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COMPARATIVE STUDY OF EFFICACY AMONG TOCILIZUMAB, ETANERCEPT AND DISEASE MODIFYING DRUGS IN COMBINATION WITH METHOTREXATE: A SINGLE CENTER STUDY FROM LANZHOU, CHINA

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Abstract Purpose*:** *The study aims to evaluate and compare the disease activities in Rheumatoid arthritis (RA) patients treated with MTX in combination with the conventional synthetic disease modifying antirheumatic drugs (csDMARD), Etanercept (ETC) and Tocilizumab (TCZ).* ***Method: *This was a prospective cohort study of patients with RA maintained at Second Hospital of Lanzhou University, Lanzhou from March 2016 to December 2018.Patients meeting criteria were grouped into three groups: group 1 treated with csDMARDs in combination with MTX (n=51), group 2 ETC in combination with MTX 2(n=49) and group 3 with TCZ in combination with MTX (n=50).* ***Result:*** *Of total patients (N=150), females were 72% (108/150) and the mean age at presentation was 43.3±9.9 years, 40.6±14.2 years, 38.2±14.7 years in group 1, 2 and 3 respectively. Baseline erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) of group 3 were statistically higher than group 1 and not different from group 2. The mean disease activity score (DAS) 28-ESR of group 1, 2 and 3 were 4.6±1.01, 4.9±0.91 and 5.3±2.0 respectively at baseline and 0.45±0.8, 0.57±0.89 and 2.16±1.5 respectively at 3months (p<0.001). The group 3 patients even though had higher baseline activity, there was a significant improvement in all parameters after 3 months as compared to other groups.* ***Conclusion:*** *TCZ in combination with MTX can be a good therapeutic option in treating moderate to severe RA compared to csDMARDs and ETC.*

Keywords **– Rheumatoid Arthritis, Tocilizumab, Disease Activity, Interleukin-6 Inhibitor**

I. INTRODUCTION

Rheumatoid arthritis (RA) with the global prevalence of 0.24% (95% CI 0.23-0.25) is considered a silent culprit leading to deformity and disability [1]. The multifactorial etiology of RA is still not fully understood; however, cytokines like tumor necrosis factor alpha (TNF-α), interleukin (IL)-1β, and IL-6 are known to play a role in the disease pathogenesis [2]. Approximately 30% of RA still cannot be controlled effectively with the conventional synthetic disease modifying antirheumatic drug (csDMARD) [3]. Methotrexate (MTX) is considered as anchoring drug among DMARDs and its monotherapy was associated with a 16% discontinuation rate mainly due to its adverse effects and did not fully achieve the ultimate therapeutic goal of either remission or at least low disease activity in RA [4, 5]. Thus, the use of MTX in combination with other DMARDs was considered to be a valuable therapeutic option. Patients who are at risk of rapid radiographic progression, the early use of biologics are considered [6]. Biological agents like TNF inhibitor (Etanercept, ETC) and IL-6 inhibitor (Tocilizumab, TCZ) in combination with MTX are recommended if MTX monotherapy is not tolerated or contraindicated [7].

In the last ten years, a rapid increase in therapeutic options, especially with the introduction of biologic agents, made it possible to induce remission and inhibit joint damage in many patients. The emerging treat to target paradigm suggested the benefit of intense and aggressive approaches in the treatment of early RA [8]. The 28 joint disease activity score, DAS28 <2.6 is commonly considered as an indicator of remission and is a validated and the most commonly used monitoring instrument [9]. Targeting patient outcomes with regular disease assessment and targeting the goal of remission is gradually evolving as the standard of care in RA management [10]. This study aims to evaluate and compare the disease activities in RA patients treated with MTX in combination with the csDMARDs, ETC and TCZ.

II. MATERIALS AND METHODS

Patient Selection

This was a prospective cohort study of patients with RA maintained at Second Hospital of Lanzhou University, Lanzhou China from March 2016 to December 2018. Patient with age ≥ 18 years presenting to the rheumatology outpatient

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department with swelling or tenderness of at least one joint and DAS28 >2.6 were included. Diagnosis of RA was made according to 2010 American College of Rheumatology (ACR)/ European League against Rheumatism (EULAR) classification criteria for RA [11]. Patient with co-morbidities like cardiac failure, renal failure, liver diseases, pregnancy and previous use of intra-articular, parental or oral glucocorticoids for arthritis were excluded. Patients refractory to csDMARDs other than MTX were invited for the study. Informed written consent was taken from the candidates who met the criteria. They were divided into three groups: those treated with csDMARDs in combination with MTX were assigned group 1(n=51), with ETC in combination with MTX were assigned group 2(n=49) and finally, with TCZ in combination with MTX were assigned group 3(n=50). A convenience sampling method was used to allocate consecutive patients fulfilling the inclusion criteria to the three groups serially.

