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Original Article

DEMOGRAPHIC, CLINICAL CHARACTERISTICS AND DRUG PRESCRIPTION PATTERN IN PATIENTS WITH RHEUMATOID ARTHRITIS IN SOUTH INDIAN TERTIARY CARE HOSPITAL

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ABSTRACT

Objective: The objective of the study was to describe demographic, clinical features and drug treatment pattern among rheumatoid arthritis (RA) patients in a south Indian tertiary care hospital.

Methods: In this retrospective study, a total of 789 patients diagnosed with RA were enrolled from October 2013 to December 2015 in tertiary care hospital irrespective of age and gender. Data of the patients were obtained from Medical Record Department (MRD), and all the data were documented in a suitable designed Case Record Form (CRF). The data were analyzed using SPSS 20.0 and Excel 2013.

Results: There were 628 females and 161 males with mean age 47.6±12.6 and 47.1±14.4 y respectively. The ratio of male to female was 1:3.9. Most of the RA patients were housewives (66.4%). The mean disease duration was 4.3±4.5 y. The majority of patients (59.3%) had disease duration of more than 24 mo. Hypertension (21.5%) was the most common comorbid condition in our study population. Iron deficiency anemia (IDA) was observed in 10.6% of RA patients. Serum C-reactive protein (CRP) was positive in 89.3%. The majority of patients (87.7%) received DMARDs. As the disease, duration increased the severity of disease also increased. Majority of patients were prescribed with dual DMARDs in combination (52.3%).

Conclusion: We observed female was dominant over the male in number and majority of patients had a later stage of the disease probably due to lack of medical facility or financial problems in the lower income groups. We observed that methotrexate plus hydroxychloroquine combination was commonly used in both high and moderate disease activity groups which may be due to a better outcome and minimal adverse effects.

Keywords: Rheumatoid Arthritis, Treatment pattern, DMARDs, Demography, DAS28 ESR, DAS28 CRP

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 [2] and approximately 0.75% of the adult Indian population [3, 4]. RA exists all over the globe irrespective of different genders, age and socio-economic status [5]. However, the prevalence of RA increases with age and it is more pervasive in women than men in the ratio of 2:1 [6]. Various environmental risk factors such as smoking, alcohol, and vitamin D deficiency affects the development of RA [7]. Cigarette smoking elevates the level of the rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (Anti-CCP) which are used as the clinical biomarker in the diagnosis of RA [8]. The occurrence and the severity of RA vary from different ethnic origin groups [4, 9, 10]. Comorbidities in RA are usually associated with poor progression and even reduce the life expectancy. Therefore, comorbidities are important in taking therapeutic decisions in RA patients [11-15].

Certain RA medications can induce comorbidities and studies have reported that these comorbidities can be appropriately managed in these patients [16-21]. The severity of the disease is represented by the disease activity score (DAS28) which uses 28 joint counts to monitor a patient's disease severity of RA [22-27] and assess the patient's response to treatment [28]. It is one of the recommended outcome measures in RA. The American College of Rheumatology (ACR) 2008 and 2012 also recommended the usage of DAS28 in therapy decision for RA due to its positive characteristics in reliability, validity, responsiveness and feasibility in clinical practice [29-31]. Disease-modifying antirheumatic drugs (DMARDs) are the mainstay in reducing the disease severity and progressive damage to joints [32, 33].

Presently there are no studies which explored the RA in detail regarding the demographics and drug treatment pattern in an Indian setting. The objective of the study was to understand the demography and drug treatment pattern in RA patients in a South Indian tertiary care teaching hospital.

