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EVALUATION OF DISEASE ACTIVITY IN EARLY RHEUMATOID ARTHRITIS TREATED WITH TOCILIZUMAB IN COMBINATION WITH METHOTREXATE: A SINGLE CENTER CROSS-SECTIONAL STUDY IN LANZHOU

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Abstract*: *In this study, we evaluate the clinical efficacy and safety of initial treatment by tocilizumab and methotrexate combination in moderate to severe cases of naive Rheumatoid Arthritis. American College of Rheumatology (ACR) and European League against Rheumatism (EULAR) recommend Tocilizumab with methotrexate combination or as a monotherapy in the management of RA if disease activity remains moderate or high despite the use of other drugs. Method: A retrospective chart review of a prospectively followed cohort of RA patients treated with tocilizumab and methotrexate was done from March 2016 to December 2018 in a tertiary center in Lanzhou. Result: Majority of patients were females (37/50; 74%), mean age at presentation was 36.3±14.7 years. All the parameters studied showed significant change with DAS28 ESR either at or below the low disease activity range (mean ±SD at 3.1±1.2).Conclusion: Combination of tocilizumab and methotrexate as initial treatment of early RA has significant improvement in disease activity.

Keywords **– Rheumatoid Arthritis, Tocilizumab, Disease Activity, Methotrexate, Interlukin-6**

I. INTRODUCTION

Rheumatoid arthritis (RA) is the common form of chronic inflammatory arthritis characterized by joint pain, stiffness, synovitis, disability, associated with increased morbidity, and mortality[1, 2]. Even though the etiology of RA is not fully understood, pro-inflammatory cytokines like tumor necrosis factor alpha (TNF-α), interleukin (IL)-1β, and IL-6 are known to play a role in disease pathogenesis by promoting inflammation, thereby resulting in joint damage and deformity [3, 4].Nevertheless, a significant leap in RA treatment, first with the use of Disease Modifying Anti Rheumatic Drug (DMARD) and then with the introduction of biologic agents, made it possible to induce remission and inhibit joint damage in many patients.

Methotrexate (MTX) is the most commonly used DMARD and is also an anchor drug in the management of RA [5].But if "treat to target" approach is not achieved by MTX monotherapy, an adjustment of treatment should be considered either by adding conventional DMARD or a biological agent according to presence or absence of adverse risk factors[6]. Elevated levels of IL-6 in serum, synovial fluid, and various tissues have been correlated with disease activity in patients with RA[7].Tocilizumab (TCZ), a new drug targeting the IL-6 pathway, is the first humanized IL-6 receptor-inhibiting monoclonal antibody which has shown its efficacy not only in improving signs and symptoms but also preventing the progression of structural damage and loss of function in RA[8-11]. ACR and EULAR recommends TCZ either in combination with MTX, or as a monotherapy, for the treatment option of RA if disease activity remains moderate or high despite the use of conventional synthetic DMARDs (csDMARD) or after failure of TNF inhibitor treatment[12, 13].There are studies showing the benefit of add-on strategy or switch-on strategy to ongoing MTX treatment with TCZ but no specific recommendations in earliest use of TCZ in combination with MTX in new-onset moderate to severe RA[14, 15].

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We aim to evaluate the clinical efficacy and safety of early use of TCZ and MTX combination in the patients with early moderate to severe cases of treatment naïve RA.

II. MATERIALS AND METHODS

Patient Selection

This was a retrospective chart review of a prospectively followed cohort of patients with RA maintained at Second Hospital of Lanzhou University, Lanzhou, China from March 2016 to December 2018. Patients with age ≥ 18 years presenting in rheumatology outpatient department with swelling and tenderness of at least one joint were included. Diagnosis of RA was made according to 2010 American College of Rheumatology (ACR)/European League against Rheumatism (EULAR) classification criteria for RA. Previously unsuccessful treatment or discontinuation of treatment or on current treatment with conventional DMARDs, MTX, TNF-α (either as monotherapy or in combination), patient with clinically unstable concurrent illness like cardiac failure, renal failure, liver disease and pregnancy were excluded. Candidates who fulfilled the inclusion criteria were invited for combination therapy strategy and an informed written consent was taken.

Follow-up Protocol

A dedicated trained resident doctor performed a detailed clinical examination of the joints and recorded the findings in a predesigned excel sheet at baseline and follow-ups. C-reactive protein (CRP, mg/L; ELISA), erythrocyte sedimentation rate (ESR, mm/hour; Westergren's method), complete blood count and liver function tests were done. Disease activity score (DAS) 28-ESR was calculated and visual analogue scale (VAS) for pain scoring done on the day of presentation at outpatient department. Follow-up at 3 months included clinical examination, joint counts, laboratory testing for ESR and CRP and VAS scoring, and DAS28-ESR calculation to evaluate the disease activity and effectiveness of treatment.

Treatment Protocol

Initial dose of 80mg/kg TCZ was administrated intravenously then subsequent dose of 400mg intravenously every 4 weeks. MTX 10 mg every week as started on the day of TCZ initial dose with folic acid once a week. The regimen was continued till 3 months follow-up assessment.

