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Prescribing pattern and efficacy of DMARDs in rheumatoid arthritis in a tertiary care teaching hospital

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Abstract
Back ground: Rheumatoid arthritis (RA) is an autoimmune disease that associated with joint deformity and bears significant health care related expenses. Approximately 1% of the adult population is affected by this disease worldwide. The drug utilization studies form an important tool for the assessment of rational or irrational prescribing. Thus keeping this in view the prescribing pattern analysis in RA patients was done and efficacy of disease modified anti rheumatic drugs (DMARDs)s in RA was analyzed.
Methods: This potential observational study was carried out jointly by the department of pharmacology and rheumatology at IMS and SUM hospital for one year. A total of 132 RA diagnosed patients were included in the study. The diagnosis was made diagnosed according to ACR revised criteria of 2010.This is an observational longitudinal open level study.
Results: Total 132 patients of RA were followed up. Number of females were 103 (78%) which was higher than the number of male i.e. 29 (22%). 83 (63%) were found in the age group of 31-50 years, which is higher than other age groups i.e. 34 (26%) in 51-70 years age group and 15 (11%) in 18-30 years age group. After 3 months, 3 drug combinations was the most prescribed group i.e. 86(65.2%), followed by 4 drugs group i.e. 30(22.7%). After 6 months, 2 drugs combination was prescribed most i.e. 96(72.7%), followed by 3 drugs combination i.e. 27(20.5%). During initiation of the DMARDs therapy HCQ (Mono and in combination) was the most preferable drug i.e. 129(97.7%). MTX was prescribed to 109(82.6%) patients. Combination therapy was preferred than monotherapy in all three time period. For mono therapy HCQ was preferred than MTX. Differences in efficacy of various ARD groups showed significant difference from the baseline DAS28CRP score with 3 months, 6 months and 1 year DAS28CRP score ($P < 0.0001$).
Conclusion: DMARDs are the primary modality of treatment and needs prolonged therapy. Among the combinations used, HCQ and MTX plus PRED was the most commonly prescribed followed by combination of HCQ plus PRED in initiation of the therapy.

Keywords: Disease modifying anti-rheumatic drugs, Rheumatoid arthritis, ARDs

Introduction
Rheumatoid Arthritis (RA) treatment is historically difficult. F Dudley Hart (1976) said of RA "The treatment of a condition for which there is no positive cure makes much greater demands on the doctor, who has to be a practical pharmacologist, human being, psychiatrist, and father confessor- he has, in fact, to be a proper physician in the fullest sense of the word" [1]. RA is an autoimmune disease with high prevalence. Approximately 1% of the adult population is affected by this disease worldwide. About 0.75% of adult Indian se population is affected by the RA [2]. Generally the onset of the disease occurs in 30 to 55 year olds, in which women get affected more often. Hallmarks of this disease are synovium inflammation, advanced bone erosion, malalignment of joint, destruction, and subsequent weakness of surrounding tissues and muscles. Presentations varies from mild to severe. Though the characteristic patient has an advanced course leading to functional limitation [3].
With the aim of ending inflammation before the harm becomes permanent, it looks practical that treatment should start very rapidly after commencement of the disease [4]. Though there are no drugs yet to completely cure the condition, to provide symptomatic relief, decrease disease activity and disability, and to prevent radiological progression, DMARDs are used

[5, 6]. EULAR has recommended lately that the first treatment strategy for active RA should be Methotrexate. To decrease the pain & inflammation of joints NSAIDs are used. Glucocorticoids are used to retard the disease progression and joint damage and decrease inflammation in the treatment of RA [6, 7]. All of Anti Rheumatoid Drugs *(*ARDs) show significant adverse effects. Since the drugs do not belong to one particular pharmacological group it becomes imperative that a thorough watch on the adverse drug effects produced by the drugs themselves in the human body is to be frequently kept and investigated into [8]. The study of prescribing pattern and Adverse Drug Effects (ADE) monitoring is very essential to provide suitable modifications in prescribing practice, so that therapeutic benefits can be obtained to the maximum with minimal occurrence of ADE. There is a paucity of data on Efficacy ADE associated with ARDs in the Indian population. Hence, this study is planned to assess the prescription pattern and efficac*y* of ARDs in RA treatment and to study associated ADE.

Methods

The study was conducted between January 2017 and June 2018 in the department of Pharmacology and Rheumatology in IMS &SUM Hospital. A total of 132 patients of either sex in the age group of 18 years to 70 years attending the clinical Immunology OPD who were fulfilling the inclusion criteria were selected for the study. The inclusion criteria was age 18 years to 70 years, disease duration <1 year, classified as RA according to 2010 ACR criteria, DMARDs naïve patients as per the information presented in the outdoor on the visiting day, disease Activity Score (DAS28CRP) ≥ 3.2. The exclusion criteria were any co-existing terminal illness like malignancy, Chronic Liver Disease, Chronic Renal Failure, active Pulmonary Tuberculosis etc. Also Juvenile Rheumatoid Arthritis or Secondary Arthritis were excluded with other immunological or connective tissue disorders like SLE, MCTD.