MATERIALS AND METHODS

A retrospective observational study was conducted in a tertiary care teaching hospital of South India. The study was reviewed and approved by the Institutional Ethical Committee (IEC) (Registration Number ECR/146/Inst/KA/2013). A total number of 789 RA in patients' medical records were collected from October 2013 to December 2015. The data of the patients were obtained from Medical Record Department (MRD). The study included patients of both genders diagnosed with RA according to the ACR classification criteria and at least admitted once in the hospital. The severity of disease was assessed by using DAS28 ESR and CRP scale. According to ACR, scales (0-9.4) were as follows: Remission: <2.6, Low: ≥2.6 to<3.2, Moderate: ≥3.2 to ≤ 5.1, High: >5.1. However, patients who were shifted from treatment with modern medicines to other systems of treatment like Ayurveda or Unani were excluded from the study. All demographic details such as age, gender, laboratory parameters, comorbid conditions, clinical manifestations and the drug treatment pattern was obtained from medical records of patients. The data was analyzed using SPSS 20.0 and Excel 2013 as a statistical tool. All the categorical variables was expressed in proportion and analyzed by Chi-Square test. A continuous variable was expressed in terms of mean±SD and analysis was carried out by Independent T-test.

RESULTS

A total of 789 patients were admitted during the year 2013 to 2015 for the management of RA. The baseline demographic characteristic of patients is presented in table 1. The study population consisted of female patients 628 (79.6%) in the majority with male to female ratio of 1:3.9. The mean age of the study population was 47.5±13.0 y. For male patients, the mean age was 47.1±14.4 y and the mean age for female patients was 47.6±12.6 y. The mean of DAS28 ESR and DAS28 CRP was 4.6±1.6 and 4.0±1.5 respectively. Based on the working status, the patients were categorized into different groups. Among the study population 524 (66.4%) were housewives followed by farmers 81 (10.3%) and manual laborers 54 (6.9%). RA patients were categorized based on the body mass index (BMI). Among them 316 (40.1%) patients

were normal, 175 (22.2%) were obese and 75 (9.5%) were overweight. A total of 137 (17.4%) patients' data on BMI was not available because patients' body weight was not recorded. Mean disease duration for the study population was found to be 4.3±4.5 y. The majority of patients 468 (59.3%) had a diagnosis of RA for more than 24 mo followed by 222 (28.1%) patients had a diagnosis of RA between 6 to 24 mo and 99 (12.5%) patients had disease duration of less than 6 mo. More than half 428 (54.2%) of the RA patients belonged to the age group of 40-59. An age-wise distribution of patients with RA is depicted in fig. 1. Hypertension 170 (21.5%) and diabetes mellitus 140 (17.7%) were the most common comorbid conditions in RA patients. Hypothyroidism was observed in 56 (7.1%) followed by osteoarthritis 51 (6.5%) as shown in table 2. In the present study, we observed that iron deficiency anemia (IDA) was the most common in 84 (10.6%) patients. A total of 20 (2.5%) patients had anemia of chronic disease (ACD) and 19 (2.4%) patients had unclassified anemia. The distribution pattern of anemia in RA patients is shown in table 3. Patients exhibited prominent symptoms like multiple joint pain 601 (76.3%), morning stiffness 409 (51.9%), fevers 156 (19.8%) and fatigue 124 (15.7%) as mentioned in table 4. Laboratory investigation in RA patients was given as in table 5. The mean erythrocyte sedimentation rate (ESR) of RA patients was found to be 59.1±28.0 mm/hr.

Table 1: Baseline demographics characteristics of rheumatoid arthritis patients

Characteristics	No (%) n=789	mean±SD
Sex		
Female	628 (79.6)	
Male	161 (20.4)	
Age		
Female		47.6±12.6
Male		47.1±14.4
Mean of DAS28		
DAS28 ESR		4.6±1.6
DAS28 CRP		4.0±1.5
Work Status		
Housewife	524 (66.4)	
Farmers	81 (10.3)	
Labourers	54 (6.9)	
Others	130 (16.5)	
Marital Status		
Married	758 (96.1)	
Single	31 (3.9)	
BMI		
BMI not recorded (Unable to stand)	137 (17.4)	
Below normal	86 (10.9)	
Normal	316 (40.1)	
Obese	175 (22.2)	
Overweight	75 (9.5)	
Smoking		
Non-Smoker	753 (95.4)	
Ex-Smoker	14 (1.8)	
Smoker	22 (2.8)	
Alcoholic		
Non-alcoholic	771 (97.7)	
Ex-alcoholic	3 (0.4)	
Alcoholic	15 (1.9)	
Duration of disease (year)		4.3±4.5
Disease duration (month)		
<6	99 (12.5)	
6-24	222 (28.1)	
>24	468 (59.3)	