Follow-up Protocol

A dedicated trained resident doctor performed a detailed clinical examination of the joints and recorded the findings at baseline and follow-up (3 months) in a predesigned excel sheet. C-reactive protein (CRP, mg/l; ELISA), erythrocyte sedimentation rate (ESR, mm/h; Westergren's method), complete blood count and liver function tests were done. The DAS28-ESR was calculated at baseline for all patients. The visual analogue scale (VAS) for pain was assessed using a 10cm straight line marked 0 on the extreme left (representing no pain) and 10 on the extreme right (representing extreme worse pain). Patients were asked to mark their level of pain on the line and a score was taken by measuring the mark from the 0 point in centimeters. Follow-up at 3 months included clinical examination, joint counts, and laboratory testing for ESR and CRP, VAS scoring for pain (in the same way as explained before), and DAS28-ESR calculation to evaluate the disease activity and effectiveness of treatment in all 3 groups.

Treatment Protocol

Group 1: Oral csDMARDs like Hydroxychloroquine (200mg twice a day) or Leflunomide (10-20 mg once daily) with MTX 10-15mg and folic acid once a week.

Group 2: 25mg ETC was administered subcutaneously twice a week with MTX per oral 10-15 mg and folic acid once a week.

Group 3: Initial dose of 80mg/kg TCZ was administered intravenously then a subsequent dose of 400mg intravenously every 4 weeks. MTX 10-15 mg per oral every week as started on the day of TCZ initial dose with folic acid once a week.
The three groups continued the regimen till 3 months follow-up assessment.

Statistical Analysis

Statistical analyses were done using SPSS 21 (IBM Corporation, USA). Simple descriptive statistics were used to describe baseline parameters. Paired sample t-test was used to assess the difference between baseline and follow-up means of each group. Analysis of variance (ANOVA) was used to compare the mean difference in baseline and follow-up parameters between the three treatment groups examined. Bonferroni test was performed post-hoc to correct for multiple comparisons and to reduce the chances of Type I error.

III. RESULTS

Baseline Parameters

A total of 150 patients were identified as eligible candidates of whom 51 patients were in group 1, 49 patients in group 2 and 50 patients in group 3. Majority of patients were females (108/150; 72%). The mean age at presentation was 43.3±9.9 years, 40.6±14.2 years, 38.2±14.7 years in group 1, 2 and 3 respectively. At baseline, ESR and CRP of group 3 were statistically higher than group 1 and not different from group 2. The mean DAS28-ESR of group 1, 2 and 3 are 4.6±1.01, 4.9±0.91 and 5.3±2.0 respectively where DAS28-ESR of group 3 was highest and the difference was statistically significant. However, mean baseline VAS for pain was not different among the three groups. The baseline parameters are summarized in table I.

Table I: Group 1, 2, 3 baseline results (N=150)

Parameters	Groups	Maximum	Minimum	Mean
Age (years)	1	24	63	43.3±9.9
	2	18	71	40.6±14.2
	3	18	74	38.2±14.7
ESR (mm/h)	1	2	130	31.1±27.1
	2	5	93	42.8±27.0
	3	2	105	47.2±30.2
CRP (mg/l)	1	0.5	50.0	11.1±12.6
	2	0.0	85.0	17.8±17.3
	3	0.0	120.0	28.9±36.9
DAS28-ESR	1	2.6	6.8	4.6±1.0
	2	3.0	7.0	4.9±0.9
	3	2.6	11.0	5.3±2.0
VAS for pain	1	4	10	7.7±1.6
	2	4	10	8.4±1.5
	3	3	10	8.1±1.9

Follow-up results at 3months

At 3months, mean changes in each parameter in each group are shown in table II.

