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Research Article

Low Dose Rituximab Trial as a First Line Biologic Therapy in Patients with DMARD Resistant Rheumatoid Arthritis

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Abstract

Objectives: An open-label, uncontrolled study evaluated the utility of rituximab (RTX) for the therapy of DMARD resistant RA cases as a first line biologic agent before the use of anti-TNF agents. The standard impressive low-dosing of rituximab is 2 × 500 mg or 1 × 1000 mg for active patients. The aim of this study was to investigate low dose the rituximab for the treatment of patients with resistant rheumatoid arthritis and with relative or absolute contraindications to TNF antagonists.

Methods: In this study is an open-label clinical trial, a total of 44 patients with active RA who had failed at least one DMARD received two rituximab infusions 2 weeks apart. 21 patients received two 500 mg doses, and 23 received DMARDs. The 28-joint disease activity index (DAS28) and European League against Rheumatism (EULAR) response criteria were recorded at baseline, 2weeks, four and six months. RF was recorded at baseline and at four and six months.

Results: There was a significant improvement in the DAS28 after four and six months, and EULAR response was observed in 20 of 21 patients (95.2%) at four months and in all of 21 patients (100%) at six months compared to control group. Improvement was also noted in CRP and ESR and RF was negative in 6 of 21 patients (28.7%) after treatment.

Conclusion: Rituximab is well tolerated in everyday clinical practice and may represent a good short-term treatment option as a first line biologic agent where anti-TNF therapy is either unavailable or relatively contraindicated.

Keywords: *Rituximab Trial; Rheumatoid Arthritis; Disease-Modifying Anti-Rheumatic Drugs; DAS28*

Introduction

Rheumatoid arthritis (RA) is a chronic, destructive and progressive joint disease that occurs in approximately 1% of adults throughout the world [1]. The etiopathogenesis of rheumatoid arthritis is highly complex and not completely understood but some remarkable details have recently been revealed [2]. More recently with the better understanding of the pathogenesis and the etiology of this disease, treatment with specific and important targets on different cells, cytokines and signaling pathways have been used for DMARD resistant patients [3]. Disease-modifying antirheumatic drugs (DMARDs) are the typical treatment of RA, among of them methotrexate (MTX) is the most often selected DMARD for initial RA therapy in combination with rituximab [4]. Rituximab (RTX) is a chimeric monoclonal antibody (mAb) that selectively targets CD20-positive B cells and is a new and different biological drug for the treatment of severing active RA [5]. In a large systematic review of 35 studies confirmed that after the failure of a tumor necrosis factor inhibitor, RTX is the most effective

management to treatment of RA [6]. For many years, RA has been considered solely to be a T cell-mediated disease, however, recently there has been increasing interest in the role of B cells in the pathophysiology of RA [7]. The first reported of MTX on RA patients back to 1985, until this time use of methotrexate (MTX) in management of RA was limited [8]. RTX can bind to CD20 and optimal depletion the peripheral B cells through cell-mediated and complement dependent cytotoxicity and promotion of cell apoptosis [3,8] In 2006 different doses of RTX was approved in patients with active RA resistant to DMARDs [9]. The standard dose of RTX for active RA are 2 × 500 mg or 2 × 1000 mg for every six months [10]. It seems that ultra-low doses of RTX is promising; nevertheless, there have been no effective strategic studies to recognize the best treatment [11]. Prescribing lower RTX doses may be possible to decrease adverse events of this disease. Therefore, we decided to use low dose the rituximab as a first-line biological agent for treatment of patients with resistant rheumatoid arthritis and with relative or absolute contraindications to TNF antagonists.

Materials and Methods

Trial design

This study is an open-label clinical trial. Forty-four patients with rheumatoid arthritis according to the American College of Rheumatology (ACR) criteria [12] were randomly selected for the study. The inclusion criteria were: 1987 ACR criteria for the classification of RA [13] positivity of rheumatoid factor (RF), active RA despite therapy with conventional DMARDs (methotrexate, hydroxychloroquine) for at least 3 months as evidenced by DAS 28 > 3/2, patients with active, resistant RA who didn't receive anti-TNF agents. Exclusion criteria were: patient with hypogammaglobinemia, patient with congestive heart failure (class IV), active current bacterial, viral, fungal, myocardial or other infections, chronic hepatitis B or hepatitis C carriers, history of severe allergic reaction to human, humanized or murine monoclonal antibodies, history of malignancies, pregnant women or lactating mothers, patients with chronic renal failure and hepatic disease.

