

Original Research Article

Prescription audit of rheumatoid arthritis patients treated at primary and secondary care level, before reaching a tertiary care centre hospital in Eastern India

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ABSTRACT

Background: To analyse the usage pattern of pharmacological agents in the treatment of rheumatoid arthritis in Eastern India at a community level before reaching a specialized rheumatology clinic.

Methods: Total 200 patients earlier diagnosed to be RA on treatment were selected and their demographic details, duration of treatment, agents prescribed, adverse drug reactions (ADRs) were analysed.

Results: At the end of the study analysis, we observed that HCQ (24.4%) and Sulphasalazine (20.9%) were the commonest disease modifying anti-rheumatoid drug (csDMARD) used, followed by Methotrexate (16.9%). Dual combination csDMARD (33.1%) was preferred. Biological therapy was a rarity (0.5%). Steroids (21.0%) and NSAIDs (22.5%) was commonly used. Complementary and Alternative Medicines (CAM) (44.0%) was used often. Polypharmacy was the trend. Not all patients diagnosed as RA met the 2010 ACR/EULAR classification criteria of RA.

Conclusions: In 15% patients, the diagnosis of RA was inappropriate according to the recent classification criteria. csDMARD was preferred either as monotherapy or combination therapy. Use of steroids and NSAID was a common practice. ADR were mild in severity.

Keywords: Prescription audit, Rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic illness in which immunologically mediated inflammation of synovial-lined joints can result in marked disruption of joint structure and function.¹ It involves flares and remissions, flares being characterised by pain.² Uncontrolled RA is associated with joint deformity and significant health care related expenses.³ The prevalence of RA in adult population in India is approximately 0.75%.⁴

Lack of adequate manpower and training facilities, staggering costs of therapy and unique problems like burden of infectious diseases, challenges adequate management of rheumatic diseases in this country.⁵ In India, like many other developing countries, the diagnosis and management of most RA patients are primarily done by family physicians, orthopaedic specialists and practitioners of alternative medicines.

This prescription audit was undertaken to assess the demographic profile of RA in this part of the country, the current treatment pattern of RA in the community as rendered by primary and/or secondary physicians and other practitioners of alternative medicine and also to assess whether the diagnosis of RA are in accordance to the 2010 ACR/EULAR classification criteria.¹³

The current standard therapy for RA is disease-modifying anti rheumatic drugs (DMARD) therapy along with anti-inflammatory therapy using non-steroidal anti-inflammatory drugs (NSAIDs).⁶ The 2012 American College of Rheumatology guidelines for the treatment of RA advocates early initiation and aggressive use of DMARDs in patients with RA.⁷ The use of csDMARDs and other drugs for RA are associated with a number of adverse drug reactions (ADRs). Of major concern, is the cost of therapy of such chronic diseases like RA. Newer agents like biological disease-modifying anti rheumatic drugs that provide rapid relief of symptoms of pain and disability in RA have been approved. However, such therapies have prohibitive costs that curtails widespread usage, and hence affects treatment outcomes.⁸

Complementary and alternative medicine (CAM) is frequently used by patients with RA both in western countries as well as in developing countries such as India.⁹ In addition, the ADRs and drug-drug interactions with CAM and the mainstream medicines remain largely unknown.⁹ The ADR associated with these regimes, as reflected in the prescriptions studied, were also taken into consideration.

METHODS

The prescription audit was conducted in the rheumatology clinic at KPC Medical College and Hospital for a period of 6 months from April 2019 to October 2019, after approval from the Institute's Ethical Committee.

Diagnosed RA patients attending the rheumatology clinic for the first time were enrolled. Participation was voluntary. A total of 200 patients were enrolled in the audit as per the inclusion criteria after taking written and verbal consent.

Inclusion criteria

- Diagnosed adult patients of RA of either sexes
- Treated for at least 6 months by primary and secondary care givers and carrying all their prescriptions
- Never before treated by specialist in rheumatology practice
- Willing to participate in the audit after giving written consent

Exclusion criteria

- Patients having associated psychiatric ailments
- Patients requiring hospitalisation in last 6 months
- Patients having diabetes as a comorbidity
- Pregnancy
- Children below the age of 14 years

Study design

Following details were recorded from each prescription: (1) patient's demographic profile, (2) details about the disease, (3) concomitant illnesses, (4) treatment details, (5) ADR as documented in the prescriptions

To study the prescription pattern, following prescribing indicators were used: (1) average number of drugs per encounter; (2) percentage of drugs with injectables prescribed; (3) percentage (%) of drugs prescribed from the WHO list of Essential Medicines, 2019.¹⁰ Leflunomide, though not in the WHO list of Essential medicine, was taken into consideration as it is a standard csDMARD used in RA.

