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Does Sarilumab 200mg Result In Functional Improvement In Patients With Rheumatoid Arthritis Who Cannot Tolerate The Traditional Line Of Treatment?

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Does Sarilumab 200mg Result In Functional Improvement In Patients With Rheumatoid Arthritis Who Cannot Tolerate The Traditional Line Of Treatment?

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A SELECTIVE EVIDENCE-BASED MEDICINE REVIEW

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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not Sarilumab 200mg results in functional improvement in patients who cannot tolerate the traditional line of treatment in rheumatoid arthritis.

Study Design: Review of three randomized control trials (RCTs), published after 2013 all in the English language

Data Sources: 1 double blind, RCT comparing sarilumab 200mg against traditional treatment of TNF-alpha inhibitor adalimumab. 2 RCTs comparing efficacy of sarilumab 200mg to different dosages in patients that had an inadequate response or were unable to tolerate methotrexate (MTX) or TNF-a inhibitor. All studies were found using PubMed.

Outcomes Measured: Each of the articles looked at the effect of sarilumab 200mg on the level of functional improvement of the patient's symptoms of active RA using the Health Assessment Questionnaire Disability Index (HAQ-DI). The HAQ-DI takes into account 8 different sections; dressing, arising, eating, walking, hygiene, reach, grip, and activities. Patients then rank their score from 0 (having no symptoms) to 3 (unable to perform). From each section, the one highest score is taken, all sections are added and averaged. The number that results is the number that is representative of the disability index.

Results: The study by Burmester et al. patients receiving sarilumab 200mg every 2 weeks (q2w) showed statistically significant functional improvement in the HAQ-DI compared to adalimumab 40mg q2w with p-values of <0.01 and a confidence interval (CI) of 95% (*ARD* 2017;76(5):840-847. doi:10.1136/annrheumdis-2016-210310). The Huizinga et al. compared sarilumab 200mg q2w with placebo plus methotrexate, showing a statistically significant improvement in the HAQ-DI for the sarilumab group for functional improvement with a p-value of 0.0019 and a CI of 95% (*ARD.* 2014;73(9):1626-1634. doi:10.1136/annrheumdis-2013-204405). Fleischmann et al. evaluated sarilumab 200mg q2w against placebo showing a statistically significant functional improvement in the HAQ-DI scores with a p-value of 0.0004 (*A&R*. 2017;69(2):277-290. doi:10.1002/art.39944).

Conclusions: Based on the current data from the three RCT's used in this systematic review, sarilumab 200mg does result in a statistically significant functional improvement in patients with RA who are intolerant to traditional treatment.

Keywords: Rheumatoid Arthritis, randomized control trial, Sarilumab, functional

INTRODUCTION

Rheumatoid Arthritis (RA) is an autoimmune disease that most commonly symmetrically targets the joints of the hands, wrists, and knees. This inflammatory process damages the internal structure of the joint leading to debilitating pain.[1] RA effects 0.5-1% of adults, and most commonly effects women and the elderly population.[2] It is known that there is a large genetic component to the disease as well as contributing environmental factors, such as smoking, that put patients at a higher risk of developing RA.[2] It is largely unknown why the autoimmune response is triggered to begin.[2] Untreated RA can be a debilitating disease causing a decrease in quality of life.[2] The cost of RA medications can reach up to $30,000 a year, and if surgery is required, patients double that cost with a knee replacement costing $31,000.[3] Cost is also increased because many RA patients cannot obtain private insurance because they are unable to work.[3]

Along with symptomatic care, disease modifying anti-rheumatic drugs (DMARDs), such as methotrexate (MTX), was one of the earliest treatments for this debilitating disease, and is considered the standard of care.[4] DMARDs have been shown to slow progression and improve symptoms of RA, yet some patients have an inadequate response to some of these drugs.[5] As biologic DMARDs have become available to regulate the body's immune response and lessen the damage done to joints, up to one third of patients are using biologics as monotherapy because they either do not tolerate methotrexate or they have a contraindication to its use.[6]

