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NOVEL DRUG APPROACH IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Abstract:

Objective: *To determine the effectiveness of treat to target approach by using DMARDS (disease modifying anti-rheumatic drugs) in patients with early rheumatoid arthritis in attaining remission or/and low disease state after treating for six months.*

Methods: *The study was conducted over a period of 11 months from March 2011 to February 2012, in FMH (Fatima Memorial Hospital), Lahore. The study design is descriptive. Inclusion criteria was patients diagnosed with RA for less than a year, by using purposive sampling technique. Diagnosis was made according to American College of Rheumatology (ACR), 1987 criteria. EULAR (European League against Rheumatism) 2010 guidelines were followed to define treat to target approach for treating RA by using DMARDS. DAS 28 criteria was used to define remission and low disease state. EULAR response criteria determined patients' response to treatment.*

Results: *50 out of 67 patients completed follow up for 6 months, remaining were lost to follow up. Mean weekly dose of 18.9±3.8 mg of methotrexate was given to all cases.34% patients achieved remission while 58% had low disease state i.e. 17 and 29 patients, respectively. 56% cases showed EULAR good response, 42% attained moderate response while 2% achieved mild response to treatment.*

Key words: *DMARDS, Rheumatoid arthritis, remission, treat to target approach, methotrexate, low disease state.*

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INTRODUCTION:

[1] Rheumatoid arthritis is an autoimmune disease which presents most commonly as symmetrical polyarthritis. The patients complain of joint stiffening that relieves with exercise and exacerbates after taking rest. [2] Disease manifests as extra-articular symptoms as well, like Caplan syndrome, Felty syndrome, Sjogren syndrome, subcutaneous nodules, scleritis, pericarditis and pleuritis. There is inflammation of joints. If not timely managed, RA can lead to severe life-threatening complications.

[3] Treat to target approach for management of rheumatoid arthritis was introduced by EULAR 2010 guidelines. Many clinical trials have been conducted so far to test the remission and low disease state in patients with RA. Multiple scores have been introduced to test disease status but most commonly used worldwide is DAS 28 score (Disease Activity Score). In these score 28 joints count is used to assess disease status. Inflamed joints which are tender to touch and swollen are counted, patients' assessment on 0 to 100 analogue scale, C reactive protein and ESR are used to assess patients' disease status.

[4,5,6] Treat to target approach by using DMARDS within first year of RA has been in practice after being accepted in EULAR guideline and their role in remission or achieving low disease state has been proved in multiple randomized controlled trials.
This research aims in determining the effect of applying treat to target approach in early RA patients amongst Pakistani population.

METHODOLGY:

This descriptive, prospective study was conducted at FMH, Lahore, rheumatology department after taking permission from hospital ethical committee and informed consent from all cases. The RA patients during their first visit in outdoor clinic of FMH, rheumatology department were enrolled in study. The mean age group of patients was 18 to 65 years. The sampling technique was non-purposive, probability.
The ACR criteria was made in use to diagnose the patients. The less than one year of RA was determined on the basis of history, starting from the date of onset of symptoms, not from the date of diagnosis or first presentation at clinic. Those patients who were not taking DMARDS or who were taking DMARDS in sub clinical dose (Methotrexate less than 15mg per week, leflunamide less than 10 mg per day and sulfasalazine less than 2 grams per day) for <3 months were included in study while those who were already on DMARDS treatment were excluded.

Active disease status was determined on the basis of DAS 28 score more than 3.7. Exclusion criteria was patients already taking DMARDS for more than 3 months in clinical dose before being enrolled in study, pregnant females, males planning for child, alcoholics, drug abusers, those on contraceptives or lactating mothers. Besides that hepatitis B, C positive individuals on ELISA, HIV positive patients, those with malignancy or active tuberculosis, cardiac disease, ILD, renal or hepatic disease were also excluded from study. Patients who took intra-articular steroids within a week before presentation, who were on steroids treatment already or patients having intolerance to DMARDS were excluded. Any syndrome besides RA was also considered as exclusion.

Treatment was started on the basis of EULAR guidelines. Patients were followed up after every 4 to 8 weeks for six months. On every follow up DAS 28 score was used to assess disease status. Starting methotrexate dose was 10 mg weekly and 2.5 to 5 mg increase in dose was made on next follow up till the dose of 15 to 25 mg was achieved. Hydroxychloroquine was added in combination with methotrexate after rheumatologist's opinion. In case of methotrexate intolerance, it was replaced with leflunamide or sulfasalazine alone or in combination with methotrexate. 15 to 25 mg weekly methotrexate, 10 to 20 mg daily leflunamide, 2 to 3 grams daily sulfasalazine was considered as optimum dose at six months. Prednisolone was advised in combination with DMARDS in a dose of less than 10 mg if need felt by rheumatologist. Steroids were tapered off slowly while the NSAIDS were given on demand. Intra articular steroid injection was once given, if needed.

