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Short-Term Efficacy and Safety of Subcutaneous Tocilizumab in Rheumatoid Arthritis Patients in Pakistan: A Real-World Experience

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ABSTRACT

Objective: To determine the real-world efficacy and safety of subcutaneous Tocilizumab in patients with rheumatoid arthritis.
Study Design: Case series.
Place and Duration of Study: Department of Rheumatology, National Hospital and Medical Centre, Lahore Pakistan, from Aug 2019 to Dec 2020.
Methodology: In this study, 33 patients receiving subcutaneous Tocilizumab 162 mg every two weeks as monotherapy or with conventional synthetic disease modifying anti-rheumatic drugs were followed per standard study protocol. Increasing or decreasing the dosing interval was allowed according to disease activity at the discretion of the treating rheumatologist. The primary outcome was patients achieving Low Disease Activity as per Clinical Disease Activity Index (>2.8-10.0) and Disease Activity Score-28(>2.6-3.2). The secondary outcome was a clinically meaningful improvement in Disease Activity Score -28 (reduction of ≥1.2 units in Disease Activity Score-28 score). Adverse events were recorded at each follow-up visit.
Results: Of the 33 patients, 25(75.8%) were biologics-naive, 9(27.2%) patients achieved the target of Low Disease Activity as per Clinical Disease Activity Index (2.9-10.0) and 8(24.2%) patients achieved Low Disease Activity as per Disease Activity Score-28(2.7-3.2). At six months, the proportion of patients achieving clinically meaningful improvement (decrease ≥1.2) in Disease Activity Score -28 was 13(54.2%). Overall, 14(42.4%) patients developed adverse events and 3(9.1%) patients discontinued Tocilizumab owing to adverse events.
Conclusion: Tocilizumab has been seen to be an effective biologic in only one-third of patients, and it was tolerated in two-thirds of the patients.

Keywords: Conventional synthetic disease modifying anti-rheumatic drugs, Efficacy, Rheumatoid arthritis, Safety, Subcutaneous tocilizumab.

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease. It is characterized by inflammation of the synovium, which often results in irreversible joint damage if left untreated.[1,2] Pro-inflammatory cytokines like tumour necrosis factor (TNF), Interleukin 6 (IL-6) and Interleukin 1(IL-1) have been implicated in pathogenesis.[3,4] TNF inhibitors have a high risk of tuberculosis (TB) reactivation, which is especially relevant in TB-endemic areas like ours. European League Against Rheumatism (EULAR) recommendation prefer TNF as the first line, but considering the above, the biologic having different pathogenic targets like IL-6 become a preferred choice in our setting.[5]

IL-6 has been implicated in pathogeneses of RA, and Tocilizumab is Food and Drug Association (FDA) approved IL-6 inhibitor made available in Pakistan a couple of years back.[6] It is the first humanized anti-IL-6 receptor (IL-6R) antibody which binds to IL-6 receptor and inhibits IL-6 mediated signaling.[7,8]

TCZ has been approved in many countries by the intravenous route, but its subcutaneous formulation was recently approved in a few countries only. The subcutaneous formulation does not require an infusion facility for admission. Data from MUSASHI, OPTION and AMBITION studies showed comparable results for the effectiveness and safety of subcutaneous TCZ either used alone or with other Disease Modifying Anti-Rheumatic Drugs (DMARDs). EULAR recommended Tocilizumab as a biologic DMARD for patients with rheumatoid arthritis refractory to conventional DMARDs. [8-10]

To the best of our knowledge, there is limited data regarding TCZ in Pakistan RA patients. Therefore, we aimed to determine the efficacy and safety of subcutaneous TCZ in patients with rheumatoid arthritis. Such studies are valuable as a real-world experiences.

METHODOLOGY

The case series was conducted at the Department of Rheumatology, National Hospital and Medical Centre, Lahore Pakistan, from August 2019 to

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December 2020 after IERB approval. Patients were recruited through non-probability consecutive sampling.

