RESEARCH ARTICLE

Efficacy of rituximab in patients with rheumatoid arthritis

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Abstract

Objective: To determine the efficacy of rituximab 2×500mg in rheumatoid arthritis patients.

Methods: The descriptive case series was conducted at the Department of General Medicine, Lady Reading Hospital, Peshawar, Pakistan, from November 25, 2018, to May 24, 2019, and comprised patients of either gender aged 30-60 years with rheumatoid arthritis diagnosis for >6 months. The patients received 2 doses of rituximab 2×500mg through intravenous infusion with pre-medications as a standard protocol. A follow-up visit was recommended for each patient after 24 weeks. The efficacy of the treatment in terms of disease progression and improvement were observed using the Disease Activity Score-28 scale at the baseline and on follow-up. Data was analysed using SPSS 20.

Results: Of the 97 patients, 83(85.6%) were female and 14(14.4%) were male. The overall mean age was 50.68±14.27 years. The baseline score was 6.68±1.14 while the follow-up score was 4.62±0.93 ($p<0.05$). In terms of efficacy, 25(25.8%) patients showed no improvement, while 72(74.2%) had improvement.

Conclusions: Rituximab 2×500mgI was found to be an effective treatment option for rheumatoid arthritis patients.

Keywords: Rituximab, Disease-modifying antirheumatic drug, DMARD, Rheumatoid arthritis, Efficacy, DAS-28 score.

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Introduction

Rheumatoid arthritis (RA), a chronic multifactorial autoimmune condition, is known to affect approximately 0.5-1.0% of the adult population in developing countries, while globally the prevalence rate is ~0.24%.[1,2] RA-associated health issues affect the quality of life (QOL) of the patients and also reduces the lifespan by 4-10 years.[3,4] Synovial hyperplasia, production of autoantibodies, destruction of cartilage and bone and joint malformation are among the common aetiological factors associated with RA. Moreover, systemic disorders, like cardiovascular, pulmonary, psychological and skeletal systems, are also involved in RA pathophysiology.[2]

The complex association of genetic and environmental factors contribute to RA pathogenesis, resulting in the failure of immune tolerance through abnormal activation of innate and adaptative immune system responses.[2] Furthermore, presentation of autoantigens with activation of antigen-specific T and B cells and abnormal production of inflammatory cytokines are also associated with RA pathology. This series of events finally leads to synovitis and destruction of subchondral bone and cartilage.[2] Based on the inflammatory theories regarding RA, inflammatory cytokines, like tumour necrosis factor alpha (TNF-α), interleukin 6 (IL-6), IL-1β and IL-17, etc. are involved in pro-osteoclastogenic activity.[5] These cytokines results in receptor activation of nuclear factor kappa-B ligand (RANKL) and macrophage colony-stimulating factor (M-CSF) which in turn causes suppression of bone formation.[5]

Targeted immunotherapies with monoclonal antibodies (mAb), such as anti-CD20 (cluster of differentiate 20) antibody rituximab (RTX), is now being used for treating severe RA patients showing inadequate response to standard immunosuppressants.[6] RTX affects the B cell concentration in the peripheral circulation, resulting in B cell depletion.[7] Several long-term clinical trials have recommended RTX as an effective treatment modality for RA.[8] Recently, a randomised clinical trial brought up RTX biosimilar truxima (CT-P10) for RTX treatment.[9] It was shown that CT-P10 is well tolerated and effective in the management of RA. Moreover, the switching caused no alteration in the efficacy, safety, tolerance, pharmacodynamics and immunogenicity that was previously observed with RTX administration.[9]

Infusion reactions, immunogenicity and hypogammaglobulinaemia are a few adverse events (AEs) associated with RTX. A study reported infusion reactions as the drawback of the RTX in comparison to other biological agents, although the rate reduced with pre-administration of glucocorticoid.[9] Immunogenicity can also be seen, but it barely affects the efficacy or the infusion reaction occurrence. While low serum immunoglobulin M (IgM) was

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observed, the malignancy and long-term risk of serious infections need to be further explored.[10] Although internationally much work has been done to explore the treatment modalities with minimum AEs among RA patients, the results cannot be generalised due to difference in bone density, cost-effectiveness and treatment availability in Pakistan. The current study was planned to determine the efficacy of rituximab 2×500mg in RA patients.

Patients and Methods

The descriptive case series was conducted at the Department of General Medicine, Lady Reading Hospital, Peshawar, Pakistan, from November 25, 2018, to May 24, 2019. After approval from the institutional ethics review board, the sample size was calculated using the World Health Organisation (WHO) STEPwise approach to Surveillance (STEPS) calculator,[11] keeping 95% confidence level with 5% margin of error. However, the sample size was inflated by 50% to cover up for dropouts and to increase the power of the study.

