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Original Research Article

Prescribing pattern and adverse drug effects monitoring of anti-rheumatoid drugs in rheumatoid arthritis patients in a tertiary care hospital

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ABSTRACT

Background: Rheumatoid arthritis (RA) is a common disease that causes substantial morbidity in most patients and premature mortality in many. All the drugs used in the treatment of rheumatoid arthritis show significant toxicity and hence it is important to monitor the drugs for adverse drug reaction. This study will estimate the prescribing pattern and bring out the possible adverse drug reactions in patients with rheumatoid arthritis.
Methods: This study included 200 patients with rheumatoid arthritis who fulfilled the study criteria were observed for three months. Their prescriptions were collected and analysed. The symptoms of adverse drug reaction were documented through questionnaire. The causality assessment was done by WHO-UMC assessment scale and severity by using modified Hartwig-Seigel severity assessment scale.
Results: This study showed most of the patients were female (86%). Majority of them were in age group of 51-60 years. Average number of drugs per prescription was 10.57. Out of 200 patients, 2% were on single DMARD and 50.5% were on two DMARDs. 40% and 7.5% were taking three and four DMARDs respectively. A total of 450 adverse drug reactions were reported, out of which 68.4% due to steroid,12.5% due to DMARDs and 19.1 due to use of NSAIDs, DMARDs and glucocortisteroids. Chloroquine maculopathy occurred in 3 patients and elevated liver enzymes due to methotrexate in 3 patients, which necessitated DMARD withdrawal. Most patients had 1-3 ADRs. 6% of ADRs were severe and 54% belongs to probable category of causality assessment.
Conclusions: Treatment of rheumatoid arthritis is mainly based on DMARDs, glucocorticosteroids and NSAIDs. So, occurrence of ADR is much common. Proper monitoring of therapy and timely modification of drugs and lifestyle can reduce the ADR occurrence.

Keywords: Adverse drug reactions, Disease modifying anti-rheumatic drug, Glucocorticosteroid, Non-steroidal anti-inflammatory drug, Rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease associated with polyarthritis and dysfunction of joints.[1] RA affects about 1% of the world population and approximately 0.75% the adult Indian population.[2-4] It can occur at any age.[5] But the peak age of onset is more common in 4-5th decade. However, the prevalence of RA increases with age and it is more common in women than men in the ratio of 2:1[6]

The primary goal of treatment of rheumatoid arthritis should aim to reach clinical remission, to prevent structural damage and to provide improved quality of life in patients.[7] Disease modifying anti-rheumatic drugs

(DMARDs) are the first line agents used in the treatment for patient with established rheumatoid arthritis.[8] Current management emphasis the benefits of early disease modifying anti-rheumatic drugs (DMARDs). These agents are characterized by the ability to reduce or reverse the signs and symptoms, disability and improve quality.[9]

DMARDs are classified into biologic and non-biologic or synthetic DMARDs. The non-biologic agents include drugs like hydroxychloroquine, azathioprine, methotrexate, sulphasalazine, leflunomide, cyclophosphamide, gold salt. The biologic DMARDs includes abatacept, rituximab, tocilizumab and Tumor necrosis factor inhibitors.[10]

Non-steriodal anti-inflammatory drugs are used in the treatment of rheumatoid arthritis to reduce the pain and inflammation of joints, but they don't prevent the progression of disease activity.[11]

Low dose corticosteroids produce a prompt anti-inflammatory effect in rheumatoid arthritis and slow the rate of articular lesion. These often are used as a "bridge" to reduce disease activity until the slower acting DMARDs take effect or as adjunctive therapy for active disease that persists despite treatment with DMARDs. Higher doses are used to manage serious extra-articular manifestations. All patients receiving long term corticosteroid therapy should take measures to prevent osteoporosis.[12]

All the drugs used in the treatment of rheumatoid arthritis show significant toxicity and hence it is very important that their use require regular monitoring for adverse reactions. The present study is design to estimate the prescribing pattern and the occurrence of adverse drug reactions in patients with rheumatoid arthritis.