ADRs, as recorded in the prescriptions were noted using the Central Drugs Standard Control Organisation ADR performa.¹¹ Causality assessment for the ADRs was performed as per the WHO Collaborating Centre for International Drug Monitoring assessment Uppsala Monitoring Centre (WHO-UMC) Scale.^{12,13}

ADRs were graded as mild, moderate, severe, and severe life-threatening as follows: (1) Mild - transient or mild discomfort; no limitation in activity; no medical intervention/therapy required. (2) Moderate - limitation in physical activity; some assistance may be needed for normal activity; no or minimal medical intervention/therapy required. (3) Severe - marked limitation in physical activity; some assistance usually required; medical intervention/therapy required, hospitalisation possible. (4) Severe life-threatening - extreme limitation in physical activity; significant assistance required; significant medical intervention/therapy required, hospitalisation necessary. The usage of CAM was assessed. Patients were asked about the type and duration of CAM usage as this is usually not recorded in the prescription.

RESULTS

A total of 200 previously diagnosed RA patients with their previous medical documents, meeting the inclusion and exclusion criterion, were included in the audit. Of them, 161 (80.5%) patients were females and 39 (19.5%) were males. The mean age of the female and male subjects was 31.7 and 46.5 years respectively (Table 1).

Table 1: Demographic details.

No of patients (n)	200
Male	n= 39 (19.5%)
Female	n=161 (80.5%)
Mean age male (Yrs) [n=39]	46.5
Mean age female (Yrs) [n=161]	31.7

The median time interval from the diagnosis to the first contact with a specialist rheumatology clinic was found to be 5.11 years and 4.89 years in case of male and female subset respectively (Table 2).

Table 2: Median time interval before attending a specialist clinic.

Male RA (n=39)	5.11 yrs
Female RA (n=161)	4.89 yrs

Table 3: Diagnosis meeting ACR/EULAR criteria.

Diagnosed before reaching rheumatology clinic	Diagnosis revised on reaching rheumatology clinic
Male (n=39)	n=28 (71.8%)
Female (n=161)	n=142 (87.6%)

Table 4: Analysis of prescriptions as per drugs prescribed.

	Male (n=39)	Female (n=161)
Average number of drugs prescribed for arthritis	4.8 (\pm 2.18)	6.3 (\pm 2.03)
Prescriptions containing injectables	3 (7.7%)	7 (4.3%)
Prescriptions containing Steroids	11 (28%)	31 (19.3%)
Prescriptions containing csDMARDs	26 (66.7%)	146 (90.7%)
Prescriptions containing NSAIDs	14 (35.9%)	31 (19.3%)
Prescriptions containing CAMs (other than Calcium)	19 (48.7%)	69 (42.8%)
Prescriptions containing bDMARDs (oral/injectables)	0 (0.0%)	1 (0.6%)

Table 5: Analysis of prescriptions as per starting of csDMARD.

	Male (n=39)	Female (n=161)
Prescriptions where csDMARD started by family physician	11 (28.2%)	79 (49.1%)
Prescriptions where csDMARD started by orthopedic specialist	12 (30.7%)	52 (32.31%)
Prescriptions where csDMARD started by RMP	3 (7.7%)	15 (9.3%)

Table 6: Disease-modifying anti rheumatic drugs (csDMARD) in prescriptions.

Monotherapy with csDMARDs	Number (% of individual drug amongst total csDMARDs use)
HCQ	42 (24.4%)
Sulphasalazine	36 (20.9%)
MTX	29 (16.9%)
Leflunomide	0 (0.0%)
Dual Combination csDMARDs	
MTX with HCQ	18 (10.5%)
HCQ with Sulphasalazine	17(9.9%)
MTX with Leflunomide	3 (1.7%)
HCQ with Sulphasalazine	19 (11.0%)
HCQ with Leflunomide	1 (0.5%)
Sulphasalazine with Leflunomide	0 (0.0%)
Triple or more Combination csDMARDs	7 (4.0%)

Of the 200 pre diagnosed RA patients included in the study only 71.8% males and 87.6% females fulfilled the diagnostic criteria of RA according to 2010

ACR/EULAR classification criteria (Table 3). The average number of drugs per prescription was 4.8 in males and 6.3 in females. Of all the drugs prescribed,

csDMARDs, the mainstay of treatment in RA was 90.7% in females to 66.7% in males. NSAID was prescribed in 35.9% in males and 19.3% in females. Steroids was used in 28% of males and 19.3% of females. CAMs was prescribed in 48.7% and 42.9% of males and females in this study analysis. Oral biologics was prescribed only in 1 female patient. Injectable medication was given to 7.7% and 4.3% of male and female patients respectively. (Table 4).