Patients were divided into two groups; Twenty-one patients were given 2 × 500 mg intravenous infusions of rituximab (MabThera®, Roche, Basel, Switzerland) on day 1 and day 15, they had also received methotrexate (up to 25 mg), prednisolone (up to 15 mg), hydroxychloroquine (5 - 6/5 mg/kg) and folic acid. As control group, we selected randomly 23 patients with resistant RA who were matched with patients group according to age, sex, duration of disease and medication steroids, methotrexate (up to 25 mg/week) and Hydroxychloroquine (Plaquenil®) (6 mg/kg), as we did not administered RTX for this group.

We allowed the use of non-steroidal anti-inflammatory drugs (NSAIDs); however, other DMARDs were stopped for at least 4 weeks prior to the study. Premedication consisted of methylprednisolone 100 mg by intravenous infusion, paracetamol 500 mg oral and chlorphenamine 10 mg intravenously. The disease activity score 28 (DAS28) based on ESR (Erythrocyte sedimentation rate) [14] was performed and data were available at baseline, 2 weeks, 4 months and 6 months.

Response was determined by the change in DAS28 and the European league against rheumatism (EULAR) response criteria (good response = DAS 28 < 3.2 plus improvement > 1.2; moderate response = DAS28 > 3.2, ≤ 5.1 plus improvement of > 0.6, ≤ 1.2 and DAS28 > 5.1 plus improvement > 1.2; low disease activity as DAS28 ≤ 3.2 and remission as DAS28 < 2.6) [15]. Immunoglobulins were measured at baseline to ensure that patients did not have hypogammaglobinemia since this is a recognized complication of repeated RTX therapy [16]. RF and CRP (C-reactive protein) were also measured at all time points. Pain was measured at baseline and weeks 4, 8, 12 and 16, using a visual analogue scale (VAS) by patients description, ranging from no pain to worst pain; a higher score indicated worse pain [17]. Patients monitored closely for drug toxicity and require dose. Informed consent was obtained from all patients in this study, with approval obtained from Ethics Committee and trial register of Mashhad University of Medical Sciences. Individual data are available upon request.

Statistical analysis

Demographic observation data were performed using SPSS software version 16 (Inc., Chicago, Il, USA). For determination of parametric and non-parametric data, the Kolmogorov-Smirnov, chi-square test and t-test were used. Furthermore, Wilcoxon test was used to comparison of the groups. Spearman test was applied for linking the data. All data were reported as mean ± SD. A P-value was considered significant if < 0.05.

Results

Participants

A total of 44 patients with active RA and inadequate response to methotrexate for at least 3 months have enrolled the study. The basic characteristics and baseline demographics of study subjects are listed in table 1. The study included 21 RA patients (11 men and 23 women; mean age, 41.76 ± 12.68 years) and 23 controls (6 men and 17 women; mean age, 45.40 ± 10.89 years) which received RTX. Nobody had received anti-TNF-α before enrolling in the study. Disease duration in patients group was 6.82 ± 5.06 and the control group was 7.93 ± 6.12. As expected, no significant difference was observed in the swollen joint count, DAS28, RF-positive, ESR and VAS between patients and control groups (p > 0.05). All patients in two groups were receiving MTX and had the highly active disease at baseline.

Characteristic		RA Patient	Control	P-value
Female/ male		16/5	17/6	P = 0.86
Age		41.76 ± 12.68	45.40 ± 10.89	P = 0.34
Disease duration		6.82 ± 5.06	7.93 ± 6.12	P = 0.52
Tender joint count	First hour	15.0 ± 10.11	16.30 ± 8.66	P = 0.65
	24 months	5.0 ± 4.85	7.17 ± 4.26	P = 0.12
Swollen joint	First hour	17.14 ± 8.15	15.95 ± 6.61	P = 0.6
	24 months	7.19 ± 5.70	9.56 ± 3.44	P = 0.1
DAS28	First hour	6.76 ± 1.59	6.70 ± 1.26	P = 0.89
	24 months	4.22 ± 0.96	5.55 ± 0.78	P < 0.001
ESR	First hour	56.52 ± 37.48	49.52 ± 24.37	P = 0.46
	24 months	19.40 ± 44.44	25.91 ± 9.56	P = 0.03
VAS pain	First hour	67.04 ± 28.47	61.17 ± 24.46	P = 0.47
	24 months	21.42 ± 18.88	30.73 ± 14.23	P = 0.07
RF-positive n (%)		20 (95.3)	23 (100)	P = 0.17

Table 1: *The basic characteristics and baseline demographics of study.*
DAS28: Disease Activity Score 28; VAS Pain: Visual Analog Scale for Pain;
ESR: Erythrocyte Sedimentation Rate; RF: Rheumatoid Factor.