DAS: disease activity score, BMI: body max index

Table 2: Comorbid conditions

Comorbidities	No (%) n=789	Comorbidities	No (%) n=789
Hypertension	170 (21.5)	Respiratory infection	13 (1.7)
Diabetes Mellitus	140 (17.7)	Psychiatric disorder	12 (1.6)
Hypothyroidism	56 (7.1)	Tuberculosis	11 (1.4)
Osteoarthritis	51 (6.5)	Dyslipidemia	9 (1.1)
Peptic ulcer	50 (6.3)	Cataract surgery	9 (1.1)
Asthma/COPD	42 (5.3)	Connective tissue disease	9 (1.1)
Cardio Vascular System Disorder	36 (4.6)	Overlap syndrome	6 (0.8)
Chikungunya	33 (4.2)	Sjögren's syndrome	6 (0.8)
Urinary Tract Infection	33 (4.2)	Ankylosis	4 (0.5)
Gonarthrosis	26 (3.3)	Osteonecrosis	4 (0.5)
Vitamin D deficiency	18 (2.3)	Glaucoma	3 (0.4)
Interstitial pulmonary disease	17 (2.2)	Stroke	2 (0.3)
Osteoporosis	13 (1.6)	Aortic arch syndrome Takayasu	2 (0.3)
Systemic Lupus Erythematosus	12 (1.5)	Raynaud's syndrome	2 (0.3)
Synovial hypertrophy	7 (0.9)	Cellulitis of other parts of limb Axilla Hip Shoulder	2 (0.3)

COPD: chronic obstructive pulmonary disease

The mean hemoglobin (Hb) of the study population was 110±18 g/l, followed by mean albumin (Alb) 37±15 g/l. Positive anti-CCP was observed in 75.7% of RA patients with a mean value of 133.3±70.9 IU/ml. DAS28 ESR and DAS28 CRP were used to categorize the patients into high, moderate, low and remission disease activity score. By DAS28 ESR, 256 (33%) patients had high disease activity whereas 399 (51.4%) patients had moderate activity.

However, 121 (27.5%) patients had high disease activity and 171 (38.9%) patients had moderate activity by DAS28 CRP. The total disease duration was compared with the severity of disease based on DAS28 ESR and DAS28 CRP in RA patients as illustrated in fig. 2 and 3. It was observed that as the disease duration increased the disease severity index also increased significantly. A large number of patients were observed with moderate disease activity (28.5% DAS28 ESR and 19.8% DAS28 CRP) followed by high disease activity (19.8 % DAS28 ESR and 15.9% DAS28 CRP) in the group which had a longer duration of illness (>24months).

In our study, we observed that 693 (87.7%) patients were prescribed with DMARDs followed by NSAIDs 510 (64.4%) as mentioned in table 6. Among the DMARDs, the majority of patients received dual therapy 413 (52.3%) followed by monotherapy 206 (26.0%). Among dual therapy methotrexate plus hydroxyl-chloroquine 279 (35.4%) was prescribed in highest number as shown in table 7. Different combinations of DMARDs were categorized based on disease severity and duration of illness in table 8. It was observed that methotrexate plus hydroxychloroquine (MTX+HCQ) combination was prescribed the most in high, moderate and low disease activity in all the RA patients.

