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Original Article

Predictors of Response to Conventional Dmards In Rheumatoid Arthritis Patients Presenting In A Tertiary Care Hospital of Pakistan

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ABSTRACT

Objective: Conventional disease modifying anti-rheumatic drugs (DMARDs) are the first line drugs in a conventional DMARDs in Pakistan.

Study Design: Prospective cohort study.

Place and Duration of Study: Rheumatology Department of FFH Rawalpindi, Pakistan from Oct 2023 to Mar 2024.

Methodology: We included 224 cases of treatment naïve early Rheumatoid arthritis with moderate to high disease activity. Disease activity was assessed by DAS28 CRP. Baseline data were collected for demographic, clinical parameters and serology. Treatment response was categorized into good (DAS28 CRP≤3.2) and poor response (DAS28 CRP >3.2) at 3 months after treatment with conventional DMARDS. Predictors of treatment response were assessed by logistic regression analysis.

Results: Females constituted 196(87.5%) patients. 118(52.7%) patients were seropositive. At 3 months, 139(62.1%) achieved remission, 65(29%) low, and 20(8.9%) moderate disease activity. 204(91.1%) patients achieved good response. The response was dependent on baseline disease activity as measured in terms of change in DAS-28 CRP.

Conclusion: Patients with higher BMI has poorer response to conventional DMARDs. Weight optimization may be important step in improving the response to DMARDs in patients with Rheumatoid arthritis.

Keywords: Body Mass Index, Disease modifying anti-rheumatic drugs, Rheumatoid arthritis, Serology

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INTRODUCTION

Rheumatoid arthritis is a chronic, inflammatory autoimmune disorder that preferably affects the small joints of the body. The disease usually affects the people aged between 35 to 60 years with relapsing remitting course. Diagnostic and treatment delays lead to joint destruction and deformities. The global prevalence of RA is around 1 percent.[1] The optimal approach to therapy requires timely initiation of treatment and a treat to target approach. It results in increased remission rates. Despite all the advances in therapy almost 20 percent of our patients fail to achieve the goal of remission.[2] A key therapeutic goal in RA treatment is prevention of radiographic progression. Conventional synthetic DMARDs are the first line therapy in the treatment of RA; the most widely prescribed and least expensive of all the drugs.[3] Among csDMARDs, methotrexate is considered to be the cornerstone of therapy because of its efficacy and safety. However, studies have shown that up to 30 to 50% patients do not achieve therapeutic targets with this drug. Therefore, it's of practical utility to predict beforehand which patients will respond better to therapy.[4]

The prediction of response to DMARDs is challenging in individual patient.[5] Several studies have been conducted to find the predictors of response to methotrexate therapy. A high disease activity at baseline and diagnostic delays have been associated with inadequate response to therapy.[6] Similarly, seropositive status and smoking are also predictors of poor response. Obesity is also an important modifiable risk factor for poor response to therapy in RA.[7] In Pakistan, methotrexate is the most commonly prescribed drug for rheumatoid arthritis.[8] However, local data regarding predictors of response to csDMARDs is lacking. The purpose of the study was to gather information on reversible and irreversible predictors of response to DMARD therapy in a prospective manner. Being a resource limited state we need to know more and more about the modifiable risk factors which predict the response to therapy so that we can make maximum usage of conventional DMARDs before moving on to the biologics.

METHODOLOGY

This prospective cohort study was conducted in rheumatology department of FFH Rawalpindi from

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October 2023 till March 2024. Patients were selected from rheumatology outpatient on basis of consecutive convenience sampling. 224 patients were included using RAO software. Population size was 20,000. Margin of error was 5%. Confidence interval was 95%. Response distribution was 70%,[9] as described in previous study of seronegative patients.

Inclusion Criteria: Adult cases of treatment naïve early RA, aged ≥18 years, diagnosed on the basis of ACR2010 criteria, presenting with moderate to high disease activity were included.

Exclusion Criteria: We excluded patients aged less than 18 years, patients with low disease activity at the time of enrolment, RA overlap with other autoimmune disorders, obese patients, pregnant females, hepatic or renal disorders, active infection, receiving biologic therapies, and those developing intolerance to medication before completion of three months.