The sample was raised using non-probability consecutive sampling technique. Those included were patients aged 30-60 years irrespective of gender diagnosed with RA for >6 months. Those who had been previously treated with other biological immunosuppressants, like tocilizumab (Actemra), certolizumab (Cimzia), etanercept (Enbrel), adalimumab (Humira), anakinra (Kineret), abatacept (Orencia), infliximab (Remicade), rituximab (Rituxan), golimumab (Simponi) and tofacitinib (Xeljanz), were excluded.

Data was collected after taking written informed consent from each patient. Disease activity markers, such as monocyte chemotactic protein-1 (MCP-1) and erythrocyte sedimentation rate (ESR), were recorded before the treatment initiation through laboratory tests. The patients were assessed for RTX efficacy using the Disease Activity Score-28 (DAS-28).[12] It was rated as very good, good, moderate and poor. Demographic and clinical characteristics, including age, gender, weight, height, body mass index (BMI), duration of RA, were recorded. In addition, the efficacy and tolerability of RTX therapy was assessed through an internally developed form.

RTX 2×500mg intravenous (IV) infusion was given to all patients on day 1, followed by the next one on day 15. Infusion was pre-medicated with IV methylprednisolone 100mg. Patient were advised to return for follow-up after 24 weeks. The DAS-28 value was taken at the baseline and then after 24 weeks at the follow-up visit.

The data was analysed using SPSS 20. Qualitative variables were presented as frequencies and percentages, while mean ± standard deviation was used for presenting quantitative variables. A paired sample t-Test was used to compare the pre- and post DAS-28 scores. Chi-square test and Fisher exact test were applied for determining the association between patients' characteristics and efficacy. $P \leq 0.05$ was considered statistically significant.

Results

Of the 97 patients, 83(85.6%) were female and 14(14.4%) were male patients. The overall mean age was 50.68±14.27 years. Mean BMI was 27.37±4.03 kg/m^2 with 31(32.0%) patients being overweight and 27(27.8%) having normal weight. The disease duration in 41(42.3%) patients was 6-9 years, while 36(37.1%) were suffering from it for >9 years. In terms of efficacy, 25(25.8%) patients showed no improvement, while 72(74.2%) had improvement (Table-1). The baseline DAS-28 score was 6.68±1.14 while the follow-up score was 4.62±0.93 ($p<0.05$) (Figure).

The efficacy was stratified according to age, gender, BMI and duration of disease, and no significant association was observed ($p>0.05$) (Table-2).

Table-1: Patient demographics and baseline disease characteristics.

Variables	Sub-groups	Mean±SD
Mean Age (Years)		50.68±14.27
Weight (kg)		64.39±9.04
Height (cm)		153.52±4.90
BMI (kg/m^2)		27.37±4.03
Duration of complaints (Months)		8.59±2.68
		n(%)
Gender	Male	14(14.4)
	Female	83(85.5)
Age Groups	<35 years	14(14.4)
	35 to 50 years	34(35.1)
	50 to 65 years	32(33.0)
	>65 years	17(17.5)
BMI Classification	Underweight	2(2.1)
	Normal Weight	27(27.8)
	Overweight	31(32.0)
	Class I obesity	19(19.6)
	Class II obesity	9(9.3)
	Class III obesity	9(9.3)
Efficacy	Very Good	8(8.2)
	Good	29(29.9)
	Moderate	35(36.1)
	Poor	25(25.8)
Duration of RA	0 to 3 years	4(4.1)
	3 to 6 years	16(16.5)
	6 to 9 years	41(42.3)
	Above 9 years	36(37.1)

*BMI: Body mass index, RA: Rheumatoid arthritis, SD: Standard deviation.

Table-2: Association between patient characteristics and Rituximab (RTX) efficacy.

Variables		Efficacy				P-value
		Very Good	Good	Moderate	Poor	
Gender	Male	3	5	3	3	0.26
	Female	5	24	32	22	
Age groups	<35 years	2	3	8	1	0.61
	35 to 50 years	3	10	12	9	
	50 to 65 years	2	10	11	9	
	>65 years	1	6	4	6	
BMI Classification	Underweight	0	0	1	1	0.531
	Normal Weight	3	6	12	6	
	Overweight	2	13	11	5	
	Class I obesity	2	7	6	4	
	Class II obesity	1	1	3	4	
	Class III obesity	0	2	2	5	
Duration of RA	0 to 3 years	0	3	0	1	0.403
	3 to 6 years	1	4	5	6	
	6 to 9 years	4	10	19	8	
	Above 9 years	3	12	11	10	

*BMI: Body mass index, RA: Rheumatoid arthritis.
*Values are given as frequency (n)
*P-value<0.05 was considered significant.