Biologic DMARDs are further subdivided into categories for which antibodies they target, mainly TNF-alpha (tumor necrosis factor alpha) and IL-6 (interleukin 6) groups. TNF-alpha biologics, such as adalimumab, is the older class, and are often poorly tolerated by patients. In patients with active RA, there are increased numbers of interleukin-6 (IL-6) in the joint synovium and blood stream, which cause synovitis, systemic inflammation, and joint

destruction.[4] Sarilumab is an anti-IL-6 that binds soluble and bound IL-6 inhibiting the inflammatory cascade.[4] Reducing the amount of IL-6 also reduces osteoclast activity and bone erosion, which is a large factor in rheumatoid arthritis.[6]

OBJECTIVE

The objective of this selective EBM review is to determine whether or not Sarilumab 200mg results in functional improvement in patients who cannot tolerate the traditional line of treatment in rheumatoid arthritis.

METHODS

The studies used in this systematic review included three, double blind, placebo controlled, randomized controlled trials. The population being considered includes patients that are 18 years or older with a diagnosis of RA that had an intolerance or an inadequate response to TNF-alpha inhibitors or methotrexate. Two randomized controlled trials considered, evaluated if sarilumab 200mg to different dosages in patients that had an inadequate response or were unable to tolerate methotrexate or TNF-a inhibitor. The other RCT assessed sarilumab 200mg against traditional treatment of TNF-a inhibitor adalimumab. The outcome measured in each study includes the efficacy of sarilumab 200mg and the patient perceived functional improvement.

All studies were found using the PubMed database using the key words “Rheumatoid Arthritis,” “randomized control trial,” “Sarilumab,” and “functional improvement.” All studies used were written in the English language and published in medical journals. Selected articles were chosen based on their relevance to the patient-oriented evidence that matters (POEM) proposed in the clinical question. Inclusion criteria necessitated that the articles be published within the last 10 years, RCT, primary research design, and patients failed traditional treatment (MTX or TNF-alpha). Exclusion criteria removed studies that involved animals and/or included

other IL-6alpha biologics that were not sarilumab. Statistics were reported using the p-value in all studies. Cochrane database was also utilized to ensure no metanalysis currently existed using the above search terms and requirements. The demographics and specific characteristics to each article can be found in Table 1.

OUTCOMES MEASURED

The outcome measured in each of the studies was the level of functional improvement in patients taking sarilumab by patient administered or provider to patient administered Health Assessment Questionnaire Disability Index (HAQ DI). The HAQ-DI takes into account eight different sections; dressing, arising, eating, walking, hygiene, reach, grip, and activities and patients rank their score from zero (having no symptoms) to three (unable to perform). From each section, the one highest score is taken, all sections are added and averaged. The number that results is the number that is representative of the disability index. The study conducted by Burmester et al. measured the HAQ-DI at week 24.[4] Huizinga et al. measured the HAQ-DI at week 12.[5] Fleischmann et al. measured HAQ-DI at weeks 12 and 24.[6]

Table 1 - Demographics & Characteristics of included studies

Study	Type	# Pts	Age-years	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Burmester[4] (2016)	Randomized, double blind, parallel group phase III trial	369	53.6±11.9 years	-≥18 years at baseline -Patients who fulfilled ACR qualifications for RA, and had a class I-III functional status -Active RA with ≥6 of 66 swollen and ≥8 of 68 tender joints -High sensitivity CRP or ESR -Patients that are not eligible for or do not tolerate/respond to MTX	Prior bDMARD experience	47	Sarilumab 200mg Q2W and Adalimumab 40mg Q2W
Huizinga[5] (2013)	Randomized, double blind, trial	306	52.2±12.3 years	-18-75 years old - Active RA with ≥6 of 66 swollen and ≥8 of 68 tender joints and CRP >10mg/L -Active RA of at least 3 months despite MTX treatment for a minimum of 12 weeks	-Pts that had other autoimmune diseases than RA -Tx with DMARD other than MTX w/i 4-12w -Use of parenteral glucocorticoids or intraarticular prednisone in 4w -Pts with history of nonresponse to anti-TNF and other biologic agents -Treatment with other biologics within 3 months	35	Placebo, Sarilumab at 100mg QW and Q2W, 150mg QW and Q2W, and 200mg Q2W
Fleischmann[6] (2017)	Randomized, double blind, phase III study	546	Placebo 51.9 ±12.4 150mg 54.0±11.7 200mg 52.9 ±12.9	->18 years old -Active RA with ≥6 of 66 swollen and ≥8 of 68 tender joints and CRP >8mg/L -Inadequate response to >1 TNF therapy	-uncontrolled concomitant disease -sig. extraarticular RA manifestations -Functional class IV, other inflammatory diseases, recurrent infections, or taking prednisone	73	Placebo, Sarilumab 150mg Q2W, and Sarilumab 200mg Q2W

RESULTS

Three, double blind, placebo controlled, randomized control trials were used to evaluate if sarilumab 200mg resulted in functional improvement in rheumatoid arthritis patients who could not tolerate the traditional line of treatment.

