ejpmr, 2020,7(7), 547-549

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

EFFICACY AND SAFETY OF VARIOUS DOSES OF RITUXIMAB IN RHEUMATOID ARTHRITIS (RA) PATIENTS: A SYSTEMATIC APPROACH TO RANDOMIZED CLINICAL TRIALS

Sanjo Saijan[1], Joicy Jose*[2], Aby Paul[3], Swetha Jos[4] and Jobin Kunjumon Vilapurathu[5]

[1,2,3,4]Pharm D Students, Nirmala College of Pharmacy, Nirmala College Road, Kizhakkekara, Muvattupuzha, Kerala, 686661.

[5]Jobin Kunjumon Vilapurathu, Asst. Professor, Pharmacy Practice Department, Nirmala College of Pharmacy, Nirmala College Road, Kizhakkekara, Muvattupuzha, Kerala, 686661.

***Corresponding Author: Joicy Jose**

Pharm D Students, Nirmala College of Pharmacy, Nirmala College Road, Kizhakkekara, Muvattupuzha, Kerala, 686661.

Article Received on 26/04/2020 **Article Revised on 16/05/2020** **Article Accepted on 06/06/2020**

ABSTRACT

Rituximab being a cytolytic monoclonal antibody is used to various disease including Non- Hodgkin's Lymphoma, Chronic lymphocytic Leukemia, Wegener's granulomatosis, microscopic polyangiitis and in combination with methotrexate for rheumatoid arthritis who failed TNF antagonist therapy.[1] Based on the clinical evidence the dose of Rituximab for Rheumatoid arthritis varies. The dose which shows the maximum efficacy in RA is still a challenging task for the physicians. This is a narrative review which emphasis on the efficacy and safety of various doses of Rituximab in RA patients.

KEYWORDS: Chronic lymphocytic Leukemia, Wegener's granulomatosis.

INTRODUCTION

The pathogenesis of Rheumatoid Arthritis include multiple genetic and environmental factors which makes it more difficult to understand. Mild to severe joint pain, inflammation and tenderness are the most common symptoms noticed in the affected patients. Although it occurs in both gender of early to middle age, women are 3 folds at higher risk compared to men due to unknown reason. Many drugs are undergoing clinical trials for RA, but their safety and efficacy is still challenging. B cells play a major role in RA, due to this the drugs should be targeted against these cells.

Being the chimeric mouse that act against CD20 molecule, it is the only biologic specific B cell targeting therapy in Rheumatoid Arthritis available in market[2]. Different doses of Rituximab is available and it is important to know which dose gives the maximum benefit and safety. In this review we are aiming to convey which dose produce the maximum safety and efficacy from these available original articles.

METHODOLOGY

Systematically searched for articles in PubMed using the key words Rituximab, Rheumatoid Arthritis, various doses and collected all the available studies, out of many articles obtained, we selected 6 original articles with English language and excluded other languages. All studies were randomized, double blind, placebo controlled, phase 3 trials, which made reviewing more effective.

In this analysis of 6 studies we included Author's names, publication year, sample size, trial design, doses, duration of study, outcomes and major findings.

RESULT

Enrolled studies

Cohen s. et.al 2006 (REFLEX trial)conducted a multi-centric, randomized, double blind study for 2 years in adults who had RA for at -lest 6 months(ACR revised criteria). Patients were enrolled from 114 rheumatology centers in US, Europe, Canada and Israel. The selected patients were on MTX treatment for last 12 week receiving a stable dose of 10-25 mg/week in combination with Folic acid ≥ 5mg/week. Patients were divided into two groups one receiving placebo and other with rituximab (2*1000mg) on 1 and 15th days along with stable dose of MTX. Methylprednisolone 100 mg was given as a pre- medication and prednisone 60 mg on 2nd and 7th days followed by 80 mg on 8th day. Use of Glucocorticoids and NSAIDs were allowed if were on a stable dose for ≥ 4 weeks and ≥ 2weeks prior to screening. All DMARDs were stopped during the trial.

Out of 520 enrolled patients, 112/201 in placebo + MTX and 254/311 in rituximab +MTX completed the 24 weeks treatments .No death were reported in both cases,

but ADRs were reported. According to ACR and EULAR criteria the response of patients receiving rituximab +MTX were statistically significant showing its high efficacy. Patients were classified as ACR20, ACR50 and ACR70, this indicate the improvement criteria. This study gives a conclusion that 2*1000 mg of rituximab along with MTX showed a positive outcome in RA patients compared to placebo.

Emery P. et.al. 2010 (SERENE trial) conducted a multi-centric, randomized, placebo controlled trial at 102 centers in 11 countries according to ACR1987 criteria. They included patients who had RA≥6 months (age between 18-80 years) taking MTX 10-25 mg/week and did not received biological treatment for RA previously. The study was conducted with consent from each individual. A washout period of 2 week is provided for all DMARDs, but administered MTX in combination with Folic acid ≥5 mg /week at a stable dose.