METHODS

It was a prospective observational study conducted from March 2018 to June 2018 in 200 patients attending Rheumatology OPD in Govt. Mohan Kumaramangalam Medical College Hospital, Salem, Tamilnadu. This study was started after getting Institutional Ethical committee approval. Written informed consent in local vernacular language was obtained from every patient included in the study at the time of enrollment. Patients diagnosed with established rheumatoid arthritis were enrolled in the study. The patients were followed up every week for a period of three months.

Demographic details, medication details and relevant lab investigation data were collected in a specially designed proforma. Prescription of the study patients collected and analysed. The medication details collected from the patients includes name of the drug or drug combination, dosage form, daily dosage, frequency, drugs prescribed by generic or brand name and all the co-prescribed drugs. Questionnaire was used for collecting ADR data (Annexure 1). Casual relationship of the adverse drug effects was done by establishing the temporal association of drug use with adverse drug reaction. Causality assessment was done by using WHO causality assessment scale and Severity assessment was done by using modified Hartwig and Siegel scale.

Data were entered in excel spreadsheet and descriptive statistics was used to analyse the data.

Inclusion criteria

- Age more than 20 years,
- Sex-both male and female patients with established rheumatoid arthritis,
- Patients who are taking anti-rheumatoid drugs for atleast three months,
- Patients who are willing to give informed consent.

Exclusion criteria

- Acute or chronic medical condition requiring hospitalization,
- Pre-existing hepatic or renal dysfunction,
- Pregnancy and lactation,
- Patient not willing to give informed consent.

RESULTS

Out of 429 patients screened, 200 patients met the study criteria were enrolled in the study. 86% of our study populations were females. Majority of the study population were in the age group of 51-60 years (Table 1). 36% of patients were in the age group of 51-60 years, 29% were in 41-50 years, 14% in 61-70 years, 13 % in 31-40%, 5% were less than 30 years and 3% of them were more than 70 years.

Table 1: Age-wise distribution of the patients.

Age group (years)	Number of patients	Percentage
<30	10	05%
31-40	26	13%
41-50	58	29%
51-60	72	36%
61-70	28	14%
>70	06	03%
total	200	100%

Majority of patients were taking two DMARDs (Table 2) and none of the them were on biologic DMARDs. The average number of drugs for prescription was 10.57. 100% were prescribed by generic names only. 2% (4) of them were taking single DMARD, 50.5% (101) were taking two DMARDs, 40% (80) were taking three DMARDs and 7.5% (15) were taking four DMARDs.

Among the DMARDs, hydroxychloroquine is the commonly prescribed drug in monotherapy and in

combination with other DMARDs (Table 3). The most common two drug combination used was hydroxychloroquine and methotrexate in 43.5% patients, 25% patients were prescribed triple drug therapy consisting of hydroxychloroquine +methotrexate+sulphasalazine and 4% patients received quadruple drug therapy containing hydroxychloroquine+methotrexate+sulphasalazine+azathioprine. NSAIDs and steroid are prescribed with DMARDs both in monotherapy as well as in combination therapy for suppression of pain.

Out of 200 patients, 165 patients have reported ADR with use of anti-rheumatoid drugs (Table 4). 82.5% patients reported ADR and 17.5 % patients were without ADR.

Table 2: Prescription analysis of rheumatoid arthritis patients.

Prescribing indicators	Results
Average number of drugs per prescription	10.57
% of drugs prescribed by generic name	100%
% of drugs prescribed by brand name	0%
Patients on single DMARD	4(2%)
Patients on two DMARDs	101(50.5%)
Patients on three DMARDs	80(40%)
Patients on four DMARDs	15(7.5%)

Table 3: Pattern of combinations of DMARDs.

