ORIGINAL ARTICLE

Conventional Synthetic Disease-modifying Drugs Remain the Mainstay of Therapy for Rheumatoid Arthritis in India

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Abstract

Background: There are limited data on the real-world utilization of disease-modifying antirheumatic drugs (DMARDs) in Indian patients with rheumatoid arthritis (RA).

Methods: This was a cross-sectional study of a multicentric observational cohort of RA patients across rheumatology clinics at six centers across India. Patients who met the American College of Rheumatology (ACR) 2010 criteria for RA were included. The demographics, disease-related parameters, and current therapy in terms of DMARDs were analyzed using a structured paper or electronic case record form.

Results: This study included 4,061 patients with RA across six centers in India. A majority were female (female-to-male ratio, 6:1), and their mean [standard deviation (SD)] age at the time of enrollment was 51 (12.2) years. Rheumatoid factor and/or anti-CCP were positive in 79 and 77%, respectively. Data on DMARDs were available for 3,550 RA patients. Conventional synthetic DMARDs alone were being used in 3,289 (93%), targeted synthetic DMARDs in 203 (6%), and biological DMARDs in 67 (2%). A total of at least 18 separate types or combinations of DMARDs were being prescribed, with the most common being a combination of methotrexate and hydroxychloroquine (22%), methotrexate monotherapy (17%), and a combination of methotrexate and leflunomide (16%). Overall, the most common DMARD prescribed (as monotherapy or in combination) was methotrexate (86%), followed by hydroxychloroquine (52%) and leflunomide (37%).

Conclusion: Cs-DMARDs remain the mainstay in the treatment of Indian patients with RA in this study, with the majority being treated with methotrexate alone or in combination with other DMARDs.

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Introduction

Rheumatoid arthritis (RA) is among the most common systemic autoimmune diseases, with a mean worldwide point prevalence of 0.5%, and an estimated prevalence in India varying from 0.3 to 0.7%. This systemic disease is characterized by inflammation of the synovial joints, with symmetrical involvement of both small and large joints.[1,2] Untreated RA leads to significant morbidity in the form of joint deformities and the need for joint replacements, and has a huge social impact in terms of absenteeism from work to job loss.[3]

The treatment of RA has undergone a major shift since the turn of the century. Prior to that time, therapy was restricted to the use of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) methotrexate, sulfasalazine, and antimalarials (and gold). Afterward, there has been a revolution of sorts with the introduction of a new csDMARD, leflunomide, followed by newer classes, biologic disease-modifying antirheumatic drugs (DMARDs) and targeted synthetic DMARDs. Thus, there is scope for tremendous choice and diversity of therapy to suit the individual patient.[4]

The prescription of any therapy, including DMARDs, in RA depends on many factors, including but not limited to efficacy, availability, affordability, physician comfort, adverse effects of therapy, and coexisting comorbidities. There is little data on DMARD prescription patterns in India, particularly on bDMARDs and tsDMARDs, and the various combinations being used.[5] Thus, this study was planned as a cross-sectional, multicenter collaborative project to look at the pattern of DMARD use in RA patients in India.

Methods

This was a multicenter, prospective study under the BIRAC-funded Clinical Trial Network involving six sites across India (https://www.biracctnrheumatology.com/).

Participating centers included academic and nonacademic rheumatology clinics, government outpatient clinics, and private hospitals. Ethical approval was provided by the local institutional boards of all participating centers, and informed consent was obtained from all patients before their inclusion in the study.

The design of this prospective study includes two successive phases. During phase 1, a cross-sectional evaluation of patients with RA (as classified by ACR/EULAR 2010 criteria)[6] seen during a 2.5-year recruitment period at each center was performed (the whole recruitment period lasted from July 2020 to October 2022). All patients recruited during this phase formed the working cohort of the study. Data was collected through a face-to-face interview and a review of records of patients who attended the rheumatology clinics of these six centers. The participating physicians entered data either through a printed form or electronically *via* a specific web form through a designed portal—https://mier.hplug.co:4443/healthplug/#/login.