The study conducted by Burmester et al. randomly assigned 369 patients of the screened 540 who had all failed methotrexate treatment to either the sarilumab 200mg group or the adalimumab 40mg group.[4] See Table 1 for inclusion and exclusion criteria. 184 patients were assigned to the sarilumab 200mg trial group and 185 patients were assigned to the control adalimumab 40mg group, which has been used as the standard escalation in treatment in patients who do not tolerate methotrexate.[4] Intent to treat analysis was performed on all randomized patients, including those who increased dosages during the study, but data after complete discontinuation of either drug was excluded in the data. Loss to follow up was <20% for both categories evaluated.[4] Of the 184 patients in the sarilumab group, 165 patients completed the trial, adverse events were responsible for the majority of the 19 patients that did not finish the trial along with lack of efficacy and poor compliance.[4] The rate of discontinuation was much higher in the adalimumab group, with 28 of the 185 patients dropping out of the trial early due to adverse effects, lack of efficacy, and poor compliance.[4] The HAQ-DI scores were taken at the start of the trial and again at the end after completing the 24 week trial to assess for functional improvement.[4] The study concluded that the mean improvement was significantly better in the sarilumab group compared to the adalimumab group. [4] The study concluded that patients demonstrated a clinically meaningful improvement in the sarilumab trial group, with a statistically significant p value of <0.01 and a confidence interval (CI) of 95%.[4] Summarized data from this randomized control trial can be found in Table 2.

Table 2 – Efficacy of Sarilumab 200mg in producing functional improvement, Burmester et al.[4]

	Sarilumab 200mg	Adalimumab 40mg
Mean Improvement	-0.61	-0.43
CI = 95%	P value = 0.0037	

Huizinga et al. conducted a randomized control dose ranging trial, screened 737 patients, and randomly assigned 306 patients with active rheumatoid arthritis who had an inadequate response to methotrexate. The 306 patients were divided into one of six groups: placebo plus MTX, sarilumab 100mg every two weeks, sarilumab 100mg once per week, sarilumab 150mg every two weeks, sarilumab 150mg once a week, and sarilumab 200 every two weeks.[5] See Table 1 for inclusion and exclusion criteria. For the purposes of this systematic review, the placebo plus MTX and sarilumab 200mg every two weeks were considered for continuity. Both the placebo and sarilumab group received 52 patients each.[5] Intent to treat analysis was performed on all randomized patients, and data on patients that discontinued the trial were included in the supplemental document. Loss to follow up was determined to be <20% as 46 out of 52 patients in the sarilumab group and 49 of 52 in the placebo group finished the trial.[5] Patients in both groups that discontinued the trial were secondary to adverse effects and lack of efficacy.[5] HAQ-DI results measured at week twelve were reported in Table 2 of the trial and concluded that, compared to placebo plus MTX, sarilumab 200mg every two weeks was clinically significant in improving patients functional abilities with a P value < 0.01 and a confidence interval of 95%.[5] Summarized data from the Huizinga et al. study can be found in Table 3.

Table 3 – Efficacy of Sarilumab 200mg in producing functional improvement, Huizinga et al.

