

SINGLE CENTRE EXPERIENCE USING RITUXIMAB TO TREAT PATIENTS WITH RHEUMATOID ARTHRITIS ALREADY ON METHOTREXATE THERAPY

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ABSTRACT

Objective: To find out the efficacy and safety of rituximab in the treatment of rheumatoid arthritis (RA) already receiving methotrexate therapy.

Methodology: This retrospective review of data was conducted in the Department of Medicine and Rheumatology of Lady Reading hospital, Peshawar. The study included 65 patients from July 2014 to November 2015. Data of patients with RA of more than one year duration and who were refractory to traditional disease modifying drugs were included with a DAS-28 score of 5.1 or more. Patients below 15 years of age and beyond 60 were excluded.

Results: The mean age of the patients was 35.95 ± 12.74 and ranged from 16 to 58 years. Females were 44 (78%). DAS 28 at the start of treatment ranged from 5.1 to 6.8 (mean 5.7 ± 0.46). DAS 28 after 3 months ranged from 1-5.5 (mean 2.8 ± 0.3). About 63% patients showed full response. Response was more evident in females as compared to males. Allergic reactions to the drug were observed in 3 patients. Overall adverse reactions in the form of leukopenia, thrombocytopenia, oral ulcers and diarrhea were observed in 1.5-9% of patients. Severe anemia was seen in only 7.7%.

Conclusion: Rituximab has shown to be an effective and safe addition in patients with rheumatoid arthritis who are refractory to the standard treatment.

Key Words: Rheumatoid arthritis, Rituximab, Efficacy, Safety

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INTRODUCTION

Rheumatoid arthritis (RA) is a multisystem disorder involving the synovial joints, mostly the small joints of the hands and feet. Extra-articular manifestations in the form of renal, lungs and eyes involvement are not uncommon. The basic pathophysiological mechanism in the development of this condition is activation of immune system against body's own antigens resulting in the development of inflammation in the synovial joints and other body tissues¹. Evidence regarding the involvement of B cells in the pathogenesis of this disease is now beyond doubt. B cells secrete inflammatory cytokines and other inflammatory markers to activate the CD 4 cells to stimulate clonal expansion and trigger other immune functions². Intercepting B cells functions may theoretically halt the progression of the disease. B cells depleting drugs are therefore a therapeutic option for the management of this condition³.

Rituximab, a B cell depleting (anti CD-20) is a chimeric monoclonal antibody, which has been used for the treatment of many malignant conditions like lymphoma

and autoimmune conditions, is considered to be acting through depletion of B cells⁴. The drug has been in the market for the management of RA for the last one decade and has been considered to be the drug of choice amongst the biological agents. It is used in combination with other traditional DMARDs like methotrexate and sulphasalazine and has proved to be effective in about 2/3rd patients. Until recently, this drug was used in patients who were unresponsive to other biological agents. But it is now used by many rheumatologists around the world as a first biological agent with good success and without any serious adverse events. Both small scale and large scale studies have shown that this drug is effective in the management of RA in reducing the inflammation which ultimately improves both short term and long term outcomes⁵.

Vast experience with this drug in many other conditions has shown that it is devoid of serious adverse effects. The drug has been used up till now in more than 3000 patients for RA without any serious adverse effects⁶. Most of the adverse reactions occurring with

the use of rituximab are related to allergies and can be avoided by slowing the infusion rate and using antihistamines and steroids during the administration.

Rituximab is in use for the treatment of RA in our country for the last 2-3 years, but data about the efficacy and safety is lacking. This study comprised of patients who were treated in our center with rituximab was aimed to find out its efficacy and safety in RA.

