EFFECTIVENESS AND TOLERABILITY OF TOCILIZUMAB IN PATIENTS WITH RHEUMATOID ARTHRITIS REFRACTORY TO CONVENTIONAL DISEASE MODIFYING ANTI RHEUMATIC DRUGS THERAPY

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ABSTRACT

Objective: To find out the effectiveness and tolerability of tocilizumab in the treatment of rheumatoid arthritis (RA) patients refractory to conventional disease modifying anti-rheumatic drugs (DMARDS).

Methodology: This cross-sectional study was conducted in the department of medicine, Lady Reading Hospital, Peshawar from September 2017 to March 2018. It included 84 patients with diagnosed RA who were refractory to conventional DMARDs therapy. Tocilizumab was given to all patients along with methotrexate (MTX) and low dose prednisolone. Effectiveness of tocilizumab therapy was evaluated by Disease Activity Scale version 28 (DAS- 28) score before and 3 after months of the end of the 3rd dose of tocilizumab. Drug tolerability was assessed by recording the early and late adverse events. Data was analyzed with SPSS version 20. Frequency and percentage were expressed for categorical variables, while mean ± SD were used for numerical variables.

Results: The response was more significant in female patients (about 70%) as compared to male patients (50%). Infusion-related allergic reactions were observed only in 2 patients. Headache was more significant which was observed in 6 patients. Overall adverse events in the form of allergy, headache, diarrhea, upper respiratory symptoms, gastritis, and oral ulcers were observed in about 24.8 % of patients. Leukopenia was observed in 4.7% but no life-threatening cytopenias or severe allergic adverse reactions were noted.

Conclusion: Tocilizumab is effective and tolerable therapeutic addition in the treatment of patients with rheumatoid arthritis who are refractory to the conventional DMARD treatment.

Key Words: Effectiveness, Rheumatoid arthritis, Tolerability, Tocilizumab

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INTRODUCTION

Rheumatoid arthritis is the most common form of chronic autoimmune disease. It is polyarticular inflammatory arthritis which consists of progressive articular destruction, bony erosions and synovial inflammation. It is related to increased mortality, morbidity, severe disability and imposes a considerable economic burden on patients and society[1]. Its prevalence is relatively constant in various populations (0.5 – 1%), being reported high in Pima Indians (5.3%) and Chippewa Indians (6.8%) while low in China and Japan[2]. The prevalence is reported as 0.142% in the urban population of southern Pakistan; however the estimated prevalence is 0.55% in northern Pakistan[3]. RA indirectly affects the quality of life. It can affect any age group but the prevalence is more reported in older age[4].

First-line treatment for RA is the conventional DMARDs'. Methotrexate is used more often but concerns regarding its safety and side effects have been raised[5]. In the past two decades, the prognosis of RA has dramatically improved because of earlier diagnosis and use of DMARDs in combinations and the availability of biological therapies[6] which is a blessing for those patients who were not improving much with the conven-

tional DMARDs. Biological treatment involves targeting B and T cells and various cytokines that play major role in the pathogenesis of RA. i.e. Interleukin 6 (IL-6) and Tumor Necrosis Factor α (TNF-α). The very first agents among the biological therapy were TNF antagonists which block specifically this pro inflammatory cytokine[7]. Other agents that are approved for the treatment of RA include Rituximab, Abatacept, and the first humanized anti-IL-6 receptor antibody, Tocilizumab (TCZ) binds competitively to the IL-6 binding site of the human IL-6 receptor, thus inhibiting the IL-6 signaling. Tocilizumab has shown to be therapeutically effective in certain diseases like RA, Castleman disease[8], polyarticular-course Juvenile Idiopathic Arthritis (JIA)[9], systemic-onset JIA[10] and Crohn's disease by alleviating the inflammatory manifestations of these diseases and normalization of the acute phase protein levels including C-Reactive Protein (CRP)[11].