Statistical Analysis

Statistical analysis was done using SPSS 21(IBM Corporation, USA). Simple descriptive statistics was used to describe the baseline parameters. Paired sample t-test was used to assess the difference between baseline and follow-up means.

III. RESULTS

A total of 70 patients were identified as eligible candidates of whom 50 patients gave consent for TCZ combination therapy. Majority of patients were females (37/50; 74%). The mean age at presentation was 36.3±14.7 years. The baseline parameters are summarized in table 1.

Table no 1: Baseline result (Day 1) n = 50

	Minimum	Maximum	Mean	Std. Deviation
Age(years)	18	74	38.26	14.755
ESR (mm/hour)	2	105	47.26	30.277
CRP (mg/L)	0	120	28.92	36.996
DAS.28-ESR	2	11	5.30	1.961
VAS for pain	3	10	8.14	1.917

At 3months, all the parameters studied showed significant change and all of the patients had DAS28 ESR either at or below the low disease activity range (mean ±SD at 3.1±1.2). The changes in individual parameters are summarized in table 2.

Table no 2: Paired Samples Test for assessing difference in mean values of different parameters at baseline and 3months

Parameter	Baseline	3months	p-value
ESR	47.2	12.2	<0.001
CRP	28.9	3.7	<0.001
DAS28 ESR	5.3	3.1	<0.001
VAS (0-10) for pain	8.14	2.76	<0.001

No major side-effects or drug withdrawal due to adverse events were reported during the study. Only 6 patients reported pain at injection site and mild nausea during the injection.

IV. DISCUSSION

Rheumatoid Arthritis is considered as the multisystem inflammatory autoimmune disease leading to joint deformities and systemic involvement. The global prevalence of RA is 0.24% (95% CI 0.23% to 0.25%) and 0.28% (95% confidence interval 0.19%–0.41%) in Chinese population[1, 2].The high quality of life, low disability rate, treat to target, and long-term remission induced by safe, tolerable, and relatively short-term treatment are the final goals for RA management[16].Many randomized controlled clinical trials in last decade supported the emerging treat to target paradigm and suggest the benefit of early aggressive approaches in treatment of early RA[17-19].Early diagnosis with appropriate initiation of treatment, early achievement of desirable target of remission and sustained absence of disease activity can help change the course of disease, ameliorate all function, halt radiographic deterioration along with

improvement in survival rate of patients and better prognostic outcomes[20].Thus, targeting patient outcomes with regular disease assessment along with the goal of remission is gradually evolving as the standard of care.

The therapeutic options for RA have increased rapidly in the last decade. Even though the majority of RA being effectively treated with csDMARDs alone or in combination, approximately 30% still cannot be controlled[21]. There is thus a need for more effective mode of treatment for RA which should be based on a better understanding of the underlying pathophysiology of the disease process. MTX was considered an anchoring drug in pre-biologic era but with the introduction and progressive spread of biological agents, the central role of MTX has been modified in the approach to RA[5]. The use of biological agents either monotherapy or in combination now have been recommended. ACR and EULAR 2016 updated guidelines recommended TCZ as a biological DMARD option[12, 13].TCZ monotherapy was generally well tolerated and provided radiographic benefit in RA patients[8]. TCZ monotherapy has shown to be efficacious than MTX monotherapy in MTX naive patients, in patients with an inadequate response to MTX and in those with a history of MTX treatment for more than 6 months[9, 22, 23].OPTION and TOWARD studies showed that treatment with TCZ at 4 and 8 mg/kg body weight in combination with methotrexate (MTX) or csDMARDs reduced the signs and symptoms of RA in patients who responded inadequately to MTX/csDMARDs alone[10, 24]. The ACT-RAY study examined the efficacy and safety of switching to TCZ monotherapy or adding TCZ to MTX in patients with active disease despite MTX therapy and the overall result suggested that TCZ performed better in combination with MTX than as monotherapy[14, 15].

This study focused on the strategy of intensively managing the early RA patients with a combination of TCZ and MTX, who were previously never been exposed to any recommended RA treatment. DAS 28-ESR was calculated to assess the disease activity, prior to and after the initiation of medication. The results were evident, showing that there is a decrease in DAS 28 score and VAS score along with a decrease in the level of CRP after 3 months of medication, thus supporting the success of initial aggressive management leading to a superior outcome with no added adverse outcomes. TICORA study in the past employed tight control of RA and showed that intensive and aggressive management provided superior outcomes[25].The BeST trial in early RA showed that targeting DAS, regardless of the treatment paradigm, resulted in improved outcomes[26].DAS28-ESR has been used worldwide and has contributed considerably to the standardization of evaluation of disease activity. DAS scores <1.6 or DAS28 <2.6 are commonly considered as indications of remission[27]. Nevertheless, high cost of medication imposed another burden to patient. Some were reluctant to start the therapy due to the cost issue and for some follow-up was difficult even after positive response to the medication leading to small sample size for the study.

V. CONCLUSION

Combination of TCZ and MTX in the treatment of early RA in this study showed significant improvement in disease activity in a very short time period. Thus, more parameters can be assessed if the study is carried out in a large population with regular follow up with medication.

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Conflicts of interest

We have no conflicts of interest to declare in association with this paper.

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