The results of phase 1 are reported here. The data were collected using the RA Baseline case report form, which included demographics, disease duration, treatment patterns, and comorbidities. Disease activity was assessed by the DAS28 (Disease Activity Score using 28 joints)–erythrocyte sedimentation rate (ESR) score, while function was assessed by the Health Assessment Questionnaire (HAQ). The serological status [presence or absence of rheumatoid factor (RF) and anticyclic citrullinated peptide antibodies

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(anti-CCP)] was recorded. All relevant extra-articular manifestations were documented. Comorbidities were recorded after reviewing the prescriptions for diseases such as hypertension, diabetes mellitus, hypothyroidism, hyperlipidemia, coronary artery disease, and tuberculosis (TB).

For each patient, the current use of medications was recorded, including nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, corticosteroids (CS), and disease-modifying drugs (DMARDs), either conventional synthetic (csDMARDs), targeted synthetic (tsDMARDs), or biologic (bDMARDs) and other immunomodulators/immunosuppressives. CsDMARDs included the four conventional drugs methotrexate, hydroxychloroquine, leflunomide, and sulfasalazine. Other immunomodulators/immunosuppressives included iguratimod and any other immunosuppressives, like azathioprine, etc.

Statistical Analysis

All analyses were performed using Microsoft Excel 2013 and IBM Statistical Package for the Social Sciences (SPSS) Statistics v. 20 software. Data were analyzed using descriptive statistics.

Demographic and descriptive continuous variables are expressed as mean [standard deviation (SD)] and median values. Categorical variables are expressed as percentages.

Results

We included 4,061 patients with RA across six centers in India. A majority were females (female-to-male ratio, 6:1), and their mean (SD) age at the time of enrollment was 51 (12.2) years. Rheumatoid factor and/or anti-CCP were positive in 79 and 77%, respectively. Baseline data are given in Table 1.

Use of Disease-modifying Antirheumatic Drugs

Data on drugs being used were available for 3,550 patients. Conventional synthetic DMARDs (csDMARDs) alone were being used in 3,289 (93%) patients, and biological and/or targeted synthetic DMARDs (b or tsDMARDs) were used in 270 (8%) patients. A total of at least 18 separate types of DMARDs or their combinations were being used by patients, with the most common being a combination of MTX and HCQ (22%), followed by MTX monotherapy (17%) and a combination of MTX and LEF (16%) (Fig. 1). Overall, the most common DMARD prescribed (as monotherapy or part of a combination) was MTX, followed by HCQ and LEF. CS was prescribed in 1,255 (35%) patients, and other immunomodulators/immunosuppressives were prescribed in 150 (4%) patients (Table 2).

Table 1: Baseline demographic and disease related parameters in study cohort (n = 4061)

Variables	*Values*
Age, years, mean ± SD	51.0 ± 12.2
Disease duration, mean ± SD	9.0 ± 7.3
Gender (F:M)	6:1
Age of onset, mean ± SD	42.0 ± 12.3
Rheumatoid factor, *n* (%)[1]	2620 (79)
Anti-CCP, *n* (%)[2]	1982 (77)
Antinuclear antibody, *n* (%)[3]	696 (46)
Disease activity (DAS28)[4]	
Remission	669 (31)
Low disease activity	496 (23)
Moderate disease activity	716 (33)
High disease activity	300 (14)
Extra-articular manifestations	
Rheumatoid nodules	334 (8)
Interstitial lung disease	212 (5)
Sicca symptoms	1019 (25)
Vasculitis	41 (1)
Comorbidities	
Diabetes mellitus, *n* (%)	453 (11)
Hypertension, *n* (%)	867 (21)
Hypothyroidism, *n* (%)	616 (15)
Coronary artery disease, *n* (%)	104 (3)
Asthma, *n* (%)	54 (1)
Tuberculosis (ever), *n* (%)	67 (2)

[1]Data available in 3315; [2]Data available in 2578; [3]Data available in 1525; [4]Data available in 2181

Table 2: Overall use of DMARD and glucocorticoids (as mono or combination therapy) in this study

