Original Article

Evaluation of prescription practices in rheumatoid arthritis at the rheumatology clinic in a tertiary care teaching hospital in Uttarakhand: A cross-sectional study

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Abstract

Objective: This study was aimed to analyze the prescription pattern of disease modifying anti-rheumatic drug (DMARD) therapy in patients with rheumatoid arthritis (RA) in a tertiary care teaching hospital in Uttarakhand, India. **Methodology:** This cross-sectional study was conducted in 150 RA patients who were given DMARD therapy. Patient's demographic details, drugs prescribed with their dosage and administration routes and the usage of complementary and alternative medicine (CAM) therapy were recorded to study the prescription pattern. **Results:** Overall, 4 DMARDs were prescribed in all the studied patients: Methotrexate (n = 150), hydroxychloroquine (n = 35), leflunomide (n = 5), and adalimumab (n = 1). Single DMARD therapy with methotrexate was prescribed to 110 (73.3%) followed by double therapy with methotrexate + hydroxychloroquine in 35 (23.3%), triple therapy (methotrexate + hydroxychloroquine + leflunomide) in 4 (2.7%) and triple therapy with biological DMARD (methotrexate + hydroxychloroquine + leflunomide + adalimumab) in 1 (0.7%) patient. Adjuvant therapy drugs included: Prednisolone (n = 150), folic acid (n = 150), naproxen (n = 150), calcium (n = 150), vitamin D (n = 150) and indomethacin (n = 40). Of the total, 61.4% patients also took complimentary alternative medicine (CAM) therapy. **Conclusion:** Our study concludes that the most commonly prescribed DMARDs in our setting, to patients of RA, in descending order of frequency were methotrexate, followed by hydroxychloroquine, leflunomide and lastly adalimumab. A total of five adjuvant medications were commonly prescribed to all patients. There was a high prevalence of self-medicated CAM therapy in the majority of these patients.

Keywords: CAM, complimentary alternative medicine therapy, disease modifying anti-rheumatic drug (DMARDs), drug utilization study in RA, prescription pattern, RA, rheumatoid arthritis therapy

Introduction

Rheumatoid Arthritis (RA) is a chronic debilitating systemic inflammatory condition, whose cause remains elusive, with the dominant manifestation marked by a symmetric, additive erosive polyarthritis involving the small and large synovial joints apart from other systemic features. Erosive arthritis with resulting deformities add to the disability and poor quality of life of these patients, with a high mortality related to accelerated atherosclerosis associated with this prolonged inflammatory state. There has been rapid progress in the treatment for RA over the last couple of decades, with newer understanding of its pathogenesis and the development of targeted therapy in the form of monoclonal antibodies against cytokines and their receptors, and newer small molecule inhibitors targeting intracellular cytokine pathways, which is a huge expansion

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to our armamentarium. The exact sequence of use of our armamentarium is not clear, with methotrexate (MTX) being in the frontline, with all comparisons of newer drugs made to this gold standard of therapy for RA.

The American College of Rheumatology (ACR) in 2015, had released guidelines on the management of RA, including the use of conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs), biologics (bDMARDs), targeted synthetic DMARDs (tsDMARDs), and glucocorticoids (GCs) in early as well as in established disease. Methotrexate (MTX) is primary agent for management of RA, unless contraindications exist, and if the treatment response is unsatisfactory, as perceived by the disease activity scores (DAS28) after an adequate trial, then additional therapy with two or three csDMARDs is attempted. If triple therapy fails, then, bDMARDs are prescribed. Glucocorticoids may be given as adjuvant bridge therapy, until the action of the initial DMARD has started.[1]

Traditional conventional synthetic DMARDs (csDMARDs) like methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ), leflunomide (Lef) are the main drugs currently being used in the management of RA worldwide, particularly in developing countries like India, where the majority of the population cannot afford biologics, and the lack of a federal health insurance policy in place. Biologic DMARDs available for use in India include anti-TNF agents (etanercept, infliximab, adalimumab, golimumab), anti-B cell therapy rituximab, anti-IL-6 tocilizumab and co-stimulation blockade abatacept.[2] Drug utilization studies analyze the current trends of prescribing pattern which can detect irrational use and provide feedback to clinicians, thereby increasing awareness in order to improve the prescribing behaviour.[3]

This study was conducted in tertiary care hospital of Uttarakhand region of India, with an aim to audit the drug prescribing patterns, and assess drug utilization in patients of RA which may help refining therapy.