Name of the combination	Numbers (%)
Hydroxychloroquine+Methotrexate	87 (43.5%)
Hydroxychloroquine+Azathioprine	5 (2.5%)
Hydroxychloroquine+Sulphasalazine	2 (1%)
Hydroxychloroquine+Leflunomide	1 (0.5%)
Methotrexate+Azathioprine	5 (2.5%)
Methotrexate+Sulphasalazine	1 (0.5%)
Total	101 (50.5%)
Hydroxychloroquine+Methotrexate+Azathioprine	9 (4.5%)
Hydroxychloroquine+Methotrexate+Sulphasalazine	50 (25%)
Hydroxychloroquine+Methotrexate+Leflunomide	19 (9.5%)
Hydroxychloroquine+Azathioprine+Sulphasalazine	1 (0.5%)
Methotrexate+Azathioprine+Leflunomide	1 (0.5%)
Total	80 (40%)
Hydroxychloroquine+Methotrexate+Azathioprine+Sulphasalazine	8 (4%)
Hydroxychloroquine+Methotrexate+Azathioprine+Leflunomide	3 (1.5%)
Hydroxychloroquine+Methotrexate+Sulphasalazine+Leflunomide	4 (2%)
Total	15 (7.5%)

Table 4: Occurrence of adverse drug reactions.

Patients with or without ADR	Number of patients	Percentage
Patient with ADR	165	82.5%
Patients without ADR	35	17.5%
total	200	100%

A total of 450 adverse drug reaction reports were obtained from 200 patients in this study. Among these, 19.7% were due to insomnia caused by steroid and the second common adverse drug reaction was gastritis which occurred in 18.2% of patient caused by steroid and NSAIDs (Table 5). 19.7% patients had insomnia, 18.2% had gastritis, 16.7% had palpitation, 15.8% had cushingoid features, 9.6% had skin rashes, 8.0% had hypertension, 5.1% had hyperglycemia, 3.1% had presenile cataract, 1.5% had hyperpigmentation, 0.7% had asthma, maculopathy, elevated liver enzymes and 0.2% had aphthous ulcer.

A 26.7% of patients had three ADRs and 20.4% had four ADRs (Table 6). 26.7% patients have three ADRs, 20.4% patients have four ADRs, 18.9% had five ADRs, 16.9% had two ADRs, 9.1% had one ADR and 8.0% patients had six ADRs.

A 63.6% of ADR belongs to mild category of Modified Hartwig and Siegel scale (Table 7). 63.6% patients were mild, 35.1% were moderate and 1.3% were severe category of Modified Hartwig and Siegel scale.

A 54% of ADRs belongs to probable category of causality assessment (Table 8). 46% belongs to possible and 54% belongs to probable and 0% belongs to certain category of causality assessment.

Table 5: Pattern of ADR in patients taking anti-rheumatoid drugs.

Name of the ADR	Number of patients	Percentage (%)	Causative drug	Assessment category
Cushingoid features	71	15.8%	Steroid	Probable
Gastritis	82	18.2%	Steroid+NSAIDs	Probable
Asthma	3	0.7%	NSAIDs	Possible
Hyperpigmentation	7	1.5%	Chloroquine	Possible
Aphthous ulcer	1	0.2%	NSAIDs, DMARDs	Possible
Presenile cataract	14	3.1%	Steroid	Possible
Skin rashes	43	9.6%	DMARDs	Possible
Insomnia	89	19.7%	Steroid	Possible
Palpitation	75	16.7%	Steroid	Possible
Hypertension	36	8.0%	Steroid	Probable
Hyperglycemia	23	5.1%	Steroid	Probable
Maculopathy	03	0.7%	Chloroquine	Probable
Elevated liver enzymes	03	0.7%	Methotrexate	Probable
Total	450	100%		

Table 6: Distribution of ADRs.

Number of ADRs in a Patients	Number of Patient	Total number of ADRs	Percentage (%)
1	41	41	9.1%
2	38	76	16.9%
3	40	120	26.7%
4	23	92	20.4%
5	17	85	18.9%
6	06	36	8.0%
Total	165	450	100%

Table 7: Severity assessment of ADRs.

Assessment category	Number of ADRs	Percentage (%)
Mild	286	63.6%
Moderate	158	35.1%
Severe	6	1.3%
Total	450	100%

Table 8: Causality assessment of ADRs.