DMARD	*n (%)*
Methotrexate	3044 (86)
Hydroxychloroquine	1871 (52)
Leflunomide	1321 (37)
Sulfasalazine	490 (14)
JAKi	203 (6)
Biologics	67 (2)
Corticosteroids	1255 (35)
NSAIDS	1364 (38)
Others	150 (4)

Others included iguratimod in 125, azathioprine in 9, tacrolimus in 8, cyclosporine in 2, cyclophosphamide in 3, mycophenolate mofetil in 3

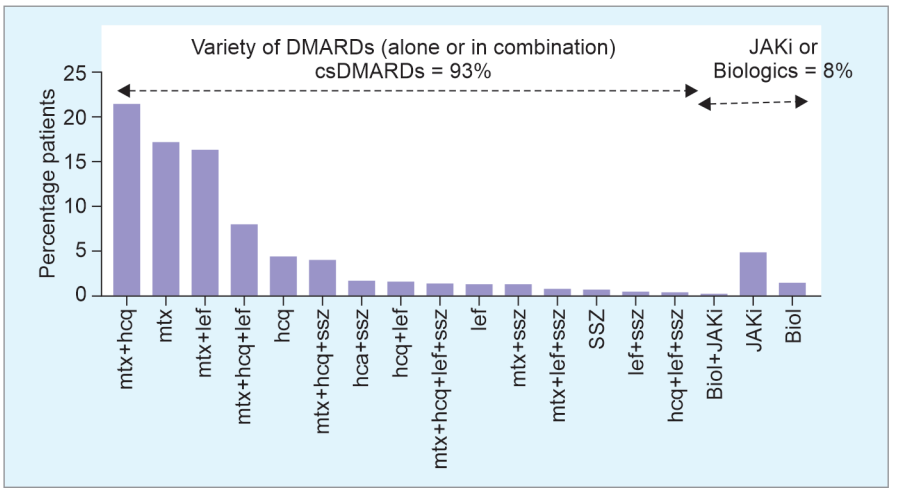

Fig. 1: Bar graph showing the various combinations/monotherapies of DMARDs prescribed to patients (n = 3550); biol, biologic; DMARD, disease-modifying antirheumatic drugs; hcq, hydroxychloroquine; JAKi, Janus kinase inhibitor; lef, leflunomide; Mtx, methotrexate; ssz, sulfasalazine; total value is above 100 due to rounding off

Conventional Synthetic Disease-modifying Antirheumatic Drugs

Among the 3,289 patients being treated exclusively with csDMARDs, monotherapy was used in 957 patients (29%), whereas combination therapy was used in 2,332 (71%) patients. In monotherapy, MTX was the most common, followed by HCQ. In combination therapy, the use of the dual combination of MTX and HCQ was most common, while in triple therapy, the combination of MTX, LEF, and HCQ was most common (Table 3).

Targeted Synthetic or Biological Disease-modifying Antirheumatic Drugs

These were used in 270 patients (8%), with tsDMARDs used in 203 (6%) and bDMARDs in 67 (2%) patients (both being used in 9 patients). Among patients receiving tsDMARDs and bDMARDs, 188 (94%) and 62 (95%), respectively, received them in combination with csDMARDs.

Discussion

Real-world data regarding the therapy of RA patients is limited in India. In the first phase of this 3-year-long prospective study, a cross-sectional evaluation of ongoing therapy from 4,061 RA patients is analyzed.

The most striking results from this study are that conventional synthetic DMARDs (csDMARDs) remain the mainstay of treatment for RA in India. We found that methotrexate, described as the gold standard and benchmark csDMARD, is by far the most used, with almost 86% of patients receiving this drug. This is higher than the use reported in most other studies from different parts of the world, which report current use of methotrexate ranging from 62.5 to 80%[7–15] (Table 4). The data from smaller studies in India are consistent with our results, with studies from Lucknow and Dehradun reporting the use of methotrexate in 75–100% and limited use of biologics.[16,17]

Expectedly, a combination of csDMARDs was more commonly prescribed than monotherapy. Combinations of two csDMARDs were more common than triple-DMARD combination therapy. Interestingly, among the csDMARDs, after methotrexate and hydroxychloroquine, leflunomide was preferred over sulfasalazine, both as part of dual and triple combination therapy (along with methotrexate). This is consistent with a study from Karnataka, which found the dual combination of csDMARDs to be the most prescribed (68.1%).[18]

