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Predictors of Response to Methotrexate Naïve Female Patients with Rheumatoid Arthritis

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ABSTRACT

Objective: To see the factors that affect response to Methotrexate in female patients with rheumatoid arthritis.
Study design: Prospective longitudinal study.
Place and Duration of Study: Department of Rheumatology, Fauji Foundation Hospital (FFH), Rawalpindi Pakistan, from Nov 2019 to Jan 2020
Methodology: Rheumatoid arthritis patients 18 to 75 years of age, 115 in number all females were selected from rheumatology outpatient department (OPD) at FFH, Rawalpindi. All patients in the study were started on Methotrexate first time. Patients were assessed at baseline and after three months. At week 0 and week 12 Disease Activity score 28(DAS28), Clinical Disease Activity Index (CDAI) and Pain Visual Analogue Scale (VAS) was calculated. Inflammatory markers were measured in blood samples. SPSS version 23.0 was used for data interpretation.
Results: About 115 were the total patients included in the study, with a mean age (in years) of 50.63±10.50. Association between response to Methotrexate and age shows that age <50 shows good response to Methotrexate in 54% while 51.7% shows good response to Methotrexate in patient's age >50 years (*p*-value 0.754). Non-smokers have 55.3% good response as compared to 33.7% in smokers (*p*-value 0.128). Sero-negativity in Rheumatoid arthritis shows a EULAR good response in 65% of patients while only 44% in seropositive Rheumatoid arthritis (*p*-value 0.024)
Conclusion: In females current smoking, seropositive status predicts worse response to Methotrexate while age, comorbidities and occupation have no impact on response to Methotrexate.

Keywords: Methotrexate, Predictors of response, Rheumatoid arthritis.

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INTRODUCTION

Rheumatoid arthritis (RA) is an immune mediated illness with involvement of joints as the main manifestation with mostly female predominance. The presenting complaints of patients include polyarthritis with tenderness, swelling and early morning stiffness which persists up to 1-2 hour if patient is not taking any treatment. Rheumatoid arthritis has a prevalence of 1% around the world.[1] In Pakistan it has a prevalence of up to 0.5-1% based upon a study conducted in 1998.[2]

American college of rheumatology (ACR) 2010 criteria is applied to classify rheumatoid arthritis (RA) which includes, number of joints involvement, inflammatory markers like erythrocyte sedimentation rate and C-reactive protein, and duration of the symptoms.[3] Rheumatoid factor (RA factor) and anti citrullinated peptide (Anti CCP) may or may not be positive in rheumatoid arthritis cases. About 70% of cases are seropositive either RA factor or AntiCCP.[4]

RA is managed by a number of different drugs that include synthetic disease modifying anti rheumatic drugs (sDMARDs) like hydroxychloroquine, sulphsalazine, Methotrexate, lefluonamide, azathioprine and minocycline and biologic DMARDs like rituximab, tocilizumab, etanercept, certolizumab, golimumab, adalimumab, abatacept and anakinra.[1]

Methotrexate is used in the treatment of RA from years and it is considered to be the most important drug in the treatment of rheumatoid arthritis and all the patients without any contraindication of methotrexate should be given a trial of Methotrexate first. The latest guidelines of rheumatoid arthritis from American college of rheumatology (ACR) and the European league against rheumatism (EULAR) recommend Methotrexate as the first line treatment of rheumatoid arthritis.[5,6] Methotrexate is an immunosuppressive agent; it competitively inhibits dihydrfolate reductase an enzyme which is involved in the synthesis of tetrahydrofolate. Another mechanism of action of MTX is anti-inflammatory, which is due to the upregulation of enzyme AICAR which leads to increase in adenosine in the blood.[7] Other indications of Methotrexate are different cancers like Acute Lymphocytic Leukemia, small cell lung cancer, lymphoma,

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psoriasis and crohn disease. In rheumatology there a number of indications of MTX apart from rheumatoid arthritis, MTX is used in psoriatic arthritis, adult onset still disease, polymyositis and dermatomyositis.[8]

Inhibition of the binding of interleukin 1-beta to its cell surface receptor is another biochemical effect of MTX in the body.

There a number of side effects of Methotrexate that includes nausea, vomiting diarrhea, sense of tiredness, fever, increased risk of infection, leukopenia, mucositis, deranged liver function tests, interstitial lung disease, lymphoma, nodules formation and skin rashes. Patients on long-term treatment should be regularly monitored for adverse effects of the medicine. Blood complete picture (CBC), liver function tests (LFTs) and renal function tests (RFTs) should be checked every 3 months if a patient is on Methotrexate. Safe alternative should be used during pregnancy and breast feeding. In those with low glomerular filtration rate lower doses may be used with caution.[1,5,6]

About 30% of the patients are intolerant to oral MTX and need either split doses of MTX or subcutaneous injection or an alternative medicine like leflunomide, sulfasalazine or some biologics to control the inflammation in joints.[9]

Predictors of response to MTX therapy include current smoking, female sex, younger age, longer duration of disease.[10]

A study conducted at Aga Khan University Hospital, Karachi showed that 13% shows excellent response, 70% shows good response, 11% have fair response and poor response in 4% in MTX treated group. There was a second group in the study that received MTX as second-line of therapy after using some other DMARD and response rate in that group was 59% had good to excellent response rate while 25% of the patients shows poor to fair response.[11]

What are the factors which lead to a good response and what are the factors that lead to poor response to MTX are studied in this study. Different parameters like age of the patient, current status of smoking, seropositivity or seronegativity of RA, occupation, link of comorbidities on response to MTX were assessed in this study. This will give us an idea of which patients have a good response to MTX and which have poor response to MTX.