Inclusion Criteria: Tocilizumab naïve patients having RA classified as per ACR/EULAR 2010 criteria,[11] and who had active disease defined by Disease Activity Score-28 and Clinical Disease Activity Index (DAS28 >3.2 or CDAI >10)12 were enrolled in the study.

Exclusion Criteria: Patients were screened for latent Tuberculosis, Hepatitis B, Hepatitis C and other infections before starting Tocilizumab. Patients who had these infections were excluded from the study. Overlap syndromes were also not included in the study.

Adult Patients aged ≥18 years were recruited from rheumatology OPD, fulfilling inclusion criteria. Informed consent was taken from the participants. In addition, demographic information, e.g., age, sex, socioeconomic status, duration of disease, educational status, along with medical history, was obtained from each participant.

Disease activity scores,[12,13] components of disease activity and outcome measures were recorded at baseline (before starting Tocilizumab), at the end of 3 months and at six months. Baseline investigations like complete blood picture, liver function tests, renal profile and lipid profile were performed before the start of the therapy. They were repeated after every four weeks after initiation of Tocilizumab. The safety of Tocilizumab was monitored at each follow-up visit. Adverse events included infections, strokes, myocardial infarctions, anaphylaxis/hypersensitivity reactions, injection site reactions, GI (gastrointestinal) perforations, hemodynamic abnormalities and elevation in hepatic enzymes. The severity of adverse events was also recorded based on requiring hospital admission.

An inadequate response to conventional DMARD or biologics, including anti-TNF inhibitors or monoclonal antibody Rituximab was defined by DAS-28>3.2 or CDAI >10. Patients received Tocilizumab 162 mg after every two weeks as a subcutaneous injection. The dose was fixed irrespective of body weight. Subcutaneous Tocilizumab injection was available in prefilled syringe dose. Patients were allowed to continue conventional DMARDs (Methotrexate, Leflunomide, Sulfasalazine) and prednisolone (≤10 mg/day). The use of Non-steroidal anti-inflammatory agents was also allowed during the study.

The primary outcome was Low Disease Activity (LDA) defined by DAS28>2.6-3.2 and CDAI >2.8-10.0. The secondary outcome was a clinically meaningful improvement in DAS-28 (reduction of ≥1.2 units).[14]

Statistical Package for Social Sciences (SPSS) version 22.0 was used for the data analysis. Quantitative variables were expressed as mean±SD and qualitative variables were expressed as frequency and percentages. One-way analysis of variance (ANOVA) was applied to gauge the mean differences among the groups. The group differences were calculated using Post Hoc test (Tukey HSD). The *p*-value lower than or up to 0.05 was considered as significant.

RESULTS

Thirty-three patients were enrolled who had an inadequate response to conventional DMARDs or biological therapy. Overall, 25 patients (75.8%) were biologically naive. The mean disease duration was 10.0±6.0 years. RAF and Anti-CCP antibodies were positive in 27(81.8%) and 23(69.7%). The dosing schedule of Tocilizumab was two weeks in all patients. The mean DAS-28 at baseline was 5.37±0.91 and CDAI 22.3±7.99. The baseline characteristics of patients and their diseases are shown in Table-I.

Table-I: Demographic and Disease Characteristics of Patients (n=33)

Parameters	n (%)
Age (Mean±SD)	47.5±14.9 years
Gender, Female	31(93.9)
Disease Duration(Mean±SD)	10.0±6 years
RF positive	27(81.8)
Anti CCP2–Positive	23(69.7)
Concomitant RA Medications	
Methotrexate	19(57.6)
Leflunomide	15(45.5)
Sulfasalazine	9(27.3)
Glucocorticoids	16(48.5)
Biologic Naive	25(75.8)
Rituximab	6(18.2)

