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Research Article

A Clinical Study on the Use of Methotrexate in Rheumatoid Arthritis Based on CDAI Score

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Abstract

Methotrexate (MTX) has been used in the treatment of rheumatoid arthritis for more than 2 decades. It has proven its efficacy in the treatment of rheumatoid arthritis in numerous randomized controlled trials. Compared with other second-line drugs, a higher percentage of patients can continue therapy with MTX over a prolonged period. However, its long-term effectiveness in RA remains unclear. Therefore, a retrospective observational study was performed from the period of 2016-21.

Objectives: To evaluate the treatment plan and use of MTX in RA patients and to determine the efficacy of MTX therapy in Rheumatoid arthritis based on the CDAI score.

Methodology: A retrospective multicentric observational study was performed for 5 years on patients who were diagnosed with rheumatoid arthritis & were on methotrexate therapy. The statistical analysis was done using SPSS version 20.

Results and Discussion: A total of 763 patients were enrolled in the study, out of which 84.53% were females and 15.46% were males. Among the subjects, 11.8 % presented with low disease activity, 50.2 % presented with moderate disease activity, and 37.7% presented with high disease activity. 14.15% of patients were put on methotrexate monotherapy while the remaining 85.85% of patients were given MTX in combination with other synthetic DMARDs. Out of the total patients that were given combination therapy, 87.94% were on MTX+HCQ treatment.

Conclusion: Methotrexate has been proven to be efficacious in the treatment of the Rheumatoid Arthritis.

Keywords: Methotrexate, Rheumatoid Arthritis, CDAI Score

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic and usually progressive inflammatory disorder characterized by polyarticular symmetric joint involvement and systemic manifestations.

RA results from a dysregulation of the humoral and cell-mediated components of the immune system. Most patients produce antibodies called rheumatoid factors; these seropositive patients tend to have a more aggressive course than seronegative patients. [1] Some patients may experience mild articular disease, whereas others may present with aggressive disease and/or extraarticular manifestations. The systemic inflammation of RA leads to joint destruction, disability, and premature death. [2] Approximately 1% of the population worldwide is affected by RA. According to a few studies it can develop at any age, but the peak age of onset is between 40 and 70 years. [3]

The drugs used for the treatment of rheumatoid arthritis are classified as Disease Modifying Anti-Rheumatic Drugs (DMARDs). DMARDs are of two types- biological and synthetic. Biological or targeted DMARDs work on a specific target site (example- TNF-alpha inhibitors) while synthetic or traditional DMARDS work on the entire immune system (example- methotrexate, hydroxychloroquine, etc). Methotrexate (MTX) is the first-line drug used in the treatment of rheumatoid arthritis and has been in use for this purpose for over two decades. Methotrexate is a folate antagonist approved by the FDA for the treatment of RA. It has various mechanisms through which it provides anti-inflammatory action. Methotrexate is usually given orally or subcutaneously once a week for at least 3 months, and if no significant therapeutic effect is observed, then the dose can be increased to a maximum of 20mg/week. It can be given as monotherapy or as a combination therapy with other DMARDs like hydroxychloroquine, leflunomide, sulfasalazine, etc. Some of the side effects of methotrexate include- oral ulcers, hair loss, folic acid deficiency, and gastrointestinal disturbances like nausea, vomiting, anorexia, and mucosal ulcers. Methotrexate is hepatotoxic [4] and some other toxicities observed due to MTX include renal toxicity and leukopenia[5].

Clinical Disease Activity Index (CDAI) is a way to assess the severity of rheumatoid arthritis in patients and is calculated based on four parameters that include- the number of tender joints and swollen joints along with the global assessment of the patient and assessor. The calculation of the CDAI score only consists of a summation of these four parameters which makes it very efficient and practical to use as compared to the other scoring systems that require a complex formula. CDAI

can also be used as a scale to determine the effectiveness of therapy by measuring the difference in its score.

Some studies suggested that combination therapy of methotrexate with other DMARDs showed better results as compared to monotherapy [6,7]. In contrast to these findings, other studies showed that although combination therapy did give better results than monotherapy for a short period, in the long run, both therapies proved to have the same effectiveness with no significant difference in their efficacy.[8,9]

No studies correlating the improvement in CDAI to MTX efficacy have been done before. In our research, we intend to study the efficacy of methotrexate monotherapy and methotrexate combination therapy with hydroxychloroquine based on the improvement in CDAI score over 1 year and 2 years. Apart from this we also aim to find out whether there is any difference between the efficacy of methotrexate monotherapy and methotrexate combination therapy with hydroxychloroquine.