Methods

This cross sectional study was conducted by the department of Pharmacology, over a period of 12 months, after taking requisite approval from the Institutional Research and Ethics Committee (Date of approval – 04-01-2018/Reference number – AIIMS/IEC/18/160). Subjects included 150 patients with RA, fulfilling the 2010 ACR/EULAR Classification Criteria of RA, presenting to the Rheumatology OPD, after obtaining a written informed consent. Patients of arthritis due to other causes like polymyalgia rheumatica, vasculitis, spondyloarthropathies, bacterial arthritis, fibromyalgia were excluded from the study. The case record forms included demographic data, relevant medical history, including complementary alternative medicine (CAM) therapy, and co-morbidities. The prescription pattern was analyzed using the following indicators: Percentage (%) of drugs prescribed, average number of drugs received by the patient, percentage of drugs given parenterally/orally. The usage of CAM was assessed by interviewing the patient.

Results

The demographic details are shown in Table 1. Of the 150 subjects interviewed, with a median age of 48 years (range 19-72 years), 21 (14%) and 129 (86%) were males and females, respectively. With regards to co-morbidities, 12.6% had osteoarthritis, 7.3% had diabetes mellitus type 2 (DM type 2), 6.7% had hypertension (HTN), 3.3% had both DM type 2 and HTN, 4% had gastroesophageal reflux disease (GERD), while 66% had none. Sixty one percent admitted to having taken some form of CAM therapy at least once during the disease duration.

Table 2 shows pharmacological agents received by these 150 patients during the study period classified according to WHO Anatomical Therapeutic Chemical Classification System (ATC). Calcium (A12A, 100%), vitamin D (A11CC, 100%), folic acid (B03BB01, 100%), methotrexate (L04AX03, 100%), naproxen (M01AE56, 100%), prednisolone (M01, 100%) were the most frequently used ATC sub category agents. The patients received a total of six drugs on average during the study duration.

DMARD therapy was divided into four regimens according to the number of drugs prescribed. Regimen 1 - monotherapy with one DMARD (MTX); Regimen 2 - double DMARD therapy or 2 DMARD therapy (MTX + HCQ); Regimen 3 - triple DMARD therapy or 3 DMARD therapy (MTX + HCQ + Lef); Regimen 4 - >3 DMARDs therapy (MTX + HCQ + Lef + bDMARD Ada). Figure 1 shows that the percentage of patients receiving each of these DMARD regimens.

Table 1: Baseline demographic data: (Rheumatoid Arthritis patients included in study)

Gender distribution	***n* (150)**	**%**
Total	150	100
Males	21	14
Females	129	86
Age (in years)		
Mean±SD	**Min**	**Max**
48.55±11.89 (Total)	19	72
53.48±9.21 (Males)	33	70
47.75±12.11 (Females)	19	72
Median Age	48 years	
Mean Follow-up visit duration	10.7 weeks	
Co-morbidities		
Condition	***n* (150)**	**%**
Mean Total co-morbidity	51	34
Osteoarthritis	19	12.6
DM Type 2	11	7.3
HTN	10	6.7
DM Type 2; HTN	5	3.3
GERD	6	4.0
Complementary Alternative Medicine (CAM) Therapy		
Received	***n* (150)**	**%**
Yes	92	61.4

Table 2: Drugs prescribed to the study population during the study, as classified according to WHO ATC code classification of drugs

ATC Code	Description	Number of subjects (*n*=150)
A	Alimentary tract and metabolism	
A12A	Calcium	150 (100%)
A11CC	Vitamin D and analogues	150 (100%)
B	Blood and blood forming organs	
B03BB01	Folic acid	150 (100%)
L	Antineoplastic and Immunomodulating agents	
L04AA13	Leflunomide	5 (3.3%)
L04AB04	Adalimumab	1 (0.6%)
L04AX03	Methotrexate	150 (100%)
M	Musculo-skeletal system	
M01AE56	Naproxen	150 (100%)
M01CA (P01BA02)	Quinolines -Hydroxychloroquine	40 (26.6%)
M01AB01	Indomethacin	40 (26.6%)
M01/S02BA03	Prednisolone	150 (100%)

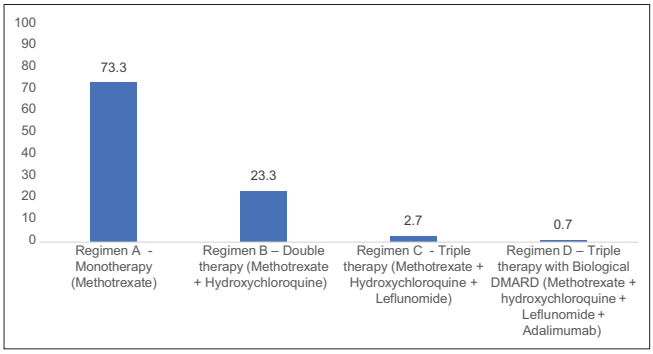

Figure 1: Percent of patients receiving different regimens of Disease modifying anti-rheumatic dugs in study population