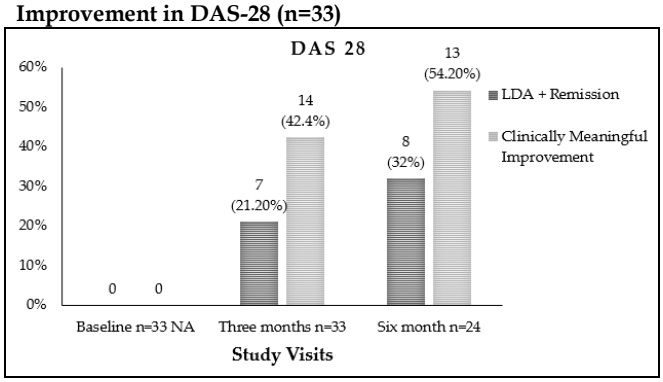
There was a decrease in tender joint count and swollen joint count for all patients in 6 months. The mean for the tender joint count at the baseline visit was 5.92±2.83; it decreased to 3.71±2.61 at six months. Similarly, swollen joint count decreased from 4.83±2.20 at baseline to 3.38±2.65 at six months (p<0.001). High DAS28 scores were observed in 22(66.7%) patients and moderate scores in 10(30.3%) at baseline visits. Clinical Disease Activity Index score (CDAI) was high in 16(48.5%) patients and moderate in 17(51.5%) patients before the initiation of therapy. At baseline CDAI score was 22.4±8.30. It decreased to 14.8±8.81 at six months.

Table-II : Efficacy Among the Study Groups (ANOVA) (n=33)

Efficacy Variables	Mean±SD	95% Confidence Interval		*p*-value
		Lower	Upper	
Tender joints Baseline (Group1)	5.92±2.83	4.83	7.00	<0.001
Tender joints 3 months (Group2)	3.92±2.19	3.04	4.75	
Tender joints 6 months (Group3)	3.71±2.61	2.67	4.75	
Swollen joints Baseline Group1	4.83±2.20	3.96	5.71	<0.001
Swollen joints 3 months Group2	3.00±2.19	2.13	3.88	
Swollen joints 6 months Group3	3.38±3.65	2.38	4.42	
PGA Baseline Goup1	6.25±1.73	5.58	6.92	<0.001
PGA 3 months Group2	4.25±1.92	3.50	5.00	
PGA 6 months group3	4.67±2.16	3.75	5.54	
PhGA Baseline (Group1)	5.13±1.39	4.58	5.67	<0.001
PhGA 3Months (Group2)	3.46±1.47	2.92	4.04	
PhGA 6Months (Group3)	3.58 ± 2.02	2.79	4.42	
ESR Baseline (Group1)	44.94±23.44	33.89	56.00	<0.001
ESR 3Months (Group2)	18.24±19.64	10.12	27.82	
ESR 6Months (Group3)	17.00±16.60	10.18	25.17	
CDAI Baseline (Group1)	22.42±8.30	19.29	25.54	<0.001
CDAI 3Months (Group2)	14.71±6.19	12.38	17.21	
CDAI 6Months (Group3)	14.83±8.81	11.33	18.50	

Patients achieving clinical meaningful improvement in DAS-28 (decrease ≥1.2 units) at 3 months was 14(42.4%) which increased to 13(54.2%) at 6 months. Figure shows the comparison of LDA and clinically meaningful improvement in DAS-28.

Figure: Comparison of LDA and Clinically Meaningful Improvement in DAS-28 (n=33)



Patient global assessment (PGA) decreased from 6.25±1.73 at baseline to 4.67±2.16 at six months. Physician global assessment (PhGA) decreased from 5.13±1.39 at baseline to 3.58±2.02 at six months (*p*-values for PGA and PhGA were <0.001). There was a statistically significant mean decrease in the number of tenders and swollen joint counts, Patient global assessment (PGA), Physician global assessment (PGA), Erythrocyte sedimentation rate (ESR), DAS28 and CDAI (Table-II & III).

A total of 14(42.4%) patients developed adverse events. Majors were transaminitis and infections. TCZ dose was stopped due to raised ALT levels in 9(27.3%) patients. URTI and LRTI were seen in 2(6.1%) patients each. Tocilizumab was discontinued in 9(27.3%) patients. Reasons for discontinuation were no improvement of symptoms, non-affordability and adverse events in 3(9.1%) each. No reported anaphylactic reaction occurred in patients. There is no death in the study population (Table-IV).