METHODOLOGY

The study was conducted at the Department of Rheumatology, Fauji Foundation Hospital, Rawalpindi Pakistan. Ethical approval was sought before the study from ethical review committee of Fauji Foundation Hospital. Patients were selected by non-probability consecutive sampling and informed written consent was taken from the patients. The duration of the study was three months (from November 2019 to Jan 2020). One hundred and fifteen patients were selected and the sample size was calculated using WHO sample size calculator anticipated population proportion is 34%, 9% absolute precision, 95% confidence interval).[10] Patients diagnosed as case of RA based upon ACR 2010 criteria 3 between 18-75 years of age were selected.

Incusion Criteria: All the patients having either early disease i.e disease <6 months or established disease i.e having disease >6 months were included in the study. 5 Patients were included in the study that were started on Methotrexate first time.

Exclusion Criteria: Patients who have previously taken Methotrexate or who were on DMARDs other than MTX were excluded from the study.

Patients were assessed at baseline and after twelve weeks. Demographic details of the patients including age, gender, occupation, duration of the disease, medications used, were entered in the study proforma. Previous history of hypertension, diabetes, ischemic heart disease, chronic hepatitis C, stroke and smoking was asked from the patients.

At week zero and week twelve Disease activity score 28 (DAS 28), Clinical disease activity index (CDAI), Pain Visual Analogue Scale (VAS) were calculated. Blood samples were taken at week zero and week 12 for erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). DAS 28 was assessed clinically by noting number of tender joints (TJ), swollen joints (SJ) and visual analogue score (VAS) for pain (0-10) and ESR or CRP using online calculator. Clinical disease activity index CDAI were calculated by noting number of tender joints (TJ), swollen joints (SJ) and visual analogue score (VAS) for pain (0-10). Rheumatoid factor (RA factor) and anti CCP positivity or negativity was noted of all patients from electronic medical record of hospital.

Data was analyzed using SPSS version 23.0. Mean and Standard deviation (SD) were calculated for numeric variables like age; pain VAS, ESR, CRP, DAS 28, CDAI. Association between different parameters like age, seropositivity and seronegativity, smoking, comorbidities and response to MTX treatment was done. Chi square test was used to see the association between the parameters and response to MTX. *p*-value was

calculated for every parameter. The *p*-value ≤0.05 was considered significant.

RESULTS

Total number of patients included in the study were 115. All were females, with a mean age (in years) of ±SD 50.63±10.50. Association between response to MTX and age shows that age less than 50 shows good response to MTX in 54% while 51.7% shows good response to MTX in patients with age more than 50 years (*p*-value 0.754) (Table-I).

Table-I: Comparison of Age Group less than 50 and more than 50 (n=115)

		Age groups ≤50	≥50	Total	*p*-value
Response to Methotrexate					
Poor	≤0.6	7(12.3%)	10(17.2%)	17(14.8%)	0.754
Good	≥1.2	31(54.4%)	30(51.7%)	61(53.0%)	
Moderate	0.6-1.2	19(33.3%)	18(31.0%)	37(32.2%)	
Total		57	58	115	

While non-smokers have 55.3% good response as compared to 33.7% in smokers (*p*-value 0.128). Seronegativity in RA shows a EULAR good response in 65% of patients while only 44% in seropositive RA. (*p*-value 0.024) (Table-II to V).

Table-II: Comparison of parameters between Smokers and Non-Smokers (n=115)

		Smoking		Total	*p*-value
		yes	no		
Response of Methotrexate					
Poor	<0.6	4	13	17	0.128
		33.3%	12.6%	14.8%	
Good	>1.2	4	57	61	
		33.3%	55.3%	53.0%	
Moderate	0.6-1.2	4	33	37	
		33.3%	32.0%	32.2%	
Total		12	103	115	

Table-III: Comparison of Parameters between Sero-Positive Rheumatoid arthritis and Sero-Negative Rheumatoid Arthritis (n=115)

Seronegative / RA +ve / Anti CCP+ve								
Sero negative		RA+ve	Anti CCP+ve	RA+v & Anti CCP +ve	Sero–ve & RA+v & Anti CCP+ve	Total	*p*-value
Response of MTX								
Poor	<0.6	6	5	4	2	0	17	0.024
		10.0%	13.9%	57.1%	18.2%	0.0%	14.8%	
Good	>1.2	39	16	1	4	1	61	
		65.0%	44.4%	14.3%	36.4%	100.0%	53.0%	
Moderate	0.6-1.2	15	15	2	5	0	37	
		25.0%	41.7%	28.6%	45.5%	0.0%	32.2%	
Total		60	36	7	11	1	115	