The csDMARDs prescribed were started by Family physicians in 28.2% of males and 49.1% of females and by Orthopaedic specialist in 30.7% and 32.3% of males and females respectively. In only 7-9% of the patients these csDMARDs were started by Registered Medical Practitioners (RMPs) (Table 5).

Table 7: Various combination therapy.

Various combination therapy	
csDMARD combination only	25
csDMARD + NSAID	31
csDMARD + steroid	17
csDMARD + NSAID + steroid	28
csDMARD + CAM	24
csDMARD + CAM + NSAID	25
csDMARD + CAM + NSAID + steroid	4
CAM + NSAID	26
CAM + steroid	9
NSAID + steroid	16

In 62.2% of the patients csDMARD was started as a monotherapy (HCQ being the commonest with 24.4%, followed by Sulphasalazine (20.9%) and Methotrexate (16.9%). In 33.1% patients dual csDMARDs were given and 4% received triple combination of csDMARDs (Table 6). Leflunomide, though a recommended csDMARD, was not started as csDMARDs were used with and without other agents like steroids, NSAIDs or CAMs (Table 7).

Table 8: Complementary and alternative medicine used by study patients.

System of medicine	No. of patient (%)	ADR
Ayurveda	41 (20.5%)	Not known
Homeopathy	37 (17.5%)	Not known
Unani	6 (3.0%)	Not known
Combination	4 (2.0%)	Not known

In our study, we found CAMs was used in 88 patients in combination with csDMARD, steroids or NSAID (Table 6). Of the CAM users found in the study, 20.5% used Ayurveda, 17.5% used Homeopathy, 3% Unani and 2% combination (Table 8).

Adverse drug reactions (ADR) were noted in some patients with the commonest being nausea and vomiting in 22%. Mucositis, drug rash, bone marrow suppression though rare was found in 3%, 2.5% and 4.5% of cases respectively (Table 9). These were from the prescriptions during the first visit. None of the ADR were severe enough necessitating hospitalisation. In the audited prescription the offending drugs were discontinued in most cases. The casualty assessment as was done according to the WHO-UCM casualty assessment scale showed the ADR to be "Probable" in 3 patients, "Possible" in 11 patients and "Unlikely" in rest cases.

Table 9: Adverse drug reactions and their incidence.

ADR	Incidence
Nausea, vomiting	44 (22%)
Epigastric pain	31 (15.5%)
Headache	8 (4.0%)
Constipation	9 (4.5%)
Diarrhoea	11 (5.5%)
Deranged liver functions	29 (14.9%)
Oral ulcer, mucositis	6 (3.0%)
Skin rashes	5 (2.5%)
Bone marrow suppression (minor or major)	9 (4.5%)

DISCUSSION

The findings of the prescription audit conducted in our Tertiary Care Hospital, Kolkata, provide an insight into the primary and secondary level care rendered to RA patients in the community before being evaluated by specialist in a tertiary care rheumatology clinic. The demographic profile, prescription trend, and ADRs were also studied. Majority of the patients were middle aged females. RA is one of the many chronic inflammatory diseases that predominate in females.³ The prevalence is about 2.5 times higher in females than males.³ Our study also showed a considerable female predominance of RA (80.5%). Another study conducted by Mittal et al. in India reported more than 80% of the RA patients to be females, which is in agreement with our study.¹⁴ The average number of drugs per prescription was found to be 4.8 in male and 6.3 in female, which is more than the WHO recommendations.¹⁴ It has been recommended that the number of drugs prescribed per prescription should be two and that justification for prescribing more than two drugs would be required because of the increased risk of drug interactions.¹⁵

Of the pre-diagnosed cases of RA in our study group, only 71.8% of males and 87.6% of females fulfilled the diagnostic criteria of RA according to the "2010 American College of Rheumatology/European League Against Rheumatism Classification Criteria for RA" at

the time of initial presentation.¹⁶ Earlier the 1987 ACR criteria for diagnosis of RA was followed, which was more stringent compared to the newer 2010 ACR/EULAR criteria.¹⁷ This clearly shows that RA is over diagnosed in our cohort, though patient memory bias during the questionnaire / interview based recall needs consideration.

