefit increase (RBI). The ABI is the increase of a good event as the result of tocilizumab plus MTX. The RBI is the proportional increase in the rates of good outcomes between the experimental and control groups. The number needed to treat (NNT) was then calculated by dividing the absolute risk reduction into 1. This result indicates the number of patients with rheumatoid arthritis that need to be treated with tocilizumab plus methotrexate in order to achieve an ACR20 response indicating a reduction in the number of swollen and tender joints. Table 3 below shows the results of the dichotomous data analysis for each of the three studies. In the Emery study, only 3 patients need to be treated in order to achieve one ACR20 response where as in both the Smolen and Maini studies, 4 patients need to be treated. However, these numbers needed to treat are very similar, indicating similar results among the three studies.

Table 3. Treatment analysis for patients receiving tocilizumab plus methotrexate vs placebo plus methotrexate for rheumatoid arthritis

Study	# completed study	CER (placebo + MTX)	EER (8 mg/kg tocilizumab + MTX)	ABI	RBI	NNT
Smolen	566	26%	59%	33%	227%	4
Emery	418	10.1%	50%	39%	495%	3
Maini	171	41%	74%	33%	180%	4

CER = Control Event Rate, EER = Experimental Event Rate, ABI = Absolute Benefit Increase, RBI = Relative Benefit Increase, NNT = Number Needed to Treat, NR = Not Reported

ACR50 and ACR70 response rates were the secondary efficacy end points of the studies and the results are summarized in tables 4 and 5 respectively. These response rates are the percentage of participants who had a 50% (ACR50) or 70% (ACR70) reduction in the signs and symptoms of

rheumatoid arthritis. In the Maini study, only the 8 mg/kg group had statistically significant achievement of both ACR50 and ACR70 responses when compared to methotrexate alone with a p-value < 0.05. Emery showed a statistically significant achievement of ACR50 and ACR70 responses in the 8 mg/kg group with p-values of p< 0.001 and p = 0.001 respectively when compared to the control group. For the 4 mg/kg group, only the ACR50 response was statistically significant when compared to the control group with a p-value <0.001. Lastly, the Smolen study demonstrated that significantly more participants in both tocilizumab groups had ACR50 and ACR70 responses than those in the control group (p-value < 0.001).

Table 4. Percentage of participants who achieved an ACR50 response

Study	Placebo + MTX (control group)	Tocilizumab 2 mg/kg + MTX	Tocilizumab 4 mg/kg + MTX	Tocilizumab 8 mg/kg + MTX
Smolen	11%	---	31%	44%
Emery	3.8%	---	16.8%	28.8%
Maini	29%	32%	37%	53%

MTX = methotrexate

Table 5. Percentage of participants who achieved an ACR70 response

Study	Placebo + MTX (control group)	Tocilizumab 2 mg/kg + MTX	Tocilizumab 4 mg/kg + MTX	Tocilizumab 8 mg/kg + MTX
Smolen	2%	---	12%	22%
Emery	1.3%	---	5%	12.4%
Maini	16%	14%	12%	37%

MTX = methotrexate

DISCUSSION

Tocilizumab (Actemra) is a humanized monoclonal antibody that targets interleukin-6 (IL-6) and prevents it from binding to the interleukin-6 receptors on cell surfaces.[2] This mechanism of action is important because in recent research, interleukin-6 has been shown to be

a key cytokine in the initiation and progression of joint inflammation and destruction. Tumor necrosis factor α and interleukin-1 have been the cytokines targeted thus far with rheumatoid arthritis therapies without maximum efficacy. Tocilizumab was approved in the United States by the FDA on January 8, 2010 for the treatment of moderate to severe rheumatoid arthritis after an inadequate response to methotrexate or other DMARD.[5] The cost for tocilizumab is estimated to be between $1,060 and $2,125 per month.[5] Currently, there are no contraindications listed by the manufacturer.[6] However, fatal infections including tuberculosis and invasive fungal, bacterial, viral, and protozoal infections are listed as a black box warning. It is important to note that most of these infections are found in patients who are using immunosuppressive therapy concurrently.[6]

There are minimal limitations to the three trials included in this systematic review. All three studies can be termed valid for the following reasons. They were randomized controlled trials, the outcomes were presented as dichotomous data, and the patients, clinicians, and study workers were blinded to the treatment. Additionally, losses to follow-up were less than 20% with the calculated numbers being 16.2% lost in the Emery study, 9.1% lost in the Smolen study, and 16.7% lost in the Maini study. The initial sample size in the Maini study was small compared to the number of participants in the Emery and Smolen studies, 200, 499, and 623 respectively. Therefore, the smaller sample size in the Maini study may have affected the results.

CONCLUSION

The systematic review of the three randomized controlled studies indicates that tocilizumab in combination with methotrexate is an effective treatment option for patients that have had an inadequate response to methotrexate alone. Optimum doses of tocilizumab have

been shown to be 4 mg/kg and 8 mg/kg. Dosing at 2 mg/kg was not proven to be statistically significant compared to the control group in the Maini study. Doses higher than 8 mg/kg have not been investigated and should therefore be avoided until further investigation is completed. The 6 month time frame used in each of these studies seemed adequate to evaluate the efficacy of tocilizumab, but future studies should incorporate observation of long term clinical improvement and/or deterioration of patients' rheumatoid arthritis. Additionally, only one of the studies was conducted in Europe and North America so future studies are needed to assess the efficacy of tocilizumab in patients with rheumatoid arthritis in the United States.