Objective

- To determine the utilization pattern and efficacy of MTX in RA patients.
- To determine the adjuvant therapy

METHODS:

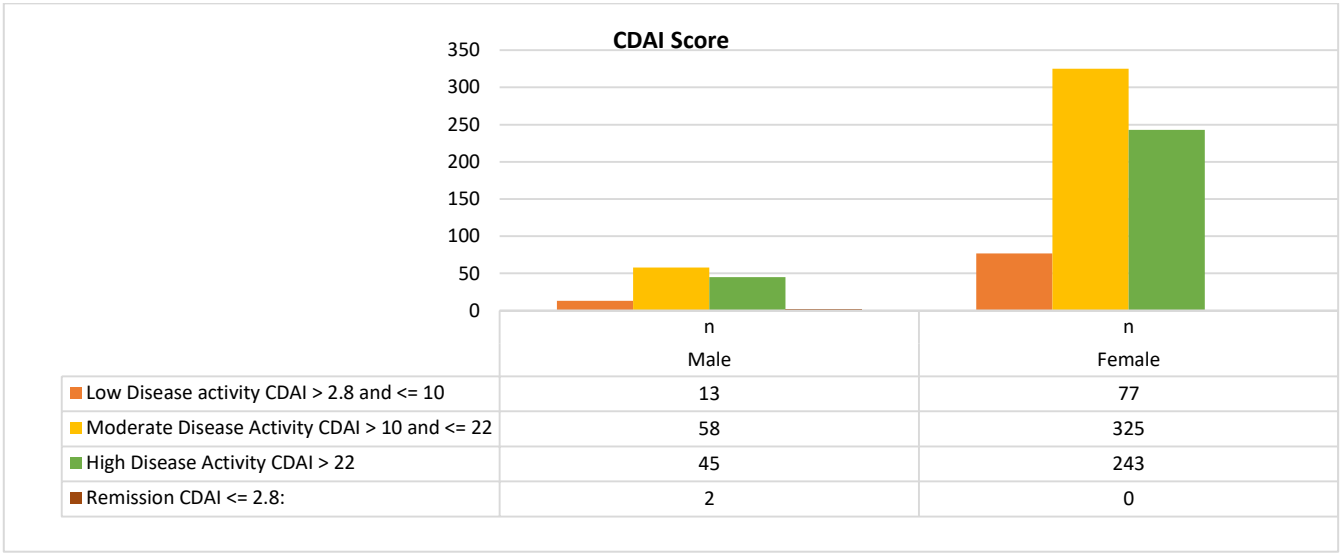
A multicentric Retrospective Cross-Sectional Observational Study was conducted in Gujarat, India. The population pool consisted of Rheumatoid arthritis patients equal to or above 18 years old. Institutional ethics committee approval was achieved. 763 Rheumatoid arthritis patients were randomly selected in the span of 5 years (2016-2022). Data entry forms and an electronic data entry portal were designed. Demographic details, CDAI score at every visit, and detailed treatment plan. The data were merged and statistically analyzed by applying Wilcoxon sign rank test and Friedman 2-way analysis using SPSS version 20.

RESULTS AND DISCUSSION:

Out of total 763 patients, 84.53% (n=645) were female while 15.46% (n=118) were male.

Clinical Disease Activity Index

Clinical Disease Activity Index (CDAI) score helps to understand the severity of the patient's condition based on the number of joints affected due to rheumatoid arthritis. Fig 1 shows the score of the patients when they came for a consultation the very first time. Out of the total patients, 11.8% presented with low disease activity, 50.2% presented with moderate disease activity, and 37.7% presented with high disease activity. [Fig 1]



	n Male	n Female
Low Disease activity CDAI > 2.8 and <= 10	13	77
Moderate Disease Activity CDAI > 10 and <= 22	58	325
High Disease Activity CDAI > 22	45	243
Remission CDAI <= 2.8:	2	0

Fig 1: Severity of the disease based on CDAI score

Treatment plan and use of MTX in RA patients

Of the total 763 patients, 14.15% (n=108) patients were put on Methotrexate monotherapy while the remaining 85.85% (n=655) were given MTX in combination with other synthetic DMARDs like hydroxychloroquine (HCQ), sulfasalazine, leflunomide or iguratimod [Table 1].

Out of the 655 patients that were given combination therapy, 87.94% of patients were on MTX+HCQ treatment. The remaining were given MTX with synthetic DMARDs other than HCQ i.e. sulfasalazine, leflunomide, and iguratimod. In some cases, more than two DMARDs with given in combination.

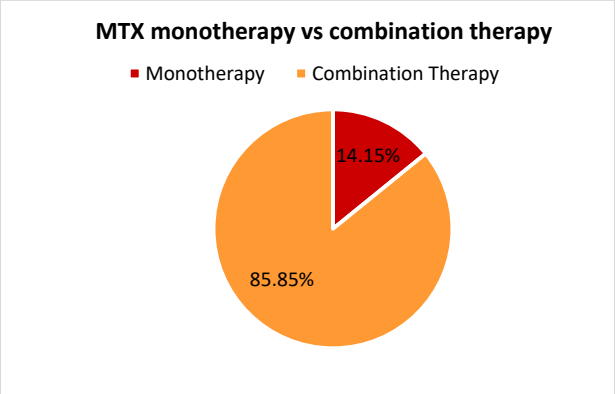


Table 1: Monotherapy vs Combinational therapy

Synthetic DMARDs (monotherapy)	Male		Female	
	n	%	n	%
Methotrexate	19	16.10 %	89	13.80%