Table-III: Inter-group Comparisons of Efficacy Among Study Groups (Post Hoc Analysis) (n=33)

Group Comparison/ Variables	Group-1 Vs Group-2	Group-2 Vs Group-3	Group-1 Vs Group-3
Tender Joints	<0.001	0.767	0.003
Swollen Joints	0.004	0.551	0.038
PGA	<0.001	0.307	0.002
PhGA	<0.001	0.804	0.003
ESR	<0.001	0.816	<0.001
CDAI	0.001	0.952	0.004
DAS 28	<0.001	0.926	<0.001

Table-IV: Adverse Effects (n=33)

Adverse Effects	n(%)
Upper Respiratory Tract Infections	02(6.1)
Lower Respiratory Tract Infections	02(6.1)
Leucopenia	03(9.1)
Transaminitis	09(27.3)
Skin Infections	03(9.1)
Total	14(42.4)

DISCUSSION

The primary objective was to assess the efficacy and safety of Tocilizumab as monotherapy or in combination with csDMARDs, in patients with inadequate response to current csDMARDs therapy or refractory

to other biologic DMARDs. IL-6 inhibition leads to a profound decrease in acute-phase reactants. There was a significant decrease in our case series, but contrary to other published studies, which have shown that DAS-28 over-represent efficacy as ESR decline due to IL-6 leads to discordance in DAS-28 and CDAI.[14,15] However, this was different in our series. The majority did not meet primary and secondary outcome measures, but there was a statistically significant decrease in all efficacy parameters from baseline to 6 months. Overall, fewer side effects were observed, along with minimizing the pain associated with Rheumatoid arthritis. In other studies, many adverse effects related to TCZ were observed like infections, infusion-related reactions, raised transaminases, diverticulosis, GI perforations, cytopenias (Thrombocytopenia & neutropenia), mouth ulcers, hypertension, hyperlipidemias, myocardial infarction, Hypersensitivity and injection site skin reactions.[16,17]

A study by Kivitz *et al*. assessed the long-term efficacy and safety of TCZ-SC in RA patients. It showed LDA and remission as per DAS-28 to be 48.5% and 36.4%, respectively, at 36 weeks. Regarding CDAI, Low disease activity and remission were 40.9% and 11.1%.[18] Genovese *et al*. showed remission responses as per DAS-28 to be 30% in the TCZ group and 3% in the control group. This study showed that overall adverse events were 73% in the TCZ group, and the greatest number of patients reporting AEs were on background DMARDs (Methotrexate and Leflunomide).[19] Ogata *et al*. showed that DAS-28 and CDAI remission rates at week 24 were 49.7% and 16.4%, respectively.[20] This study compared TCZ-SC with TCS-IV as monotherapy in RA patients. The incidence of infections in a study by Ogata *et al*. was 41.6% in the TCZ-SC group.[20] Our study observed total AE in 14 patients (42.4%) and SAE in only 2(6.1%). We observed that more patients in this study developed transaminitis (27.3%). It is probably because of concomitant conventional synthetic DMARDs therapy. This study though small, highlights that TCZ is an effective biologic in only 27.2% of patients, which is much less than reported in real-world studies. Patients who did not adhere to the dose regimen were less likely to achieve remission or low disease activity. There were financial constraints regarding long-term treatment with Tocilizumab.

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LIMITATIONS OF STUDY

This study has several limitations. First, it did not include a control and comparator group. All patients received Tocilizumab subcutaneous formulation. Discontinuation and missing data were high.

CONCLUSION

Tocilizumab was an effective biologic in only one-third of patients. On the other hand, it was well tolerated by two-thirds of the patients.

Conflict of Interest: None.

Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

TM & MAS: Study design, drafting the manuscript, data interpretation, approval of the final version to be published.

SG & NIB: Data acquisition, data analysis, critical review, approval of the final version to be published.

SFR & NMA: Concept, critical review, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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