This is an observational longitudinal open level study. Data were collected from the Outdoor during their visit to the outdoor. Within a period of one and half years, 132 patients *w*ere followed up for one year each and data taken.

Sample size was calculated using the formula:

$n = NX/[(N1)E2 +X]$ $X=Z(c/100)^2$ $r(100-1)$

$E = (N-n)/ n(N-1)$

N= population size, r = Fraction of response, $Z(c/100)$ = Critical value for confidence

All patients were interviewed with structured questionnaires (Proforma), prepared in the department of Immunology and Pharmacology, and that proforma was approved by IEC, IMS & SUM Hospital and Medical College. Prior to their inclusion into the study, written consent was taken. All measures are taken to protect the confidentiality of the patients and patient identity is held in strict confidence. The drugs prescribed for the RA were analyzed, by using drug utilization WHO indicators as drugs prescribed per prescription, drug formulations, fixed dose combinations (FDCs), drugs prescribed by brand names, drugs from national essential list of medicines 2015 were analyzed.

Result

Table 1 shows that total number of RA patients were 132. 103(78%) were females and 29 (22%) were males. Maximum number of RA patients 83(63%) were found in the age group of 31-50 years followed by 34(26%) in age group 51-70 and 15(11%) in age group 18-30 years. The number of female patients were higher in all age group in comparison to male patients. Table 1 also shows that the baseline parameters of the disease activity such as CRP level 54.5+45.8 (Mean+SD), HAQDI score 2.8+0.3 (Mean+SD) and DAS28CRP score 4.0+0.54 (Mean+SD).

Table 1: Demographic and disease activity related data

Demographic and Disease Activity Data		
No of Pts. (n)	132	
Males	29(22%)	
Females	103(78%)	
Age group of 18-30 years	Females (12)	Totals=15(11%)
	Males (3)	
Age group of 31-50 years	Females (69)	Total=83(63%)
	Males (14)	
Age group of 51-70 years	Females(22)	Total=34(26%)
	Males(12)	
Baseline DAS28CRP score (Mean ±SD)	4.0± 0.54	
Baseline CRP level (mg/l) (Mean ±SD)	54.5± 45.8	
Baseline HAQ-DI score (Mean ±SD)	2.8± 0.3	

Table 2: Pattern of Drug Combinations used (n=132)

Combination	**For 3 months**	**For 3m to 6 month**	**For 6m to 12 month**
Monotherapy			
MTX	-	-	2(1.5%)
HCQ	-	-	6(4.5%)
Dual Therapy			
MTX+HCQ	-	3(2.3%)	90(68.2%)
MTX+PRED	-	4(3%)	-
HCQ+PRED	1(0.8%)	9(6.8%)	6(4.5%)
Triple Therapy			
MTX+HCQ+PRED	3(2.2%)	86(65.2%)	27(20.5%)
MTX+HCQ+ETX	2(1.5%)		

MTX+PRED+ETX	3(2.3%)	-	-
HCQ+PRED+ETX	22(16.7%)	-	-
Quadruple Therapy			
MTX+HCQ+PRED+ETX	101(76.5%)	30(22.7%)	1(0.8%)

MTX-Methotrexate, HCQ-Hydroxychloroquine, Pred-Prednisolone, ETX-Eterocoxib

Table 2 shows pattern of drug combinations used during the treatment. Initial treatment with quadruple therapy of 2 DMARDS+PREDNISOLONE+ETEROCOXIB were used in most number of patients, i.e. 101(76.5%), followed by triple therapy i.e. 30(22.7%) and dual therapy i.e. 100.8%). After 3 months, triple therapy with 2 DMARDs+PRED were used most i.e. 86(65.2%), followed by quadruple therapy i.e. 30(22.7%) and dual therapy i.e. 16(12.1%). After 6 months, quadruple therapy was used in only 1(0.8%) case. Dual therapy with 2 DMARDS 90(68.2%) and 1 DMARDs+PRED 6(4.5%) were used most i.e. 96(72.7%), followed by triple therapy with 2 DMARDS+PRED i.e. 27 (20.5%). Monotherapy with 1 DMARDs were used in 8(6%) cases

Table 3: Prescription pattern of DMARDs (n=132):

DMARDs	For 3 month	For>3-6 month	For>6-12 month
MTX	3(2.3%)	4(3%)	2(1.5%)
HCQ	23(17.4%)	9(6.8%)	12(9.1%)
MTX+HCQ	106(80.3%)	119(90.2%)	118(89.4%)