	Sarilumab 200mg	
Mean Improvement compared to placebo + MTX	-0.57	
CI = 95%		P value = 0.0019

The study conducted by Fleischmann et al. screened 1,224 patients and randomly assigned 546 patients that fit the criteria of having active RA who had an inadequate response to anti-tumor necrosis factor treatment. Patients were divided into three groups: placebo, sarilumab 150mg every two weeks, and sarilumab 200mg every two weeks.[6] See Table 1 for inclusion and exclusion criteria. For continuity, the placebo group and sarilumab 200mg every two weeks are considered in this systematic review. The placebo group received 181 patients at the start of the trial and concluded with 100 patients, making loss to follow up 44.8%.[6] The majority of patients discontinued the trial secondary to adverse effects and lack of efficacy.[6] Sarilumab 200mg every two weeks started with 184 patients and concluded with 133 patients, resulting in a loss to follow up of 27.8%.[6] Adverse effects were responsible for 68.0% of discontinuation in the sarilumab 200mg every two weeks cohort.[6] Other reasons patients discontinued treatment in either trial group was poor compliance, cost, and difficulty obtaining treatment. Intent to treat analysis was performed and a last observation carried forward (LOCF) was conducted on patients who did not complete the study.[6] HAQ-DI scores were taken at week twelve and twenty-four during treatment, and concluded that sarilumab 200mg every two weeks showed statistically significant functional improvement versus placebo with a P value of 0.0004 and an improvement from

baseline (≥0.22 units of improvement) of 56.0%.[6] Summarized data from the Fleischmann et al. study can be found in Table 4.

Table 4 – Efficacy of Sarilumab 200mg in producing functional improvement, Fleischmann et al.

	Placebo	Sarilumab 200mg
Mean Improvement from baseline at week 12	-0.26	-0.47
Improvement from baseline = 56%	P value = 0.0004	

DISCUSSION

The three randomized control trials included in this systematic review evaluated the efficacy of sarilumab 200mg and the functional improvement in patients who cannot tolerate the traditional line of treatment for rheumatoid arthritis. All three studies concluded that there was a statistically significant functional improvement in patients with RA with "P" values of 0.0037, 0.0019, and 0.0004 with 2 studies having a confidence interval of 95% and the third having an improvement from baseline at 56%. [4,5,6]

In the Burmester et al. study, after week sixteen, if patients did not achieve ≥20% improvement in tender swollen joint counts, they were allowed a dose escalation from once every two weeks to once per week of either adalimumab or sarilumab depending on their assigned group.[4] In the Fleischmann et al. study, if patients did not achieve >20% improvement in baseline in joint assessment, they were offered rescue treatment with labeled sarilumab 200mg every two weeks.[6]

Sarilumab was FDA approved on May 22nd, 2017 to treat RA, and its only contraindication is if the patient has a hypersensitivity to the active ingredient.[7] The US boxed warning for sarilumab are for infection and tuberculosis (pulmonary and extrapulmonary).[7] Other warnings related to the drug include, gastrointestinal perforation, hyperlipidemia, malignancy, and viral reactivation.[7] Some of the most common side effects of sarilumab are sensitivity reactions, urinary tract infection, abdominal pain, hematemesis, hematochezia/melena.[7] Infection was a leading cause of discontinuation of the trial due to adverse effects in all three trials.[4,5,6]

The largest limitation to all of these studies were their brief length. The Burmester et al. study was twenty-four weeks, Huizinga et al. was twenty-two weeks, and Fleischmann et al. included a four week screening, twenty-four week trial, with six weeks added for follow up.[4,5,6] Without further follow up or extended trial times, the systematic review is restricted in making generalized conclusions about the drug's actual effect on functional improvement. The Fleischmann et al. study also limits the overall conclusions of the systematic review because the trial of sarilumab was paired with methotrexate in patients that had tried a TNF-alpha inhibitor, whereas in the other two studies, the patients had failed methotrexate.[4,5,6] The Fleischmann et al. study was also limited because of the substantial amount of loss to follow up of 27.8%.[6]

CONCLUSION

Based on the studies available at this time, the conclusion can be drawn that sarilumab 200mg q2w is effective in producing a functional improvement in patients HAQ-DI scores who cannot tolerate traditional line of treatment. All RCT studies included in this systematic review presented statistically significant data that supports the functional improvement of the patients studied.[4,5,6] The duration of each trial ranged from 22-34 weeks, making the length of each trial not sufficiently long to further assess side effects and further efficacy of the drug on functional

improvement. Taking this into consideration, an extended trial for further evaluation of side effects and long term effect of the drug, or a follow up study on the patients that participated in the presented trials in this systematic review would further solidify the initial conclusion that sarilumab 200mg does result in functional improvement in patients with active rheumatoid arthritis.

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