Assessment Category	Number of ADRs	Percentage (%)
Certain	0	0
Probable	243	54.0%
Possible	207	46.0%
Total	450	100%

DISCUSSION

Rheumatoid arthritis is a chronic auto immune inflammatory illness characterized by polyarthritis of small and large joints which in the course of time may progress to disability.[13] Treatment with disease modifying anti rheumatoid drug (DMARD) plays a pivotal role in the management of rheumatoid arthritis.[14]

The study of prescribing pattern and adverse drug reaction monitoring is very essential to provide suitable modifications in prescribing practice so that maximum therapeutic benefits will be obtained with minimal occurrence of adverse drug reaction.[15]

In this study, 200 patients were evaluated for the prescription pattern and adverse drug reaction. Our study revealed that prevalence of Rheumatoid Arthritis was more in female patients 172 (86%) than male patients. Recent study conducted by Mittal et al in india has reported that more than 80% of the RA patients were females, in agreement with our study.[16] The ratio of the disease among female: male is 6.14:1which is similar to

the study conducted by Owino et al.[17] This higher ratio can be attributed to the hormonal difference between female and male patients.

The average number of drugs per prescription was 10.57. This is high when compared to the study done by Gawde et al were the average number of drugs per prescription was found to be 6.17 in Mumbai.[18] As the study was done in government medical college hospital, all the drugs were prescribed by generic name and only non-biologic DMARDs were prescribed to the patients due to the non-availability of biologic DMARDs in the institution.

The overall drug usage describes that two DMARDs (50.5%) was used in majority of the patients. This is comparable to the study by Kashefi et al, were majority of the patients were on two DMARDs (52.3%).[19] The most frequently prescribed DMARDs combination was methotrexate and hydroxychloroquine (43.5%). According to the ACR 2015 guidelines to treat rheumatoid arthritis recommends that regardless of the disease activity level, combination therapy can be started only when the disease activity remains high in spite of the monotherapy.[8] Glucocorticoids and NSAIDs were widely used in addition to DMARDs in the study. Drugs like ranitidine, omeprazole, antacid, folic acid, iron, calcium, vitamins and bisphosphonates were given in addition to the standard drugs to manage the adverse drug reaction.

Total of 450 adverse drug reactions were reported in our study. Many patients had 1-3 ADRs. The most common adverse drug reaction is insomnia due to use of steroids. It is followed by gastritis due to use of NSAIDs and steroids. The most serious adverse reaction which was irreversible and required drug withdrawal was chloroquine maculopathy which occurred in 3 patients. The other reaction that required drug withdrawal was elevated liver enzymes due to methotrexate occurred in 3 patients. These results were less compared to adverse drug reaction study done by Machodo et al.[20]

On assessing severity score, 63.6% of ADR were only mild in nature, 35.1% were moderate and 1.3 % were severe. WHO causality assessment of ADR was done and found that 54% belongs to probable and 46% belongs to possible category of assessment.

CONCLUSION

Occurrence of ADR is much common in patients treated for rheumatoid arthritis especially in those associated with Disease modifying anti-rheumatic arthritis drugs. But with proper monitoring and timely modification of drugs and lifestyle, we can reduce the risk in these patients.

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Annexure 1: Study questionnaire.

Name			
Age /Sex			
Address			
Duration of the disease			
Other concomitant drug intake	Yes/No		
Do you have the following symptoms?			
1) Cushingoid features	O Yes	O No	O don't Know
2) Gastritis	O Yes	O No	O don't Know
3) Asthma exacerbation	O Yes	O No	O don't Know
4) Hyperpigmentation	O Yes	O No	O don't Know
5) Aphthous ulcer	O Yes	O No	O don't Know
6) Presenile cataract	O Yes	O No	O don't Know
7) Skin rashes	O Yes	O No	O don't Know
8) Insomnia	O Yes	O No	O don't Know
9) Palpitation	O Yes	O No	O don't Know
By examination and lab Investigations			
1) Hypertension	O Yes	O No	
2) Hyperglycemia	O Yes	O No	
3) Maculopathy	O Yes	O No	
4) Elevated liver enzymes	O Yes	O No	