Remission was defined as DAS 28 less than 2.9 and low disease state was defined as score less than 3.2.EULAR response was defined according to the proven guidelines into mild moderate and good response. SPSS 17 was used for data analysis. Percentages were used to present qualitative data while mean and standard deviation for quantitative data. EULAR response, remission and low disease state were noted at the end of treatment. Percentages and frequencies were recorded about all outcome variables. ANNOVA was applied to assess data normality, DAS 28 score. Other variables were assessed by applying Friedman test.

T-test was applied in comparing the patients who received prednisolone and DMARDS in combination

and those who were given DMARDS alone. Categorical data was compared by applying chi-square. P-value of <0.05 was considered significant. Mann Whitney test was applied to compare prednisolone and DMARDS combination and DMARDS alone patients.

RESULTS:

50 out of 67 completed six months, remaining were lost to follow up. Mean age group was 39±12 years. There were 31 females i.e 62%, others were males. Anti CCP antibodies was available with 58% patients (29) out of which 26 were positive i.e 89%, while RA factor was positive in 90% cases. DAS 28 score was 6.1±1.1. Mean MTX dose was 18.9±3 mg weekly. Hydroxychloroquine and MTX combination therapy was given to 41 patients and dose was 253±85 mg daily. Prednisolone was given to 21 patients with mean dose of 3.6±1 mg daily after 24 weeks of treatment initiation.

Data stratification was done on basis of prednisolone combination therapy, patients' biodata, and disease presentation. DMARDS and prednisolone combination therapy was compared with DMARDS alone treatment by applying t- test. AT treatment initiation patients who were on prednisolone had higher mean VAS in comparison with DMARDS alone patients with P-value 0.01. Remission frequency was similar in both groups, P-value 0.49.

34% cases achieved remission while 58% achieved low disease state. DAS 28 was 5.8±1.8, which at 24 weeks was 3.2±.9. 56% cases showed good EULAR response, 42% moderate response while 2% showed mild disease response to treatment.

Table:1. Patients and disease characteristics.

Age (years)	39±12 years
Females	62% (n=12)
Duration of disease (months)	7±4.9 months
RA factor +ve	90% (45)
Anti-CCP +ve	86% (26)

Table: 2. Variables change from 0 week to 24 weeks of treatment.

variables	0 weeks	12 weeks	24 weeks	p-value
Tender joints	8 (6.2)	4 (3)	2 (3)	<.0001
ESR	43 (35.7)	27 (20.8)	20.5 (22.5)	<.0001
DAS 28	5.9±1.1	4.3±0.8	3.2±.9	<.0001
Swollen joints	4 (3)	1 (2.3)	0(1)	<.0001
Pain VAS	77.5 (50)	40 (25)	20 (20)	<.0001

Table:3. Comparison of patients, disease characteristics and variables with prednisolone and DMARDS combination therapy and DMARDS only therapy.

Variables	DMARDS	DMARDS + prednisolone	p-value
Age	37±12	41±12	0.23
Females	18(62%)	61% (16)	0.99
Disease duration	6.7±4	7.6±3	0.41
RA factor	25 (86)	20 (95%)	0.29
Anti-CCP antibodies	17 (85)	9 (100%)	0.22
Tender joints	7 (4.5)	9 (10)	0.27
Swollen joints	3(3)	5 (3)	0.21
ESR	40(41)	45 (32)	0.88
Pain VAS	70 (30)	100 (40)	0.01
DAS 28	5.8 (1)	6 (1.5)	0.20
Low disease state target	18 (62)	11 (52)	0.49

DISCUSSION:

Treat to target approach was not in practice before 2010, after EULAR guidelines this approach was introduced for achieving remission and low disease state in early RA patients. Despite of it, its use is limited only to developed countries. In developing countries like Pakistan this approach is not much in practice. This study aims in testing the effectiveness of treat to target approach so that remission can be achieved in RA patients within first year of disease

onset and serious complications or extra-articular manifestations can be reduced or prevented.

[6,8] Many controlled trials have been conducted in this regard. The efficacy of this approach has been tested and approved by many researchers earlier as well by using different study samples. [5]Farman S, et al. in a study conducted in Pakistan concluded that treat to target approach can be used to achieve remission and low disease state. Similarly in another research conducted by [3]Solomon DH, et al elaborated the effectiveness of treat to target approach in treating rheumatoid arthritis.

CONCLUSION:

The treat to target approach should be practiced by clinicians to achieve disease remission and low disease state in early rheumatoid arthritis patients.

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