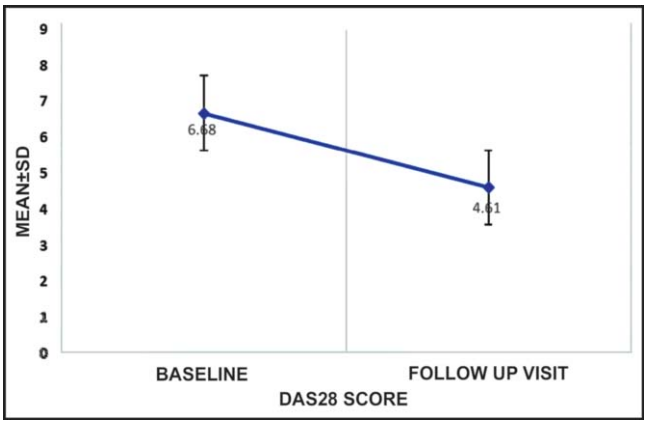

Figure: Mean change in Disease Activity Score-28 (DAS-28) over time from baseline to follow-up visit (week 24).

Discussion

The results of the present study indicated that a single course of RTX was effective for RA patients when the IV infusion was provided twice with a gap of 2 weeks. There was significant reduction in mean DAS-28 score from baseline to follow-up. Similar results have been reported earlier.[13,14]

RTX is distinct in its mode of action, and functions via B cell depletion, while other biological agents target T cells.[15] Numerous studies support RTX in terms of efficacy,[13,14] and 74.2% patients in the current study found RTX to be efficacious. A study indicated RTX as the accurate drug of choice with optimal efficacy and recommended it as the first biological disease-modifying antirheumatic drug (bDMARD).[16] No significant association was found between age, gender, BMI, duration of disease and efficacy among the RA in the current study. In contrast, a study reported that one of the prime factors behind failure to achieve a DAS ≤2.4 on initial therapy was increased BMI.[17] Supported by another study, increasing BMI had a profound impact on DAS28 score, the obese RA patients had the DAS28 score of 0.23 while the normal-weight RA patients had a DAS28 score of 0.11, and these correlations were more common in females compared to males.[18]

The effectiveness of different doses of RTX in treating RA had been studied extensively, multiple phase 3 and phase 4 trials have tested the two different dosing schedules i.e. 2×500 mg and 1×1000 mg.[19] These are the recommended doses of RTX, but ultra-low doses of RTX (×50 to ×100 mg) have also been effective in treating RA based on a few case studies resulting in intense B cell depletion.[20] In support of these evidences, an open label study had a sample of 14 RA patients provided with a single RTX dose (100 mg). Depletion in peripheral B-cell was observed after two weeks among 11 of the 14 cases.[21] Based on the economic burden, low RTX dose is cost-effective, although its efficacy in comparison to higher dose is debatable and it has not gained much acceptance among the healthcare providers.[22] RTX both in low and high doses is the least expensive bDMARD,[23] where the cost of lower regime is further reduced almost by half of the higher doses.[24] Being a developing country with limited healthcare resources and declining health status, the current study utilized RTX 2×500 mg to focus mainly on the efficacy of the drug and provide treatment via cost-effective regime.

The dosage of RTX 2×500 mg was well-tolerated, but RTX doses are associated with minor side-effects which mainly include mild to moderate infusion which can be prevented with glucocorticoids premedication.[10] An RCT reported that infusion reactions were common in approximately 25% of the cases during the first course of RTX, coupled with symptoms, such as headache, itchiness, throat irritation, flushing, hypertension, rashes and pyrexia.[25] The current study did not assess the side-effects, which is a limitation, but IV methylprednisolone 100mg was given to prevent infusion reaction.

Further research is required comprising large dataset with RA patients from different health sectors of Pakistan in order to represent more relevant statistics regarding the efficacy of the drug in the local population. The efficacy was assessed using an internally developed proforma which has limited the validity of the treatment outcomes. The study focused on only 1 treatment group when comparative efficacy needed to be checked in order to explore treatment options ensuring fast recovery, efficacy and cost-effectiveness. Inter

(same drug; different doses) and intra (different drugs) treatment modalities must also be investigated. Moreover, the current study represented data of only 1 follow-up visit after 24 weeks. Multiple and long-term follow-ups are recommended for better safety evaluation.

Conclusion

RTX was found to be effective and generally well-tolerated when given to RA patients. The mean change in DAS28 score strongly supported the effectiveness of the drug regime in RA management in the local population. Additionally, glucocorticoid pre-medication does seem to reduce and prevent infusion reactions.

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