METHODOLOGY

This descriptive study concerning the safety and efficacy of rituximab in RA was conducted in the Department of Medicine and Division of Rheumatology at Lady Reading Hospital Peshawar. The study included 65 patients from July 2014 to November 2015. All these patients received rituximab therapy and the data about safety and efficacy of the treatment was recorded on a proforma. Data of patients with RA of more than one year duration and who were refractory to traditional disease modifying drugs were included with a DAS-28 score of 5.1 or more. Patients were receiving methotrexate before and after rituximab therapy. Patients below 15 years of age and beyond 60 were excluded. Other exclusion criteria were Hemoglobin of less than 9 g/dl, TLC of less than 4000 /cmm, platelets of less than 150000 /cmm, co-morbidities like diabetes mellitus, other chronic illnesses and patients receiving high doses of steroids. A total of 2 doses of rituximab 1 gm were infused in a space of 15 days (along with 250 mg of hydrocortisone and an antihistamine as premedication before the start of infusion). During this period, patients continued their methotrexate (10-15 mg weekly), with or without prednisolone (less than 15 mg daily). The use of non steroidal anti-inflammatory drugs was permitted during and after treatment.

Efficacy of rituximab therapy was assessed by DAS-28 score at the start of therapy, and 3 months after the end of 2nd dose of rituximab. Remission (complete response) was defined as a DAS-28 score of 2.6 or less, partial response as 2.7-4, and no response was defined as DAS-28 score of more than 4 at the end of 3 months⁷.

Safety was assessed by recording events in a separate proforma indicating early adverse events in the form of allergic reactions during and 24 hours after infusion. Late adverse events like infections (requiring intravenous antibiotics), reactivation of tuberculosis, cytopenias, angioedema and neurological manifestations in the next 3 months were observed.

The baseline characteristics of the study population, safety data, DAS-28 scores, at each time point (at the start of therapy and after 3 months) were described as the means and SDs for quantitative variables and as percentages for qualitative variables. The baseline population characteristics and efficacy and safety data were

compared between age groups.

The study has been approved by the Institution Research and Ethics Board (IREB) of Lady Reading Hospital. The data recorded was under the observation of a trained rheumatologist and a trained physician with more than 15 years experience.

RESULTS

The study included 65 patients. The mean age of the patients was 35.95 ± 12.74 and ranged from 16 to 58 years. Females were 44 (78%) and males were 21 (22%). Duration of disease was more than 5 years in 51 patients and was less than 5 years in rest of patients (table-1). DAS 28 at the start of treatment ranged from 5.1 to 6.8 (mean 5.7 ± 0.46). DAS 28 after 3 months ranged from 1-5.5 (mean 2.8 ± 0.3). Details of complete response, partial response and no response have been shown in table-2. About 63% patients showed full response and 20% showed no response. Response was more evident in females as compared to males (2/3rd of females responded as compared to 50% males).

Safety data has been shown in table-3. Allergic reactions to the drug were observed in 3 patients and treatment of one patient was discontinued and was later lost to follow up. Overall adverse reactions in the form of leukopenia, thrombocytopenia, oral ulcers and diarrhea were observed in 1.5 to 9% of patients. Anemia was more remarkable which was observed in 1/3rd of patients while severe anemia was in only 7.7%. No neurological untoward effects or angioedema were observed during and after treatment within the observed period.

DISCUSSION

This is the first study about the efficacy and safety of rituximab in rheumatoid arthritis in Pakistan, as the mainstay of treatment of this disease consists of analgesics, steroids and traditional DMARDs. The introduction of biological agents in the management of rheumatoid arthritis is opening new avenues in the management of this condition. However, data regarding the safety of this drug in our country is deficient. Another factor regarding the use of this drug in the perspective of this region is the cost of the novel treatments. But the government agencies has started providing rituximab for the last 2 years free of cost to people who are not able to afford the cost of the therapy. This has resulted in the inclusion of this drug in the management of rheumatoid arthritis by rheumatologists and physicians.