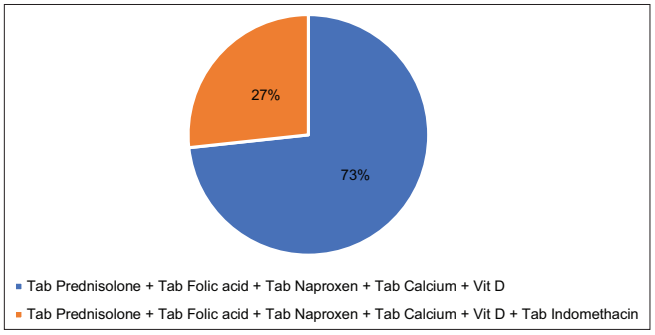

Figure 2: Percentage of patients receiving adjuvant drug therapy in study population

Table 3 compiles the details of DMARD therapy received by the study subjects. All the 150 subjects in the study received MTX, of which 12 (8%) received methotrexate monotherapy at a dose of 10 mg as an oral tablet once a week and 70 (46.6%) received a dose of 15 mg. Parenteral methotrexate, as a subcutaneous injection weekly, given to the rest 68 (45.3%), was given together with either hydroxychloroquine and/or leflunomide and/or adalimumab.

Hydroxychloroquine was given once daily at night, in either of two doses, 200 mg or 300 mg, based on the body weight of the patient. Five patients also received leflunomide as 20 mg oral tablet once daily along with MTX, HCQ, and/or adalimumab. Of the total 150, only a single patient received the biological DMARD adalimumab (Ada) as 40 mg subcutaneous injection, once in a fortnight. Combinations of DMARD therapy received by the patients is shown in Figure 2.

Discussion

In this drug utilization study conducted at a tertiary care hospital in Uttarakhand, North India, a total of 150 patients of RA were enrolled over a period of one-year duration, whose prescription pattern was analyzed.

RA is a chronic inflammatory disease, with multifactorial aetiology predominantly affecting females (2.5:1),[4] as also seen in our study, in which 86% were females. Various other studies conducted in different settings have reported similar female predominance in their study varying between 76.7% and 87%.[4-8] The reasons for this feminine predominance in auto-immune diseases are not clear, though genetic (X-linked) factors and hormonal relation have been attributed.[9,10] In the present study, the median age was 48 years which was comparable to other studies which showed that the peak prevalence of RA was in fifth decade.[4,6,11,12]

Co-morbidities were present in 51 (34%) in this study, with OA being the most common, followed by DM type 2 and HTN. A study from Tamil Nadu, India, reported higher incidence of HTN in 60% and DM in 26.66%,[13] while other studies report similar incidences.[14,9]

In the present study, more than 60% of the subjects had received CAM at least once during their disease course, quite higher as compared to another study where alternative medicine was used by hardly 13% patients.[4] Despite such high use of CAM, the majority of these patients had reported no benefit. The reason for such a high incidence of CAM in our study can be attributed

Table 3: Dosage, formulation and route-wise distribution of DMARDs received by the study population (*n*=150)

DMARD agent	Doses	Formulation	Frequency	Number of patients *n* (%)
Methotrexate (MTX)				150 (100)
1. Single	10 mg	Tablet	Once a week	12 (8)
2. Single	15 mg	Tablet	Once a week	70 (46.6)
3. Single	20 mg	Tablet	Once a week	28 (18.6)
4. MTX+HCQ/+LFM/+ ADM	20 mg	Injection	Once a week	40 (26.6)
Hydroxychloroquine (HCQ)				40 (100)
1. (+MTX/+LFM/+ADM)	200 mg	Tablet	OD	17 (42.5)
2. (+MTX/+LFM)	300 mg	Tablet	OD	23 (57.5)
Leflunomide (LFM)				5 (100)
1) (+MTX+HCQ/+ADM)	20 mg	Tablet	OD	5 (100)
Adalimumab				1 (100)
1) (+MTX+HCQ+LFM)	40 mg	Injection	Once every other week	1 (100)

to the easy access and availability of these alternative treatments in Uttarakhand.