Tocilizumab has also shown promising results in patients of renal insufficiency associated with RA in whom MTX is not a better choice in terms of its safety[12]. Therefore the first IL-6 receptor inhibitor (tocilizumab) might be helpful in the treatment of RA and alleviating the signs and symptoms in those who do not show a response to methotrexate or other conventional DMARDs alone[13]. Tocilizumab as monotherapy shows inhibitory effect on joint destruction[14]. However, it has shown to be less efficient in the treatment of elderly patients[15]. In the light of various clinical studies performed in various countries regarding the safety and efficacy of this drug in certain autoimmune conditions and co morbidities, it has been shown that this drug is devoid of any serious adverse effects as compared to other standard treatments. In a study conducted in Japan the general risk of infection associated with tocilizumab was comparable to that of TNF inhibitors[16]. This drug is now being used in more than half of patients of RA without any life-threatening adverse reactions. Long-term monotherapy with tocilizumab has shown good efficacy and safety[17]. Tocilizumab is used by most of the rheumatologists in our country for the last few years but no clinical study regarding its effectiveness and tolerability is reported. So this study was designed to get clinical data regarding the effectiveness and tolerability of tocilizumab.

METHODOLOGY

This cross-sectional study was conducted on 84 patients in department of Medicine, Lady Reading Hospital Peshawar from September 2017 to March 2018. Patients were recruited with convenient sampling. Proper informed consent was taken from all the patients. All the patients included in the study received tocilizumab. It included all patients attending this department during the study period having RA for a duration of more than 01 year and were refractory to conventional DMARDs with a Disease Activity Score 28 (DAS-28) of 5.1 or more. Exclusion criteria included total leucocytes count of less than 4000/cmm, platelets below 150000/cmm, comorbidities like diabetes mellitus and those patients who were receiving high doses of steroids (0.5 to 1mg/kg prednisolone). Patients continued to receive methotrexate or any other DMARD which they were already taking, before and after tocilizumab therapy. Tocilizumab in a dose of 4-8 mg/kg was given once every 04 weeks. An antihistamine and 250 mg of hydrocortisone were also given as pre medication before starting the infusion. During the study period, patients continued methotrexate (10- 15 mg weekly) with prednisolone (less than 15 mg daily) as needed. The use of non-steroidal anti-inflammatory agent was also allowed during the study. Baseline investigations like complete blood count, liver function tests, renal profile, and lipid profile were performed before the start of the therapy and were repeated every 4 weeks of initiation of treatment.

Effectiveness of tocilizumab therapy was evaluated by DAS- 28 score before starting the therapy, and then 3 months after the end of the 3rd dose of tocilizumab. No response was defined as DAS-28 score of greater than 4, partial response as 2.7-4, and remission (complete response) was defined to be a DAS-28 score of 2.6 or less at the end of 3 months. Drug tolerability was assessed by recording the events on a separate proforma displaying allergic reactions as early adverse events during and after 24 hours of the infusion. Late adverse events were observed in the next 03 months like infections (requiring intravenous antibiotics), headache, oral ulcers and gastritis. A self- designed proforma was used to collect data. Data was incorporated from Microsoft Excel sheet into SPSS version 20 and statistical analysis was performed. Demographic features and the drug effectiveness and tolerability was obtained and expressed as percentage for categorical variables, while Mean ± SD were used for numerical variables.

RESULTS

The demographics and disease duration are shown in table 1. Mean DAS 28 score at the start of treatment was 5.8 ± 0.52 which decreased to 2.41 ± 0.53 after treatment with tocilizumab as shown in table 2. Effectiveness data of complete, partial and no response is shown in table 3. About 85.2% of the patients showed improvement in their DAS 28 scoring as either complete or partial response. Tolerability data is shown in table 4, which shows that around 25% of the patients reported various minor adverse reactions. There were no life-threatening cytopenias or severe allergic adverse reactions during and after the treatment within the observed time period.