Response to therapy

RTX group had statistically significantly greater relief of pain as measured by the VAS-pain. The difference between-group was statistically significant at all time points after 4 weeks (P = 0.05 for all time points from weeks 8 - 24). All patients received RTX and tolerated it well. EULAR response was seen in almost all patients in the RTX group which were assessed by DAS28 (P < 0.0001 at all-time points) (Table 2). Few patients were not available for some of their follow-up appointments thus we could not measure their DAS28 at the considered time points. DAS28 after 24 months was a significant difference in patients group (4.05 ± 1.10) against controls group (4.97 ± 0.67) (p = 0.002).

	Case				Control				P-value
	DAS28	ΔDAS	EULAR n (%)	Good Response n (%)	DAS28	ΔDAS	EULAR n (%)	Good Response n (%)	
Baseline	6.76 ± 1.59	0	-	0 (0)	6.7 ± 1.26	0	-	0 (0)	-
2 weeks	5.48 ± 1.38	1.28	8 (38)	0 (0)	6.48 ± 1.15	0.22	0 (0)	0 (0)	P = 0.03
16 weeks	4.22 ± 0.96	2.54	20 (95.2)	3 (14.28)	5.55 ± 0.78	1.15	17 (73.9)	0 (0)	p < 0.001
24 weeks	3.97 ± 1.13	2.79	20 (100)	6 (30)	4.97 ± 0.67	1.73	19 (82.6)	0 (0)	p < 0.001

Table 2: *Treatment response EULAR and DAS28 at different intervals in case and control groups. Comparisons were made by the X^2 test (for categorical data), Mann-Whitney and T-test. VAS: Visual Analogue Scale; ΔDAS: Change in DAS28.*

The EULAR response was observed in 20 of 21 patients (95.2%) at 4 months and all patients (100%) in the RTX group at 6 months. In the methotrexate alone group 17 of 23 patients (73.9%) at 4 months and 19 of 23 patients (82.6%) at 6 months had EULAR response. In Rituximab group three of 21 patients (14.3%) achieved a good EULAR response at 4 months, and 6 of 20 patients (30.0%) at 6 months compared with no patients in the methotrexate group at that time point. T-test analysis for ESR shown that there was a significant difference between patients and control groups (P < 0.01) at 16 months.

Improvement of CRP was also evident at all time points: at baseline, CRP was positive in all patients. at 4 months, 17 of 19 patients (89.5%) and at 6 months, 17 of 18 patients in the Mabthera group (94.4%) had negative CRP compared with 15 of 23 patients (65.2%) at 4 months(P = 0.06) and 20 of 23 patients in the methotrexate group (87.0%) at 6 months (P = 0.41).

At 6 months, 5 (25%) of 20 patients who were positive for RF became seronegative, but in the methotrexate group none of patients became seronegative for RF.

Adverse events

Adverse events were seen in 9 of 21 patients in the Mabthera group including: mild reaction at the injection site in 1 patient (4.7%), paresthesia and itching in 2 (9.5%), hypertension in 1 patient (4.7%), headache in 2 patients (9.5%), flashing in 2 patients (9.5%) and sepsis and upper respiratory tract infection each in 1 (4.7%) patient in the second week after the second injection of mabthera at sixth month of the following one 60 years old patient became anemic and was investigated in colonoscopy a tumor was biopsied and colon adenocarcinoma was diagnosed. After 2 months he died. No cases of tuberculosis were seen at 6 months after the first injection.

Discussion

There are lots of studies which evaluated the efficacy of rituximab in RA patients but patients in those studies usually had failed anti-TNF therapy before using Mabthera [18-20], while our report focused mainly on patients who failed only DMARDs. This study showed that B cell depletion by rituximab significantly improves the signs and symptoms of RA in our patients who had not previously received anti-TNF therapy. Some published data suggest that the duration of treatment responses following one course of rituximab in patients that have not previously failed TNF antagonists is longer [20,21].