Pre-designed patient record form was used to collect the data. At baseline, data were collected regarding demographics, clinical features, concomitant treatments (NSAIDs, steroids) and disease activity was calculated. Gender, age, height (cm), weight(kg), BMI (calculated using formula weight in kg divided by height in meters square).[10], age at onset of disease, disease duration, smoking status were recorded. Patient was examined for tender and swollen joint count, patient visual analogue scale (VAS), physician VAS for assessing the RA disease activity. Laboratory for RA factor, anti-citrullinated C peptide antibody, and C reactive protein were sent at baseline. Patients were started on Methotrexate (MTX) or other conventional DMARD by the treating physicians as deemed appropriate in context of patient characteristics and preferences. MTX dosage and route was adjusted according to the European League Against Rheumatism (EULAR) guidelines until patient experienced side effects or maximum dosage of 20mg/week was reached. Patients were followed at 3 months for assessing disease activity using disease activity score (DAS)-28 CRP.

Disease activity was assessed by DAS-28 CRP[18]. It is a composite disease activity index which divides the disease activity into four classes: Remission at the score of <2.6, low disease activity at 2.6-3.2, moderate disease activity at >3.2-<5.1, and high disease activity at the score of ≥5.1. RA was considered sero-positive if either RA factor or anti-CCP antibody was above the normal value for the testing laboratory. Treatment response was defined as good response if remission or low disease activity was achieved at 3 months after starting the treatment, and poor response if the disease activity was moderate or high after 3 months of treatment.

Data analysis was performed using Statistical package for social sciences (SPSS) version 23. Quantitative variables were checked for normality by Shapiro-Wilk test. All the quantitative variables in study were nonnormally distributed except age which was normally distributed. Median and inter-quartile ranges (IQR) were used to describe the variables which were not normally distributed. Categorical variables were described by frequencies and percentages. Dependent variable was disease activity status and other parameters were used as independent variables. Statistical significance was defined as *p*-value of ≤ 0.05 using chi Square test.

RESULTS

Data was collected for two hundred and twenty four patients of RA. 87.50% (n=196) were females. Median age was 52.63±11.52 years. The median duration of RA was 3 months. 118(52.70%) patients were seropositive. 13(5.8%) patients were smokers. Median BMI of the study patients was 23(22-28)kg/m2. Median DAS-28 CRP was 4.4 (4-4.9) at baseline. After three months of follow-up median DAS-28 was 2.1(1.9-2.9) median change in DAS28 was 1.9(1.3-2.5). At baseline 186(83%) patients had high disease activity. At 3 months, 139(62.1%) achieved remission, 65(29%) achieved low disease activity, and 20(8.9%) moderate disease activity. Overall 204(91.1%) patients achieved good response, whereas response was poor in 20(8.9%) patients.Table I shows the baseline characteristics of the study patients.

In patients who achieved good response, median DAS-28 CRP score at three months was 2.9(1.9-2.8) and in poor responders, the score was 3.8(3.8-3.9). Table-II presents the comparison of demographic and clinical parameters between patients with good and poor treatment response at three months. The median age was slightly lower in the good response group [52.0 years (45.0–60.0)] compared to the poor response group [56.0 years (53.0–64.0)], but this difference was not statistically significant (*p* value= 0.64). Similarly, BMI did not differ significantly between groups (*p* value = 0.26), indicating that age and BMI were not significant predictors of treatment response in this cohort. Baseline disease activity measured by DAS28-CRP was comparable between the two groups (*p* value

= 0.23), suggesting that initial disease severity did not significantly influence response status at three months. However, DAS28-CRP at three months was significantly lower in the good response group [2.1 (1.2–2.9)] compared to the poor response group [3.9 (3.1–4.2)] (p value = 0.001). This variable was a strong predictor of treatment response, with an odds ratio (OR) of 4.20 (95% CI: 1.08–6.01), indicating that patients achieving lower disease activity at three months were approximately four times more likely to have a good treatment response. Additionally, the change in DAS28 score was significantly greater in the good response group [1.9 (1.3–2.5)] compared to the poor response group (*p* value= 0.02). The odds ratio of 4.00 (95% CI: 2.55–7.22) further supports that greater improvement in disease activity is a significant predictor of favorable treatment response.