Table II: Group 1, 2 and 3 mean changes in each parameter at 3 months (N=150)

Parameter	Groups	Maximum	Minimum	Mean
ESR changes (mm/h)	1	-35	96	8.9±21.5
	2	-57	81	10.9±25.9
	3	-21	96	35.0±29.2
CRP changes (mg/l)	1	-22	44	3.5±12.8
	2	-53	83	6.5±19.8
	3	0	117	25.1±35.3
DAS28-ESR changes	1	-2	2	0.4±0.8
	2	-1	2	0.5±0.8
	3	0	7	2.1±1.5
VAS for pain changes	1	-3	8	2.2±2.8
	2	-6	8	3.2±3.4
	3	2	10	5.3±2.3

The group 3 patients treated with TCZ in combination with MTX, even though had higher baseline activity, there was a significant improvement in all parameters as compared to group 1 and group 2 i.e. patients treated with csDMARDs in combination with MTX and ETC combination with MTX respectively.

The parameters showing significant changes as summarized in table III.

Table III: Changes in all parameters in group 3 compared to group 1and 2

Parameters	I Group	J Group	Mean Difference (I-J)	Standard Error	p-value
ESR change (mm/h)	3	1	26.098	5.124	< 0.001
		2	24.102	5.176	< 0.001
CRP change (mg/l)	3	1	21.611	4.883	< 0.001
		2	18.589	4.932	< 0.001
DAS28-ESR change	3	1	1.709	0.223	< 0.001
		2	1.589	0.226	< 0.001
VAS for pain change	3	1	3.125	0.580	< 0.001
		2	2.135	0.585	< 0.001

Reporting of Side-effects

No major side effects or drug withdrawal due to adverse events were reported during the study in all the three groups. Few reported pain at the injection sites and few had mild nausea during injection.

IV. DISCUSSION

Early diagnosis, prompt initiation of treatment and early achievement of the desired target of remission in RA help to change the course of the disease, prevent further joint damage and ameliorate prognostic outcomes [8]. Over the last decades, owing to the ever-increasing knowledge of the disease progression, RA treatment has taken major strides and there has been progressive expansion of the arsenal of available drugs. From the early days of DMARDs, we have come as far as the introduction of novel targeted therapies such as biological agents. On one hand there is a wide range of treatment options, but on the other hand, there is a need for comparisons between available drugs in order to better define the strategies achieving drug-free remission [12].

The use of csDMARDs as monotherapy may not be sufficient for treating moderate to severe RA, as meta-analysis combining direct and indirect comparisons was not able to designate the superiority of one csDMARD over another [13]. The changes in disease activity in group 1 suggested that the combination of MTX with other csDMARDs can be an option for those who fail to respond to DMARD monotherapy but the changes were not significant enough indicating that the patient may be at risk of rapid disease progression thus warranting the early use of biologics.[14] On the other hand, group 2 treated with ETC in combination with MTX displayed better outcomes compared to group 1. Past studies have also shown that the combination of ETC and MTX is effective than MTX monotherapy or ETC monotherapy in reducing disease activity in patients with persistently active RA [7, 15]. However having said that 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 [16, 17]. ACR and EULAR recommend TCZ as a treatment option for management of RA with or without MTX if disease activity remains moderate or high despite the use of csDMARDs or after the failure of TNF inhibitor treatment [18]. There are studies showing the benefit of add-on strategy or switch-on strategy to ongoing MTX treatment with TCZ [19, 20]. TCZ in combination with MTX can be a reasonable therapeutic option compared to ETC combination therapy in a patient not only with inadequate response to csDMARD but also with an inadequate response to at least one biological DMARD.[21] TCZ in combination with csDMARDs or MTX, give adequate response in decreasing high baseline disease activity in moderate to severe RA [22-24]. In group 3, even though the baseline activities were higher, the superiority of TCZ in combination with MTX is statistically significant in improving all parameters and disease activity compared to group 1 and group 2. This indicates that TCZ possesses a capacity as first-line biologic for the treatment of severe RA intolerant to DMARDs or non-responders to TNF inhibitors [23].However, high cost of medication imposed burden to patient and were reluctant to continue medication even after significant positive response. Further, large clinical studies may be conducted using TCZ initially in treating RA with high baseline disease activity with continuing maintenance therapy with relatively affordable medication.

V. CONCLUSION

TCZ in combination with MTX can be a good therapeutic option in treating moderate to severe RA compared to csDMARDs and ETC. Also, the study suggested that achieving low disease activity and targeting remission, regardless of the treatment paradigm, resulted in improved outcomes.

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Conflicts of interest

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

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