Patients were divided into 3 randomized treatment groups ie;2*500 mg rituximab +MTX (n=167), 2*1000 mg rituximab+ MTX(n=170) and a placebo group+ MTX(n=172)(1 and 15 day with IV infusion). Before administration of these drugs methylprednisolone 100mg was given. Patients who were not in remission were provided with second phase of drug, patients who initially received placebo were changed to rituximab 2*500mg.159 patients in placebo, 162 in rituximab 2*500 mg and 166 in rituximab 2*1000 mg completed the 24 weeks treatment. Also 154 in placebo, 157 in rituximab 2*500 mg and 2*1000 mg each completed the 48 weeks of drug therapy. Two patient experienced infusion related reaction in 2*100 mg rituximab group. Three adverse events reported in placebo and rituximab 2*500 group and seven in rituximab 2* 1000 mg group. Two deaths were reported in patients receiving rituximab 2*500 mg. ACR20 response was taken as the primary outcome along with EULAR, ACR50 responses as secondary outcome.

Through this study they reveal the effect of two doses of rituximab suggesting that both doses showed same clinical response.

Roth A.R. et.al 2010(MIRROR trial) conducted a multi-centric, randomized, double blind, phase 3 clinical trial in 81 centers of 18 countries. Patients were selected according to the ACR criteria (1987) ie; should have active disease ≥6 months, with MTX 10-25mg/week a stable dose ≥4 weeks. Outcome was checked after 48 days of treatment with the trial drugs. The patients were randomized into 3 groups ie; 2*500mg rituximab+ MTX for 24 week followed by 2*500 for next 24 week, First 2*500mg + MTX then dose was increase on 24th week to2*1000 mg rituximab +MTX 2*1000mg + MTX for 48 weeks. Methylprednisolone was given as the premedication and study was done for 48 week. Out of 378 selected patients, 123 in first, 128 in 2nd and 127 in 3rd group were assigned. ACR20 criteria along with EULAR response was taken as the primary outcome. No deaths were reported and few ADRs were reported including infections in some due to low IgM antibodies .This study also concludes that the efficacy of 2*1000mg rituximab for 48 weeks is more effective as compared to other doses. Response expect that the dose 2*1000 mg reduced the progression of joint damage.

Tak PP. et. al. 2011(**IMAGE trial**) conducted their randomized, double bling, phase 3 study from January 2009- September 2007 in169 centers of Europe, Latin America, USA, Asia and Australia. The patients were selected according to ACR 1987 criteria and were divided into placebo, 2*500mg and 2*100mg rituximab receiving groups. All DMARDs were stopped but allowed use of corticosteroids and NSAIDs for stable patients. Out of 755 patients assigned, 249 patients were included in placebo and 2*500mg rituximab each and 250 in 2*1000 mg group. The primary outcome was difference in the Genant –modified sharp score (mTSS) at week 52 along with ACR20, ACR50, ACR70 and EULAR response. Three deaths were reported in placebo group. Even though the occurrence of ADR is same in all the groups, placebo groups reported serious infections (5%) compared to 2*500(3%) and 2*1000(2%). From this study they concluded that both doses of MTX is effective in improving clinical outcomes of RA, improvement in joint damage is mostly seen in patients administered with 2*1000mg of rituximab +MTX.

Mease P. et.al 2014(SUNRISE trial) conducted a randomized double- blind study which included patients from 18-80 years of age with active RA for ≥6 months (ACRcriteria-1987). Selected patients had inadequate response to TNF inhibitors previously and should stop the use of all DMARDs prior to the treatment with rituximab. MTX 10-25 mg/kg for≥ 4 weeks is needed, and use of corticosteroids and one NSAIDs were permitted. Patients with other rheumatic disease were excluded. Selected patients were randomized into rituximab receiving group (2*1000mg) +MTX and placebo + MTX group. Methylprednisolone 100mg was given as premedication.

The primary outcome was the ACR 20 score in 48th week of treatment and secondary outcome was ACR50, ACR70 till ACRn scores and also from the EULAR response. From selected 559 patients, 475 were randomized ie; 318 in rituximab + MTX and 157 in placebo +MTX group.79% were females with an average age of 54 years. At week 24 ACR20 score was higher for patients receiving rituximab, which shows its high effectivity. Patients who were retreated after 24th week with rituximab for second course ie; 48 weeks showed much response compared to placebo treatment after 24 weeks. One death were reported in each group due to SARDS in rituximab group and death due to unknown etiology in placebo group. Infusion related reaction was more seen in rituximab group, but serious adverse event occure in same rate in both groups. Patients who

received rituximab + MTX for 48 weeks showed much efficacy in RA treatment as compared with the placebo.