MTX-Methotrexate, HCQ-Hydroxychloroquine

Table 3 shows that during initiation of the therapy most of the patients were with 2 DMARDs namely Methotrexate and Hydroxychloroquine i.e. 106(80.3%). Single DMARDs were prescribed for 26(19.7%) patients, out of which 23(17.4%) were on HCQ and 3(2.3%) were on MTX. After 3 months of therapy, most of the patients were on MTX+HCQ i.e. 119(90.2%), followed by HCQ İ.E. 9(6.8%) and MTX i.e. 4(3%). After 6 months, still MTX+HCQ combination therapy were prescribed for maximum number of patients i.e. 118(89.4%), followed by HCQ i.e. 12(9.1%) and MTX i.e. 2(1.5%).

Table 4: Efficacy assessment of ARDs by comparing the DAS28CRP score (Mean±SD) after 3,6,12 months with baseline:

ARDs (DMARDs, PRED)	DAS28CRP score (Mean±SD)			
	At baseline	After 3 months	After 6 months	After 12 months
MTX+PRED	5.6±0.18(n=3)	3.5±0.08(n=4)	2.4±0.49(n=4)	0
MTX+HCQ	5.4±0.13(n=2)	4.3±0.14(n=2)	2.6±0.55(n=3)	2.5±0.7(n=90)
MTX+HCQ+PRED	5.9±0.56(n=104)	3.9±0.53(n=104)	2.9±0.57(n=116)	2.6±0.72(n=27)
HCQ+PRED	5.9±0.54(n=23)	4.2±0.58(n=23)	2.6±0.62(n=9)	3.3±0.25(n=7)

MTX-Methotrexate, HCQ-Hydroxychloroquine, Pred-Prednisolone

Table 4 shows baseline DAS28CRP score for most of the patients were highest i.e. 5.9+0.56 and started with triple ARD İ.e. MTX+HCQ+PRED (n= 104), followed by 5.9+0.54 and started with HCQ+PRED (n= 23), 5.6+0.18 and started with MTX+PRED (n=3) and 5.4+0.13 and started with MTX+HCQ (n=2). After 3 months, the DAS28CRP score were decreased in each group i.e. 3.9+0.53 in MTX+HCQ+PRED, 4.2+0.58 in HCQ+PRED, 3.5+0.08 in MTX+PRED and 4.3+0.14 in MTX+HCQ group. After 6 months, the DAS28CRP score of each group were further decreased i.e. 2.9+0.57 in MTX+HCQ+PRED (n=116), 2.6+0.62 in HCQ+PRED (n=9), 2.4+0.49 in MTX+PRED (n=4) and 2.6+0.55 in MTX+HCQ (n=3) group. And after 12 months, all groups except HCQ+PRED group showed further decrease of DAS28CRP score i.e. 2.5+0.7 in MTX+HCQ (n= 90), 2.6+0.72 in MTX+HCQ+PRED (n= 27), 2.3+0.46 in HCQ (n= 6), 1.7+0.33 in MTX (n= 2). HCQ +PRED group (n= 7) showed increase of DAS28CRP score i.e. 3.3+0.25.

Table 5: Analysis of Adverse Drug Effects (n=25)

ADE	Number	Causative drug	Causality assessment	Severity assessment
Gastritis	7(28%)	PRED,ETX	Probable	Mild
Weight gain	3(12%)	PRED	Probable	Mild
Elevated liver enzymes	8(32%)	MTX	Probable	Severe
Aphthous ulcer	1(4%)	ETX,MTX	Possible	Mild
Retinopathy	1(4%)	HCQ	Probable	Severe
Anaemia	2(8%)	MTX	Possible	Moderate
Diarrhoea	1(4%)	HCQ	Possible	Moderate
Dermatitis	1(4%)	MTX	Possible	Mild
Alopecia	1(4%)	MTX	Probable	Mild

MTX-Methotrexate, HCQ-Hydroxychloroquine, Pred-Prednisolone, ETX-Eterocoxib

Table 5 shows causality and severity assessment of all adverse drug effects (ADE). Most of the cases of ADE were associated with MTX i.e. 13 (52%) cases, out of which 8 (32%) cases developed severe ADE like elevated liver enzymes. 2 patients on MTX developed anaemia which was moderate ADE and rest 3 cases were mild ADE i.e. aphthous ulcer, alopecia and dermatitis. HCQ therapy associated ADE was found in two (8%) cases i.e.

retinopathy and diarrhoea out of which retinopathy was severe ADE. Other ADE like gastritis (28%) and weight gain (12%) were associated with PRED. ETX was associated with gastritis (28%) and aphthous ulcer (4%).