Table-IV: Comparison of response to MTX in patient having Comorbidities (n=115)

		Cormobids				Total	*p*-value
		Hypertension	Diabetes	Hepatitis C	nil		
Response of Methotrexate							
Poor	<0.6	2	1	1	13	17	0.103
		40.0%	33.3%	100%	12.3%	14.8%	
Good	>1.2	1	1	0	59	61	
		20.0%	33.3%	0.0%	55.7%	53.0%	
Moderate	0.6-1.2	2	1	0	34	37	
		40.0%	33.3%	0.0%	32.1%	32.2%	
Total		5	3	1	106	115	

Table-V: Comparison of Parameters between Occupations of Patients (n=115)

		Occupation			Total	*p*-value
		House wife	Teacher	Student		
Response of Methotrexate						
Poor	<0.6	17	0	0	17	0.557
		15.0%	0.0%	0.0%	14.8%	
Good	>1.2	60	1	0	61	
		53.1%	100.0%	0.0%	53.0%	
Moderate	0.6-1.2	36	0	1	37	
		31.9%	0.0%	100.0%	32.2%	
Total		113	1	1	115	

DISCUSSION

Methotrexate is the most important drug for the management of rheumatoid arthritis and if a patient shows response to MTX it is a very good for patients overall disease prognosis. In around 50% of the cases MTX monotherapy can control the disease without addition of any other DMARD.[12] But most of the time there are a few complications and side effects of MTX like oral ulcers, deranged liver function tests and pancytopenia which leads to stopping the drug. Another factor is that MTX is a chemotherapy drug and its taste is not very palatable and patients complain of severe vomiting &nausea associated with its usage.[13] Even in some cases patients start having nausea and loss of appetite on the day of MTX intake, this effect is psychological. These adverse effect lead to lack of compliance which results in decrease in response to treatment and that finally results in disease getting uncontrolled and patient came with recurrent flares of RA. In these cases patients need other therapies like other synthetic or biologic DMARDs or patient can be shifted to subcutaneous MTX which causes less gastrointestinal side effects and increased efficacy according to studies.[14,15]

This study focused on the factors which leads to a good response and what are the factors that leads to poor response towards Methotrexate treatment. In this study we see different parameters like age of the patient, current status of smoking, serpositivity or serone-

gativity of RA, occupation, link of comorbidities on response to MTX.

In our study the most important predictor of MTX response is active smoking which leads to poor response to MTX in patients of RA. Although the *p*-value was not significant for response to pain VAS, DAS 28 and ESR. Smoking is not only a factor in the development of rheumatoid arthritis especially seropositive type but also results in decrease response to MTX. In an other study conducted in Sweden by Saedis Saevarsdottir and colleagues active smoking leads to worse response to MTX.[10] An other study conducted in Korea suggest that active smoking shows a poor response to MTX as well as other biologics.[16] So every patient of RA and even other rheumatological disease smoking should be stopped not only it decrease and control disease, non-smokers have a good response to a number of drugs like MTX, rituximab and anti TNF drugs.[16-18]

Another factor or predictor of response to MTX is seropostivity and seronegativity of the patient. In a study conducted by Choi S and colleagues it is stated that the seronegative rheumatoid arthritis disease has although aggressive disease than seropositive but seronegative RA have a good response to conventional DMARDs as compared to seropositive rheumatoid arthritis patients. [19,20] The results are consistent with our study with 43 patients shows EULAR good and moderate response in seropositive RA (either anti CCP or RA factor positive) as compared to 54 patients in seronegative RA (having both RA and antiCCP negative) with staistictically significant *p*-value (*p*-value 0.024).

Another predictor which was seen in our population was age of the patient. In our study there was no significant difference in response to MTX in patients having younger age group i.e <50 as compared to patients who have age more than 50(*p*-value 0.754). This is consistent with an old study by C Bologna and colleagues which shows that there is no significant effect of age on response to MTX therapy.[21] But in a new study conducted in 2010 at Sweden younger age group shows worse response to MTX.[10]

The impact of comorbidities like diabetes and hypertension on response to treatment cannot be assessed due to few patient having comorbidities in our sample population.

So this study shows that all the patients should be asked to quit smoking who have rheumatoid arthritis. And this study helps the clinicians beforehand that patients having both RA factor and antiCCP negative will have good response to MTX as compared to seropositive patients. But there is no effect of age on response to Methotrexate both young and old age have same type of response to MTX.

LIMITATIONS OF STUDY

Limitations of our research includes limited time duration, non-probability sampling technique, single hospital study, no comparison group, less number of patients with comorbidities, no male RA patients in our study as male have good response to MTX as compared to females.

CONCLUSION

Current smoking, seropositive status predicts worse response to MTX while age, comorbidities and occupation have no impact on response to MTX.

Conflict of Interest: None.

Author's Contribution

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

SNA & SM: Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

BS & ZA: Data acquisition, data analysis, approval of the final version to be published.

PZ & AA: Critical review, concept, 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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