Rituximab is being used nowadays in a number of medical conditions like lymphoma, SLE and other autoimmune disease and data regarding the safety and tolerability is now extensive in the west. This drug has now been used in more than 300000 patients for these diseases without serious concerns of neurological dis-

Table 1: Baseline characteristics of patients

Parameters		Total patients	Mean	SD	Minimum	Maximum
Age		65	35.95	12.74	16	58
Gender	Male	21	*	*	*	*
	Female	44	*	*	*	*
Duration of disease	>5 years	51	*	*	*	*
	<5 years	14	*	*	*	*
DAS28 (at the start)		65	5.7	0.46	5.1	6.8
DAS 28 (at the end)		64	2.83	0.3	1	5.5

Table 2: Response to rituximab therapy

		Gender				Total	%
DAS 28	Response	Females (out of 44)	%	Males (out of 21)	%		
	Complete Response	31	70.45	10	47.62	41	63.08
	Partial response	6	13.63	4	19.05	10	15.38
	No response	7	15.92	7	33.33	14	21.54
Total		44	100	21	100	65	100

Table 3: Adverse reactions to rituximab therapy

Adverse events		Frequency	percentage
Allergy	No	62	95.4
	Yes	3	4.6
Infections	No	64	98.5
	Yes	1	1.5
Anemia	No: (Hb >11 g/dl)	45	69.2
	Mild to moderate: (Hb 8-11 g/dl)	15	23.1
	Severe: (Hb <8 g/dl)	5	7.7
Leukopenia	No	62	95.4
	Yes	3	4.6
Thrombocytopenia	No	61	93.8
	Yes	4	6.2
Diarrhea	No	60	92.3
	Yes	5	7.7
Oral ulcers	No	59	90.8
	Yes	6	9.2

orders and concerns associated with the depletion of B cells in the body⁸. Eight randomized control trails involving more than 3000 patients have proven the efficacy and safety of this drug either alone or in combination with other DMARDs in the management of rheumatoid arthritis⁹. Patients with baseline low DAS28 score have been shown to have better response, but in our study

the baseline DAS28 score was selected as more than 5¹⁰. This may be the reason of about 60% complete response in our patients. Other factors of good response are positive anti-CCP and previous use of other biologic agents¹¹. But we did not check anti-CCP before the start of therapy in most of these patients. Therefore this factor was not included in the data collected for this

research.

Infusion reactions occur in about 25% of patients especially during the first infusion¹². In our study, it was seen in about 4.6%. Infusions reactions can be avoided by premedication with antihistamines and co-medication with intravenous hydrocortisone, which we used in all patients¹³.

In literature, many adverse effects have been shown to be associated with the use of rituximab therapy including reactivation of infections especially hepatitis B virus infection, tuberculosis, development of Guillain-Barre syndrome and leuko-encephalopathies in extremely rare cases¹⁴. Our study revealed only one case of reactivation of latent tuberculosis. Only one patient developed community acquired pneumonia requiring intravenous antibiotic therapy. This small number of adverse events in our study may be the result of limited number of participants registered. We did not check hepatitis B status at the start of therapy in our study, and did not record minor respiratory or other infections during follow up of these patients.

Leukopenia and lymphopenia is seen in about 14% and 48% of patients respectively in patients using rituximab for different conditions¹⁵. In our observation, this frequency is very low (4.6%). This may be because of small number of participants in the study. The figures mentioned above have been taken from data where rituximab was used in lymphoma and other malignant conditions, where it is used in conjunction with other cytoreductive drugs. We had not checked the absolute lymphocyte count or isolated B cells count in our study. Anemia was observed in 1/3rd of patients treated with rituximab, which was mostly normocytic normochromic, but we were unable to describe the true linkage with rituximab as it might be associated with the primary disease itself as we had not included the pretreatment hemoglobin in our study. Further studies are needed to show clear linkage of anemia with rituximab therapy in rheumatoid arthritis.

Other adverse events like oral ulcers and diarrhea (7-9%) are comparable to international studies and both conditions are probably associated with white cell depletion¹⁶.

CONCLUSION

Rituximab has shown to be an effective and safe addition in patients with rheumatoid arthritis who are refractory to the standard treatment. It is nowadays used as first line or when traditional DMARDs and / or Tumor necrosis factor inhibitor (TNFi) fails. The results of this study will encourage the use of this drug in our country, but further studies of this kind are needed to substantiate the use of this drug at the primary level in the context of safety issues.

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CONTRIBUTORS

MK conceived the idea, planned the study, and drafted the manuscript. FA and JIF helped acquisition of data and did statistical analysis. AT supervised the study and critically revised the manuscript. All authors contributed significantly to the submitted manuscript.