Table-I: Baseline Characteristics of Study Population (n=224)

Variables	Values
Age (years) Rheumatoid arthritis mean±SD)	52.63±11.52
Gender	
Male Female	28.00(12.5%) 196.00 (87.5%)
Disease Duration (months)(median(IQR)	3.00 (2.00-4.00)
Education	
Graduate Undergraduate	17.00(7.60%) 207.00(92.40%)
Serology status	
Seropositive Seronegative	118.00 (52.70%) 106.00 (47.30%)
Smoking status	
Smokers Non smokers	13.00(5.80%) 211.00(94.20%)
Disease Activity Score-28 C-reactive protein (median(IQR)	4.20 (3.90-4.80)
Disease Activity Score-28 C-reactive protein (median(IQR)	2.10(1.90-2.90)
Disease Activity Score-28 change (median(IQR)	1.90(1.30-2.50)
Body Mass Index (kg/m2) (median(IQR)	23.00 (22.00-28.00)

** n(%) for qualitative and median(IQR) for quantitative variables*

Table-II: Results for Predictors of Rheumatoid Arthritis Treatment response at Three Months (n=224)

Factors	Response			Odds Ratio (95% CI)
	Good response	Poor response	*p*-value	
Age	52(45-60)	56(53-64)	0.64	
Body Mass Index	23(22-240	31(30-32)	0.26	
Disease Activity Score-28 C-reactive protein	4.3(3.9-4.90)	4.8(4.7-4.9)	0.23	
Disease Activity Score-28 C-reactive protein at 3 months	2.1(1.2-2.9)	3.9(3.1-4.2)	0.001	4.20(6.01-1.08)
Change in Disease Activity Score-28	1.9(1.3-2.5)	0.9(1.2-1.8)	0.02	4.00(7.22-2.55)

DISCUSSION

This study was conducted to see the different clinical parameters which impact the response to conventional DMARDs in RA patients. It revealed that response to therapy was not dependent on different variables. Those variables include BMI of the patient, seropositivity and seronegativity; and smoking status and its association with treatment response was also seen but no significant results were found in this case. Only significant predictor is disease activity at baseline.

About 40 percent of the world population is obese.[11] According to different studies obesity has a prevalence in RA as high as sixty percent. Moreover, obesity is also a risk factor for RA.[12-13] Previous studies show poorer response to therapy in obese patients including high inflammatory markers and increased disability.[14] Obesity is also related to poorer quality of life. Adiposity is an inflammatory state so it can independently increase the disease scores.[15]

Rheumatoid Arthritis factor and anti CCP are very important diagnostic and prognostic tools in RA.[16] More aggressive treatment may be required in seropositive patients.[17] It has also been shown in various studies that seropositivity is associated with more radiographic progression18. Nevertheless, less data is available on how it otherwise affects the disease activity.

This study has shown that BMI is associated with poorer response even in those with early disease. The possible justification may be that our patients usually report late due to limited resources. Therefore, subclinical disease would have been going on by the time they first presented to us. Moreover, this study showed lack of association between smoking and response to disease modifying drugs. It may be due to the fact that smoking is considered a taboo especially among females. So true data may not have been provided.

This study concludes that disease activity at baseline is an important predictor of response to therapy in treatment naïve RA patients. Limitations included poor educational status of the patients and their poor ability to understand the questions especially while calculating the disease activity scores which included patient's global assessment. Patients who were both obese and seropositive it was difficult to comment whether poor response was because of seropositivity or increased BMI.

Recommendations based on this study are that we should aggressively treat the patients with high baseline disease activity. Future research is needed regarding the impact of BMI in those with established disease. Moreover, regarding the seropositive status how it impacts the disease outcomes besides rapid radiographic progression.

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Authors' Contribution

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

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

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

SP & BS: Conception, data acquisition, 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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