A total number of 986 drugs were prescribed in the total of 150 patients in our study, out of which 196 were DMARDs. All the patients received methotrexate, while hydroxychloroquine, leflunomide, and adalimumab were prescribed in 26.6%, 3.3%, and 0.6% patients, respectively. This pattern was consistent with recent guidelines, which advocate MTX as the first line DMARD in the treatment of RA. Methotrexate was used in 3 different doses i.e., 10 mg, 15 mg, and 20 mg in this study with a frequency of once weekly administration. The reason for this variation in MTX dosage used in our study might be attributed to the fact that patients included were of varying duration of disease and treatment and maintenance dose of MTX ranges from 7.5 to 30 mg per week in clinical practice, signifying that patients require individualised dose for optimal disease control.[15]

The European League Against Rheumatism (EULAR) gives no recommendations for titration but does state a maximum MTX dosage as of 20–30 mg/week. A starting dose of 10 mg/week has been recommended by Spanish guidelines. The weight-based dose for a 70 kg adult is 0.2 mg/kg or 15 mg/wk, translating to a starting oral MTX dose of 10–15 mg/week, with gradual increase by 5 mg every 2–4 weeks up to a maximum dosage of 20–30 mg. American College of Rheumatology (ACR) guidelines does not provide any dosage recommendations for MTX, but 25–30 mg/week is regarded as the highest tolerable dose for RA.[16,17] None of the patients in our study received the highest tolerable dosage recommended.

A study conducted on RA, reports that the patients received the same dosage of MTX by both parenteral and oral route, indicating a bioavailability ranging from ~ 20% to >100%.[17] This variability might be attributed to the variable absorption of oral MTX' probably due to *SC19A1* gene polymorphisms. About 27% patients in our study received parenteral MTX via subcutaneous route at 20 mg once weekly. The injectable was usually given in combination with other DMARDs, which can be corresponded to the practice of giving injectable MTX in case of poor response to MTX monotherapy with oral doses higher than 15 mg weekly.

Two doses of HCQ, 200 mg, and 300 mg, were used in oral tablet form, administered once daily at night. The recommendation for HCQ for RA is 200 to 400 mg daily as a single daily dose or in 2 divided doses. Exceeding the toxic concentration of the drug makes a patient susceptible to the risk of retinal toxicity. Majority patients should not receive a daily dose more than 5 mg/kg/day using actual body weight or 400 mg, whichever is lower.[18]

In the present study, the different regimes used in decreasing order of frequency were MTX (Regimen A), followed by MTX + HCQ (Regimen B), MTX + HCQ + Lef (Regimen C) and MTX + HCQ + Lef + Ada (Regimen D). Hence, monotherapy was the most popular in this setting, followed by double DMARD therapy. These results were in concurrence of recent ACR 2020 guidelines, which recommend conventional synthetic (csDMARD) monotherapy followed by csDMARD double combination therapy and csDMARD triple combination therapy.[19]

In our study there was variability of dosage of MTX and HCQ within regimens. These variations can be attributed to various factors like dosing according to weight of the patient, response to therapy, duration of therapy, etc.

A single DMARD monotherapy, MTX, was used in the majority of RA patients in our study setting, while combinations of DMARDs were prescribed when the disease was uncontrolled. The preferred DMARD in our study was MTX, prescribed in all the patients, either alone or in combination, consistent with other studies which also report it as the most preferred agent.[4,6] According to the ACR 2020 guidelines, it is recommended that MTX monotherapy should be the first treatment of choice for patients with DMARD-naïve RA with low, moderate or high disease activity.[19] In contrast to our study where the majority (73.3%) received MTX monotherapy, most other studies have reported two DMARD combination as the most frequently used regimen to manage RA.[20] Only one study with similar use of methotrexate monotherapy was found which reported majority patients on single DMARD therapy.[21] Various other studies have reported combinations of three conventional synthetic DMARDs as the most commonly used regimen.[4,6] The variation

in number of DMARDs prescribed might be due to the varied severity of disease encountered in different hospital settings.