The low use of biologics in our study (2%) is likely due to their higher price compared to csDMARDs (even for biosimilars). Although it is difficult to compare different studies from other parts of the world due to their varying publication years, it seems that the use of biologics was much lower than in most other countries, where it varied from 15 to 49% (except for low usage in Korea and Poland) (Table 4). Obviously, the use of biologics also depends on the provision of these medications by a nationalized health system or a high rate of health insurance that covers biologics. In India, the majority of patients are self-funded for purchasing therapy, with few having health insurance. A similar low use of biologics has been found in most other publications on RA from India.[16–18]

Interestingly, in our cohort, the rate of tsDMARDs, although higher than biologics, was still low. Currently, tofacitinib and baricitinib are licensed in India; however, only tofacitinib is

Table 3: cDMARDs used as part of mono or combination therapy (*n* = 3289)

Type of use of cDMARDs	*n (%)*
Monotherapy	957 (29)
Methotrexate	699 (17)
Hydroxychloroquine	178 (4)
Leflunomide	52 (1)
Sulfasalazine	28 (0.5)
Dual therapy	1739 (53)
Methotrexate + hydroxychloroquine	875 (22)
Methotrexate + leflunomide	661 (16)
Hydroxychloroquine + leflunomide	63 (2)
Hydroxychloroquine + sulfasalazine	68 (2)
Methotrexate + sulfasalazine	52 (1)
Leflunomide + sulfasalazine	20 (1)
Triple therapy	536 (16)
Methotrexate + hydroxychloroquine + leflunomide	323 (8)
Methotrexate + hydroxychloroquine + sulfasalazine	161 (4)
Methotrexate + leflunomide + sulfasalazine	34 (1)
Hydroxychloroquine + leflunomide + sulfasalazine	18 (0.5)
Quadruple therapy (all four)	57 (1)

Table 4: Current use of DMARDS across different countries in recent publications compared to the current study

Site	*Current (%)*	*Quest RA 2007*[7]	*Ziegler 2010*	*Eriksson 2013*[10]	*Batko 2017*[11]	*Won 2018*[12]	*Thomas 2018*[13]	*Nakajima 2020*[8]	*Pombo-Suarez 2021*[14]	*Grellman 2021*[15]
	India N = 3550	*Worldwide N = 5499*	*Germany N = 3323*	*Sweden N = 10094*	*Poland N = 1957*	*Korea N = 14081*	*Greece N = 2491*	*Japan N = 825772*	*Spain N = 859*	*Germany N = 2171*
DMARD type										
CsDMARDS	93	>62.5	84.6	84		97.77	82	95	79.3	
Biologics	2	19	16.2	15	2.94	2.09	42	22.9	48.7	
tsDMARDS	6							0.9		
Corticosteroids	35	49	54.3	67	42.5	86.9	40	42.1	57.3	
csDMARD type										
Methotrexate	86	62.5	56.4	74	80.1	57.9	77	63.4		38.3
Hydroxychloroquine	52		7.3		4.14	73.04	18			
Leflunomide	37		12.2		7.03	13.53	17			10.1
Sulfasalazine	14		7.8		14.43	31.16	1	24.9		7.4

available as a generic medicine at a reasonably low cost since 2020. Their current low rates may be related to the recent introduction of generics at a reasonable price and perhaps the apprehension of physicians to prescribe a new drug. It is possible that the share of tsDMARD prescriptions may increase in the future.

This study has many limitations, the primary one being that it was cross-sectional, thus making an association between drug treatment and disease activity not attempted. Although this study was multicentric with the inclusion of large rheumatology centers in the north, south, and west of India, there were no centers in the east or northeast of India. Strengths of our study include a large cohort and a mix of private, charitable, and government-funded hospitals. In conclusion, csDMARDs remain the mainstay of therapy for patients with RA in India, with methotrexate being prescribed in the majority, either alone or in combination. Biologics and targeted synthetic DMARDs were found to be low in this study.

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