Discussion

Drug utilization studies can actually analyze the recent trend of prescription pattern which will further help to identify the problems and provide feedback to prescribers. Hence awareness can be created about irrational use of the drugs. Defining drug prescription and utilization pattern provides advantageous feedback to the prescribers in order to improve the prescribing behavior [9].

In our study, total 132 patients of RA were followed up. Number of females were 103 (78%) higher than the number of male i.e. 29 (22%). which is similar to the previous study by Bajraktari IH *et al*. [10]. In the present study the most commonly affected age group was found 83 patients (63%) in the age group of 31-50 years, which is higher than other age groups i.e. 34 (26%) in 51-70 years age group and 15 (11%) in 18-30 years age group. Similar type of observation was found by Owino *et al*., the peak prevalence of RA was in age groups of 20-29 years and 40-49 years [11].

The number of anti-rheumatoid drugs used in the treatment of RA in this study shows that maximum number of patients had been given 3 drugs, but with varying combinations. So the patients received a minimum of 2 and maximum of 3 drugs to keep the symptoms at bay [12]. Steroids are drugs with potential side effects, but their use in low doses markedly improves patient function in RA [13]. This study almost confirms with the prescribing pattern of prednisolone. The adverse effects of prednisolone in this study was mostly gastritis and weight gain which are mild in nature. DMARDs are the pivotal prescriptions in case of RA. Castrejón I, *et al*. (2013) have reviewed that combination therapy with DMARDs is a preferred approach [14]. This study corroborates this finding in that double DMARDs were used in most of the cases. The type of combination therapies and the prescribing pattern in this study was in accordance with those of the Guidelines for the management of Rheumatoid Arthritis [70]. HCQ by various trials like HERA trial (1995) and studies by Alam MK *et al*. 2012, was found to be efficacious in cases of RA [15]. In this study, HCQ was the most frequently prescribed drug either alone or in combinations with MTX. The use of HCQ as the most common agent in this setup is justified by the finding that HCQ has serious ADE in least number of patients in contrast to the ADE of patients with MTX therapy which had required withdrawal of the drug (Table-5). But the combination of MTX and HCQ was undisputedly the most frequently prescribed combination in this study, which reiterates the findings of Gowde *et al*. (2013) [2]. Various authors like Castrejón I, *et al*. (2013), have repeatedly shown the efficacy and use of triple DMARDs combinations, but the present study shows that no patients received a triple DMARDs combination therapy. This may be due to the higher cost of drugs and side effect profile in the present setup and scenario [14].

Use of other DMARDs like Leflunomide, Sulphasalazine, Gold, D-penicillamine, cyclosporine, azathioprine and biological agents was not seen in this study though their efficacy in RA has been studied by various authors [17]. This is possibly due to serious ADRs with these drugs like 100% male sterility with alkylating agents [18], drug withdrawal in up to 30% with azathioprine [19], 50% toxicity with penicillamine use [20], more than half the patients having gastrointestinal intolerance with gold therapy etc. Approximately 81% of the patients carry on well with the ARD therapy while the rest 19% of the patients (25 cases) show some kind of non-serious or serious side effects which includes events like retinopathy, hepatic enzymes elevation and haematological disruption in 9% of patients who required withdrawal of the offending drug, while skin reactions, aphthous ulcer and gastrointestinal features were found in rest 10% of patients and are considered as minor risk factors.

Retinopathy was another limitation seen in DMARDs use mainly with HCQ. Prolonged therapy has been associated with fundal defects, reduced peripheral vision etc. Drug dose more than 400 mg/day have been shown to cause mild reversible retinopathy (Suarez-Almazor ME, *et al*. 2000) [21]. Current opinion favours HCQ as having the best safety profile [21]. This study data is consistent with these reports and HCQ was the most frequently prescribed drug. Though this case suffered from mild reduction of sensitivity and decreased field of vision, was advised to stop the medication and switch to alternate therapies to prevent further progression of retinopathy. Combination therapies in this study did show increased incidence of adverse effects profile in comparison to monotherapy. This suggests that along with ADE monitoring of monotherapy there is a need of more cautious and thorough ADE monitoring of multiple anti-rheumatoid drugs regimen.

Conclusion

In conclusion, RA is a disease of midlife. Age groups most commonly affected are 3 to 4 decade and females suffered in more numbers than the males. DMARDs are the primary modality of treatment and needs prolonged therapy. DMARDs aim at decreasing disease activity to prevent further damage to the joints and improve the quality of life. All anti-rheumatoid drugs and their combinations showed moderate to good response after therapy. Among the ARD combinations used, HCQ and MTX plus PRED was the most commonly prescribed ARD, followed by combination of HCQ plus PRED in initiation of the therapy. The study of prescription pattern is an important component of medical audit which helps in monitoring, evaluating and making necessary modifications in the prescribing practices to achieve a rational and cost effective medical care.

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