In this study, we also used Mabthera 500 mg versus 1000 mg in two separate doses, 2 weeks apart. The Dose-ranging assessment international clinical evaluation of rituximab in rheumatoid arthritis (DANCER) trial is a randomized, placebo-controlled trial that examined

two different doses of rituximab in patients with active moderate to severe RA who were randomized to three different treatment arms; (all containing MTX), placebo (MTX alone) and rituximab (500 mg and 1000 mg, each dosage with 2 weeks interval). At the end of the study (24-weeks), the response rate was significantly better in each of the rituximab groups when compared to MTX alone. The 500mg and 1000mg doses show little differences in the ACR20 and 50 groups, but of those achieving an ACR70 response; the 1000 mg group had a more significant response [22,23]. In DANCER trial, patients who received rituximab with no prior exposure to biologic agents received an ACR20 response rate of 62%, which is closer to previously reported rates [9]. In the SERENE trial (Study Evaluating Rituximab's Efficacy in MTX inadequate responders), patients received up to two courses of treatment 6 or more months apart with low and high doses of rituximab. There was no significant difference in responses between two doses, however, infusion reactions to the first infusion were more frequent with the 1000mg infusion [23]. In the IMAGE trial in methotrexate naive and active RA patients, there were not any significant differences in clinical responses between the low and high doses of rituximab [24]. However, significant inhibition of radiographic progression was seen only in the high dose group [25]. In a trial which is conducted by Mc gonagle., *et al.* they also administered two doses of rituximab (500 mg and 1000 mg) 2 weeks apart for active and resistant RA patients who failed DMARD therapy. Only 3 out of 39 patients had used and failed TNF antagonist before receiving rituximab. They showed that low dose Mabthera seemed to be effective. These two studies are in parallel with our study and proposed that rituximab can be used with the lower dose (500 mg) and before TNF antagonists. Although, some studies have noted that the response rate and ACR 70 score in 500 mg regimen were less, compared with the 1000 mg regimen [4]. Nevertheless, some patients on the low dose had good responses lie in with our study.

In this study, it is proposed that the use of concomitant glucocorticoids may enhance the early response of rituximab (up to 4 weeks) because of their anti-inflammatory properties, however, they play no significant role in the improvement of DAS28 response at 24 weeks. The adverse events reported were similar between groups, and like the DANCER trial, many were mild or moderate. Infection was the most serious adverse events in our study, importantly sepsis and upper respiratory infection. One of our patients died because of colon adenocarcinoma. It is not clear the reason is Mabthera or not, because the time between the receiving of Mabthera and the diagnosis of adenocarcinoma was short. On the other hand, at the beginning of the study, the patient did not have any sign or symptoms of gastrointestinal involvement or any anemia. (Hb = 15.5 g/dl). We routinely prescribe intravenous corticosteroids and antihistamines as premedication before rituximab infusion and none of our patients experienced serious infusion reactions. It is believed that this premedication reduced the incidence and severity of infusion associated events. The responses were seen in this open-label study support the hypothesis that B cells are key contributors to the immunopathogenesis of RA through several potential mechanisms.

Time for repeating the dose was based upon symptom relapse. Thus, patients will need to be repeatedly treated and they may become hypogammaglobulinaemic and their humoral immune response will not be efficient. However, this has not been related to infectious complications thus far [26]. These results further support the usefulness of this drug due to its effect in reduction of the number of B cells which results to decreased autoantibody production and therefore less structural joint damage, which then causes improvement in clinical symptoms. It is unknown if patients do not respond, whether they respond to higher doses or not [22].

Our study had some limitation. First, although the time of trial was 6 months and was efficient for efficacy judgment, continuous clinical and functional improvement needs long-term to follow up. Second, inhibition of structural damage is an important aspect of rheumatoid arthritis treatment but was not investigated here. Third, we did not determine long-term safety of this drug and because of high cost for providing the drug and difficult availability of it, we could not do double-blind study and because of this, the number of our patients was limited.

Our study showed that Mabthera 500 mg 2 weeks apart resulted from significant improvement in DAS28 core sets compared to Methotrexate alone group. Improvement in acute phase reactants such as ESR and CRP was also seen. Thus this drug could be an effective agent for treatment of patients with moderate to severe RA that is resistant to multiple DMARDs and it is suggested to start with the lowest

possible effective dosage [27]. This report suggests that rituximab is a very effective first-line biological drug in clinical practice and can be safely given to patients who have relative contraindications for anti-TNF agents.

Conclusion

Rituximab is an effective and safe drug in RA therapy. In patients with sustained response standard RTX doses were determined. We concluded that prescribing low doses of RTX has suitable effects. Therefore, with regard to the lower cost, it can be used as an effective standard regimen for the treatment of active RA.

Conflict of Interest

There is no conflict to posing the current manuscript.

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