Mease P.J. et.al 2019 (DANCER trial) conducted a randomized, double blind, phase 3 trial in 95 centers. Patients were enrolled according to the ACR criteria 1987. The selected patients were divided into placebo, 2*500mg, and2*1000mg rituximab receiving on days 1 and 15, along with 3 doses of gluccocorticosteriods. The patients were on 10-25mg/week of MTX and methylprednisolone was given as a pretreatment. ACR20 response was taken as the primary outcome after 24 weeks and ACR50 and ACR 70 as secondary outcome along with the EULAR response. After 24 weeks the patients on rituximab showed much improvement compared to the placebo groups. In conclusion both rituximab treated showed clinical improvement, also ACR70 and EULAR response indicate that health related quality of life for patients (HRQOL) was relatively improved with 1000mg dose compared to 500 mg dose.

DISCUSSION

In these articles of randomized, multi centric, double bind, phase 3 clinical trials the efficacy and safety of various doses of rituximab is analyzed. These studies point out that rituximab in combination with methotrexate 2*500mg and 2*1000mg is effective to improve the clinical outcome of RA. Reduced progression of joint damage is noticed in 2*1000 mg dose.

As all these studies are randomized trials and was done for a long duration in large population. We can conclude that 2*1000mg dose of rituximab is more effective in treatment of RA. Rituximab being a B cell depleting biological agent, it has caught attention in treatment for RA.(REF: **cocrain**e) Many studies are done to evaluate the effectiveness and safety in RA but the dose which gives maximum efficacy was still a difficult task to converge. The safety and efficacy of a drug depend on the administered dose, so it is important to identify the correct dose. Through this study we were able to find it.

Conducting more randomized trials will give an idea about the duration of the therapy. In these studies the duration is still confusing because some studies are conducted for 24 weeks and others for 48 weeks. Even though duration depend upon the patients individual characteristics, it is also essential for the clinical outcome of the therapy.

CONCLUSION

All these studies concluded that Rituximab is an effective drug for rheumatoid arthritis when given in combination with methotrexate to improve the clinical outcomes. A dose of 2*1000mg rituximab along with methotrexate showed decreased progression in joint damage along with improvement in clinical symptoms compared with 2*500mg dose.

REFERENCES

1. FDA
2. Chi Chiu Mok, Rituximab for the treatment of rheumatoid arthritis: an update, Drug Des Devel Ther., 2014; 8: 87-100.
3. P. Emery, A Deodhar, WF Rigbuy et.al. Efficacy and Safety of Different Doses and Retreatment of Rituximab: A Randomised, Placebo-Controlled Trial in Patients Who Are Biological Naive With Active Rheumatoid Arthritis and an Inadequate Response to Methotrexate (Study Evaluating Rituximab's Efficacy in MTX in responders (SERENE)), Ann Rheum Dis., 2010 Sep; 69(9): 1629-35.
4. Stanely B. Cohen, Paul Emery, Mria W. Greenwald et.al. Rituximab for Rheumatoid Arthritis Refractory to Anti-Tumor Necrosis Factor Therapy: Results of a Multicenter, Randomized, Double-Blind, Placebo-Controlled, and Phase III Trial Evaluating Primary Efficacy and Safety at Twenty-Four Weeks, Arthritis Rheum, 2006 Sep; 54(9): 2793-806.
5. Philip J. Mease, Stanley Cohen, Norman B.Gaylis et.al. Efficacy and safety of retreatment in patients with Rheumatoid arthritis with Previous Inadequate Response to Tumor Necrosis Factor Inhibitors: Results from the SUNRISE Trial. Journal of Rheumatology, 2010; 37: 917-927.
6. Andrea Rubbert-Roth, Paul P.Tak, Christiano Zerbini et.al. Efficacy and safety of various repeat treatment dosing regimens of rituximab in patients with active rheumatoid arthritis: results of a Phase III randomized study (MIRROR). Rheumatology, 2010; 49: 1683-1693.
7. Philip J.Mease, Dennis A.Revicki, Jacek Szechinski et.al. Improved Health-Related Quality of Life for Parents with Active Rheumatoid arthritis Receiving Rituximab- Results of the Dose-Ranging Assessment: International Clinical Evaluation of Rituximab in Rheumatoid Arthritis (DANCER) Trial. The journal of Rheumatology, 2008; 35: 20-30.
8. P P Tak, W F Rigbuy, A Rubbert-Roth et.al. Inhibition of joint damage and improved clinical outcomes with rituximab plus methotrexate in early active rheumatoid arthritis: the IMAGE trial. Ann Rheum Dis., 2011; 70: 39-46.