Synthetic DMARDs (Dual therapy)	Male		Female	
	n	%	n	%
Methotrexate, HCQS	93	78.81%	483	74.88%
Methotrexate, Leflunomide	0	0%	3	0.46%
Methotrexate, Sulfasalazine	1	0.85%	7	1.08%
Methotrexate, Iguratimod	0	0%	12	1.86%

Synthetic DMARDS (Triple therapy)	Male		Female	
	n	%	n	%
Methotrexate, Sulfasalazine, HCQs	0	0%	11	1.70%
Methotrexate, Iguratimod, Leflunomide	0	0%	3	0.46%
Methotrexate, HCQs, Leflunomide	4	3.39%	12	1.86%
Methotrexate, HCQs, Iguratimod	1	0.85%	9	1.39%
Methotrexate, Sulfasalazine, Iguratimod	0	0%	4	0.62%

Synthetic DMARDS (quadruple therapy)	Male		Female	
	n	%	n	%
Methotrexate, HCQs, Iguratimod, Leflunomide	0	0%	6	0.93%
Methotrexate, Sulfasalazine, HCQs, Leflunomide	0	0%	2	0.31%
Methotrexate, Sulfasalazine, HCQs, Iguratimod	0	0%	1	0.15%

MTX is normally prescribed through oral tablets or subcutaneous injections. 57.1% of patients were given MTX through the oral route, 19.7% were given MTX through the subcutaneous route and 23.2% of patients were given MTX therapy that alternated both these routes. [Fig 2]

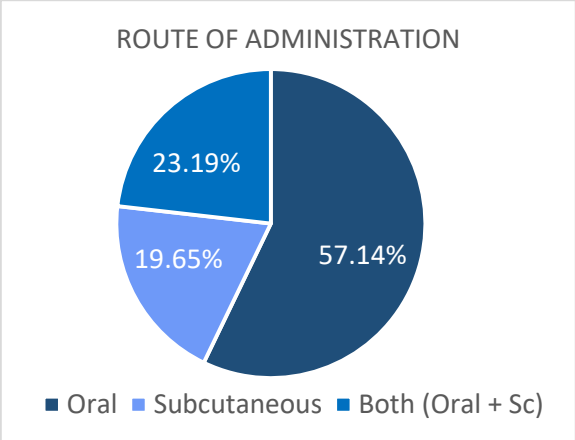


Fig 2: Preferred Route of administration for MTX

More than 70% of patients were started at 15mg/week. The patients with lower disease activity were given either 10mg/week or 7.5mg/week depending on the severity. [Table 2.1& 2.2]

Table 2.1: Starting dose of MTX

STARTING DOSE	Number of patients
10 mg	165
15mg	539
2.5 mg	1
20 mg	11
25 mg	1
5 mg	9
50 mg	6
7.5 mg	31

Table 2.2: Maintenance dose of MTX

MAINTENANCE DOSE	Number of patients
10 mg	158
15 mg	503
2.5 mg	2
20 mg	17
25 mg	1
5 mg	17
50 mg	2
7.5 mg	63

Efficacy of MTX monotherapy based on improvement in CDAI score.

The improvement in patient condition was assessed by comparing the CDAI score of patients when he/she first presented their CDAI score after one year and two years of therapy. Here the CDAI scores of patients on MTX monotherapy was taken and statistics were applied.

In patients with low disease activity, the Wilcoxon sign rank test was applied for 2 variables to compare the starting CDAI score with the CDAI score after 1 year. [Table 3.1] For both therapies, the p-value was </=0.001 which showed significant improvement in the patient's condition after 1 year.

In patients with moderate and high disease activity, Friedman's two-way analysis was applied for 3 variables to compare the starting CDAI score with the CDAI score after 1 year and 2 years. [Table 3.2, Table 3.3] For both the therapies, the p-value was <0.001 which showed significant improvement in the patient's condition after 2 years.

Table 3.1: Efficacy of MTX in Low Disease Activity

MTX in Low Disease Activity		
Mean of Starting CDAI	Mean of CDAI after 1 year	Significance
7.58 ± 1.74	4.54 ± 1.74	0.001

Table 3.2: Efficacy of MTX in Moderate Disease Activity

MTX in Moderate Disease Activity			
Mean of Starting CDAI	Mean of CDAI after 1 year	Mean of CDAI after 2 years	Significance
17.66 ± 2.42	11.73 ± 3.06	7.39 ± 3.07	<0.001

Table 3.3: Efficacy of MTX in High Disease Activity

MTX in High Disease Activity			
Mean of Starting CDAI	Mean of CDAI after 1 year	Mean of CDAI after 2 years	Significance
27.00 0 ± 5.82	19.55 ± 7.09	12.86 ± 6.93	<0.001

CONCLUSION

It was observed that about 85.85% of patients were given combination therapy of Methotrexate with other DMARDs while the remaining were given MTX monotherapy. Among the patients given combination therapy, 87.94% were given methotrexate in combination with hydroxychloroquine. When the CDAI scores of patients on MTX monotherapy and MTX+HCQ combination therapy after 1 year and 2 years were analyzed, it was concluded that there was no significant difference between the effectiveness of the two different therapies. Thus, it can be concluded that MTX is efficacious in the treatment of RA.

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