In our audit HCQ (24.4%) was the commonest csDMARD used in the community followed by Sulphasalazine (20.9%), instead of methotrexate (16.9%) which is the csDMARD of the choice according to ACR and EULAR recommendations. ACR 2008 Task Force Panel (TFP) recommended Methotrexate as the first-line treatment in patients with active RA, unless contraindicated or not tolerated.¹⁸ Leflunomide may be used as an alternative to methotrexate, although gastrointestinal adverse effects are more common. Sulfasalazine or hydroxychloroquine is recommended as monotherapy in patients with low disease activity or without poor prognostic features (e.g., seronegative, nonerosive RA).¹⁹ These recommendations were often not followed in the prescriptions by the primary and secondary level caregivers.

Approximately 7% patients were on combination csDMARDs with 3 drugs and 33.6% on dual csDMARDs using permutation and combinations of MTX, sulfasalazine, and hydroxychloroquine. Various meta-analysis and recommendations shows that combination therapy with two or more csDMARDs is more effective than monotherapy, however, adverse effects may also be greater.²⁰ Yet in this study cohort monotherapy with csDMARD (62.2%) was widely used compared to combination csDMARDs.

In another Indian study by Sukhpreet et al it was found that combination of two csDMARDs was commonly prescribed and the study by Shini et al reported that majority of the patients were on single csDMARD.^{21,22}

The variation in number of csDMARDs prescribed might be due to the varied severity of disease encountered in different communities. Leflunomide, though a recommended csDMARD after MTX, was not generally used in the study group patients.

The reason behind the underusage might be because of its ADR profile and lack of proper knowledge regarding the subsequent routine monitoring parameters at the primary and secondary care level. csDMARD was prescribed in 45% of cases by primary family physicians and 32% by orthopaedic specialists, compared to only 9% by RMPs, though csDMARDs/bDMARDs are the mainstay of treatment in RA patients according to all recommendations.¹⁸ Delay in treat-to-target therapy with

DMARDs in RA only increases joint destructions, mortality and long term mobility.¹⁸

Use of steroids (28%: 19.3%::M:F) and NSAID (35.9% : 19.3% :: M:F) was reported in these patients prior to attending the tertiary rheumatology clinic. Ideally, NSAIDs and corticosteroids are used only for short-term management.²³ Long term used of steroids and NSAID only increases the side-effects associated with these agents.^{18,6,7} Usually with judicious use of csDMARDs the usage of NSAIDs and steroids can be minimised.⁶

Calcium and Vitamin D3 supplements and PPI were also present in a significant number of prescriptions. Though they are not as a part of the regular recommendations of ACR or EULAR guidelines, these agents were probably given to prevent ADRs such as epigastric pain or to manage steroid-associated osteoporosis. Folic acid was co-prescribed to prevent methotrexate associated toxicity.

ADRs were reported from a significant number of patients. However, majority of the ADRs were mild in nature and did not require any significant intervention. Overall the use of too many drugs in a prescription only leads to increased chance of drug-to-drug interaction, loss of efficacy, leading to non-compliance from the patient perspective.¹⁶

Biological agents (anti-TNF, anti-CD20, anti-T-cells, etc) approved for treatment of RA were neither prescribed nor administered to our study group of patients before they attended the tertiary rheumatology clinic.

Only one patient received oral JAK inhibitor Tofacitinib. The reason might be because of the high cost of biological therapy and lack of expertise regarding the use of these newer molecules by the treating physicians at the primary and secondary care level.

The usage of CAM was relatively low in the study population. However, no ADRs were recorded from the use of these agents as per the data obtained from screening the prescriptions. Nevertheless no one can be certain of their contribution to drug-to-drug interactions with the csDMARDs and other drugs used resulting in consequent ADRs.

The recent recommendations and guidelines for treatment on rheumatological diseases needs widespread circulation amongst the primary and secondary care givers and only then the RA patients in the community will be benefited at large.

CONCLUSION

In this cohort of pre-diagnosed RA patients, not all fulfilled the classification criteria of RA. According to

our prescription audit, significantly higher number of drugs per prescription was used. Treatment of RA was found to be primarily based on csDMARDs, though not prescribed to all patients of RA, ignoring the present recommendation. The concomitant use of multiple csDMARDs was prescribed, though monotherapy with csDMARD was more frequently used. MTX, the mostly recommended drug for RA, was not used in most patients. Use of steroids and NSAID though recommended only for short term use, was used on long term basis in our cohort of RA patients. ADRs reported were generally mild in nature. CAM usage was relatively low in the study population. Usage of biological agents for the treatment of RA was negligible.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee of K.P.C. Medical College

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