Combination DMARD therapy should be initiated when the disease activity score remains high, despite adequate MTX monotherapy, or at the very onset in a sub-group of patients with aggressive disease associated with high risk factors including, smokers, female gender, high tender, and swollen joint counts, markedly elevated acute phase reactants, high disease activity scores, marginal erosions on X-ray at baseline, high rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (anti-CCP) titres and severe disability indicated by high health assessment questionnaire scores.[1] Various studies have concluded that combination DMARD therapy is effective in RA, with the strongest evidence in established RA for combinations of MTX + anti-TNF and/or SSZ/HCQ, given to patients who have partially responded to DMARD monotherapy.[22] In our study, MTX + HCQ was the most frequently prescribed DMARD combination, in concurrence with two other Indian studies where this combination therapy was prescribed in more than 50% of RA patients.[11,13] Hence, in the Indian scenario, MTX + HCQ is the most frequently used combination of DMARDs. This is also the most popularly prescribed combination DMARD, in the USA and Canada. Consistent with our results, none of the other studies have reported use of biological/biosimilar DMARD (bDMARDs) or Janus Kinase Inhibitors (JAKinibs) at the treatment initiation. Most probable reason for this can be the high cost and the current recommendation of these agents only after failure of primary therapy with combination csDMARDs.

Along with DMARDs, all patients received prednisolone, similar to another study where the majority of patients received oral/intramuscular glucocorticoids (GCs). Recent recommendations also advocate the use of glucocorticoids in lowest possible dose for the shortest possible duration in RA.[23] A study has demonstrated the radiological and clinical improvement with low-dose GCs (≤10 mg/day prednisone) in the treatment of RA.[24] According to EULAR, the insertion of low dose GCs (<7.5 mg/day) to DMARDs in early RA leads to significant reduction in radiographic progression and the chronic use of GCs up to 15 mg/day ameliorates disease activity.[25] The main aim in giving intra-articular GCs in RA is pain relief. According one study, combined treatment with MTX and intra-articular GC lead to remarkable disease control and clinical response even at 2 years.[26]

All patients in our study also received vitamin D (vit D) supplements. In a study conducted in 2012, vit D deficiency was found to be highly prevalent in patients with RA, and was observed to be linked to disease severity. Vit D deficiency has been related to diffuse musculoskeletal pain. Vit D supplementation may be prescribed for prevention of osteoporosis along with some pain relief in patients with RA.[27] In another study, vit D has been implicated in preventing the onset and RA pathogenesis and also promoting anti-inflammatory response.[16]

Calcium was a regular component of the adjuvant therapy, since RA leads to bone loss.[28] All patients were prescribed folic acid, which reduces the adverse effects of MTX, a folate antagonist. The incidence of gastrointestinal side effects and hepatic dysfunction is significantly reduced by Folic or folinic acid which thus reduces the likelihood of discontinuation of MTX by patients. Concurrent use of folic acid and MTX reduces the clinical efficacy of MTX, while folic acid administration, the day after MTX, prevents this interaction by inhibiting the competition between folate and MTX for absorption.[17]

Majority of patients (73.3%) in our study received combination of 5 adjuvant drugs. One study revealed approximately similar results, where they reported that other medicines such as folic acid, proton pump inhibitors (PPIs), and calcium supplements were also prescribed with the DMARDs.[6] In our study, 68.7% of patients were on PPIs and 24% of the study population was given calcium supplements. This was in concurrence with other studies, where calcium supplements and gastroprotective agents were also present in a significant number of prescriptions.[4] These agents are probably given to prevent drugs ADRs such as epigastric pain and RA related osteoporosis/glucocorticoid induced osteoporosis.

Non-steroidal anti-inflammatory drug (NSAID), naproxen was given in all patients for acute management of pain, while another 26.7% received indomethacin. Similar to our study, one more study mentioned that indomethacin, diclofenac, and naproxen represented nearly 60% of the total NSAIDs prescribed for RA, although it was difficult to determine the reason for these preferences.[29] A probable combination of personal experience, learnt habits and a classic clinical association that these three NSAIDs provide greater pain relief in the RA patients, may be the possible reason for this preference.[30]

The few limitations to our study, are the small sample size assessed and the inclusion of all patients, both old as well as new, in the study which could confound the exact results.

This study will help primary care physicians get the data about the most commonly prescribed DMARD therapy in RA patients along with adjuvant therapy which is most suitable, and spread awareness about polypharmacy in RA, thus helping physicians make more aware choices about the RA drug prescriptions and limiting polypharmacy when not needed.

Conclusion

Our study concludes that in our institute in Uttarakhand, India, the most commonly prescribed DMARD in RA was MTX, followed by HCQ, Lef and lastly Ada. The most commonly used regimen was MTX monotherapy followed by MTX + HCQ combination. Along with DMARDs, adjuvant medications were also commonly prescribed to all patients. On average each patient received a total of six drugs at a time during the study duration. There was a very high prevalence of CAM therapy in the patients

here due to availability and accessibility despite poor response to this therapy.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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