Table 1: Demographic characteristics of patients

Parameter		Total Patients	Mean	SD	Minimum	Maximum
Age	84	34.44	16.38	18 years	60 years	
Gender	Males	18	*	*	*	*
	females	66	*	*	*	*
Duration of disease	>6years	72	*	*	*	*
	<6years	12	*	*	*	*

Table 2: DASS 28 score before and after therapy with tocilizumab

	Mean	SD	Minimum	Maximum
DAS 28 (at the start)	5.8	0.52	5.3	7.1
DAS 28 (at the end)	2.41	0.53	1.88	5.94

Table 2: Response to tocilizumab therapy

		Gender				Total	%age
DAS28	Response	Male (Out of 18)	%age	Female (Out of 66)	%age		
	Complete	9	50%	46	69.6%	55	65.4
	Partial	6	33.3%	11	16.6%	17	20.2
	Nil	3	16.6%	9	13.6%	12	14.2
TOTAL		18	100	66	100	84	100

DISCUSSION

In our study, most of the patients showed a clinically significant response to treatment with tocilizumab. Apart from alleviating distressing symptoms of the polyarticular disease, less side effects of the drug were observed. In literature, many adverse effects have been shown to be related to the use of tocilizumab therapy including infections, increased alanine aminotrasferase (ALT), headache, infusion-related skin reactions, cytopenias (thrombocytopenia and neutropenia) mouth ulcers, hypertension, hyperlipidemia, gastritis etc.

In our study, 5 patients developed upper respiratory tract infection but only 1 required antibiotic treatment. Deranged liver functions and thrombocytopenia as a side effect of therapy is also mentioned in literature but was not noted in our study. No serious side effects requiring dose adjustment or stopping of the therapy were noted. On the basis of good results in several clinical trials, it has been approved for the treatment of moderate to severe RA both as a monotherapy and in combination along with other DMARDs and TNF inhibitors[8]. A meta-analysis reported the efficacy of tocilizumab monotherapy with tocilizumab combination therapy (TCZ plus conventional DMARDs), a slightly greater number of patients achieved a DAS-28 score of less than 2.6 with the TCZ combination therapy[18]. Another study in Korean population showed that tocilizumab is highly effective in the treatment of active RA where other conventional DMARDs had been less effective including methotrexate[19]. Regarding the usage of this drug in our country, apart from lack of data regarding its safety and efficacy, there are financial constraints of the treatment although the government has started providing tocilizumab free of cost for the last 2 years to patients who are unable to afford the drug. This has led to the addition of tocilizumab in the management of rheumatoid arthritis by physicians and rheumatologists. Response to therapy was much significant especially with TCZ dose of 8mg/kg which is comparable to a study conducted in Saudi Arabia in which TCZ in a dose of 8mg/kg along with a non biologic DMARD or a TNF inhibitor provided a rapid and constant improvement in RA symptoms[20]. Thus our results are comparable to the study conducted in Saudi Arabia[20]. Limitations of our study were less number of patients and shorter duration of follow up.

CONCLUSION

Tocilizumab was effective and well tolerated addition in the treatment of patients with RA who were refractory to the conventional DMARDs treatment. The results of this study may encourage the use of tocilizumab in our country yet well-designed controlled studies are needed to assess the long-term outcome and safety profile of this drug and also its use as monotherapy.

Table 3: Adverse reactions to tocilizumab therapy

Adverse Event		Frequency	Percentage
Mild Allergic Reactions (Rash)	Yes	2	2.3
	No	82	97.7
Life Threatening Allergic Reaction	Yes	0	0
	No	84	100
Upper Respiratory Infections	Yes	5	6
	No	79	94
Life Threatening Infections	Yes	0	0
	No	84	100
Anemia	No (Hb >11g/dl)	62	73.8
	Mild to Mod (HB between 8 to 11 g/dl)	19	22.6
	Severe (<8g/dl)	3	3.52
Leukopenia	Yes	4	4.7
	No	80	95.2
Thrombocytopenia	Yes	0	0
	No	84	100
Diarrhea	Yes	2	2.3
	No	82	97.7
Oral Ulcers	Yes	1	1.2
	No	83	98.8
Gastritis	Yes	5	6
	No	79	94
Headache	Yes	6	7
	No	78	93

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CONTRIBUTORS

MK conceived the idea, planned the study, wrote initial manuscript and collected data. AN, MAT, GS, AMK and ZUK helped in collecting data, revising the manuscript, carried out corrections and bibliography. All authors contributed significantly to the submitted manuscript.