Table 3: Frequency of anemia among the rheumatoid arthritis patients

Types of anemia	No (%) n=789
IDA	84 (10.6)
ACD	20 (2.5)
Unclassified anemia	19 (2.4)
Dual anemia	6 (0.7)
Vitamin B12 deficiency	4 (0.5)
Autoimmune hemolytic anemia	1 (0.1)
Aplastic anemia	1 (0.1)

IDA: iron deficiency anemia, ACD: anemia of chronic disease

Table 4: Prominent symptoms among rheumatoid arthritis patients

Symptoms	No (%) n=789
Multiple joint pain	601 (76.3)
Morning stiffness	409 (51.9)
Fever	156 (19.8)
Fatigue	124 (15.7)

Table 5: Distribution of lab values and serological biomarkers in rheumatoid arthritis patients

Lab parameters	mean±SD	Positive (%)
ESR	59.1±28.0 mm/hr	
RF	111.5±48.6 IU/ml	68.4
Anti-CCP	133.3±70.9 IU/ml	75.7
CRP	37.1±46.4 mg/l	89.3
Hb	110±18 g/l	
Alb	37±15 g/l	
Iron	6.2±3.6 µmol/l	
TIBC	50.5±15.4 µmol/l	
Ferritin	3.2±5.5 pmol/l	

ESR: erythrocyte sedimentation rate, RF: rheumatoid factor, Anti-CCP: anti-cyclic citrullinated peptide, CRP: C-reactive protein, Hb: hemoglobin, Alb: albumin, TIBC: total iron binding capacity

Table 6: Treatment pattern in rheumatoid arthritis patients

Treatment	No (%) n=789
DMARDs	693 (87.7)
Corticosteroid (prednisolone)	321 (40.7)
NSAIDs	510 (64.4)
2 DMARDs+1 NSAIDs	162 (20.5)
2 DMARDs+1 NSAIDs+1 Steroid	42 (5.3)
2 DMARDs+2 NSAIDs	61 (7.7)
2 DMARDs+1 Steroid	77 (9.8)
Biological DMARDs	1 (0.1)
Multivitamin	214 (27.1)
Calcium with Vitamin	257 (32.6)
Glucosamine supplement	47 (6.0)

DMARDs: disease-modifying antirheumatic drugs, NSAIDs: nonsteroidal anti-inflammatory drugs

Table 7: Treatment pattern of non-biological DMARDs combination

DMARDs combination No. (%)	Non-biological DMARDs	No (%) n=789
Monotherapy	SSZ	34 (4.3)
206 (26.0%)	MTX	84 (10.6)
	LEF	5 (0.6)
	HCQ	80 (10.1)
	AZA	3 (0.4)
Dual drug combination	MTX+SSZ	50 (6.3)
413 (52.3%)	MTX+HCQ	279 (35.4)
	MTX+LEF	5 (0.6)
	SSZ+HCQ	69 (8.7)
	HCQ+LEF	5 (0.6)
	SSZ+LEF	2 (0.3)
	HCQ+AZA	3 (0.4)
Triple drug combination	MTX+LEF+HCQ	5 (0.6)
73 (9.2%)	MTX+SSZ+HCQ	67 (8.5)
	SSZ+MTX+LEF	1 (0.1)
Four drug combination	MTX+SSZ+HCQ+LEF	1 (0.1)
1 (0.1%)		
No DMARDs		96 (12.2)

SSZ: sulphasalazine, MTX: methotrexate, HCQ: hydroxychloroquine, LEF: leflunomide, AZA: azathioprine

Table 8: DMARDs vs. DAS28 ESR and duration of disease

DAS28 ESR													
DMARDS	Disease activity score	High			Moderate			Low			Remission		
	Duration of disease	<6	6-24	>24	<6	6-24	>24	<6	6-24	>24	<6	6-24	>24
No DMARDs		1	4	7	7	15	31	1	2	9	1	4	10
SSZ		0	2	7	3	6	7	2	2	3	2	0	0
MTX		2	11	18	2	14	29	0	0	2	0	2	1
HCQ		3	7	8	6	13	23	1	3	10	0	1	4
MTX+SSZ		0	4	18	3	6	12	0	1	2	0	1	3
MTX+HCQ		15	34	66	17	39	70	0	5	16	0	3	9
MTX+LEF		0	0	1	0	0	3	0	0	1	0	0	0
SSZ+HCQ		2	7	10	11	9	22	1	1	1	1	2	2
MTX+SSZ+HCQ		1	7	14	12	13	14	3	0	2	0	0	1

DMARDs: disease-modifying antirheumatic drugs, SSZ: sulphasalazine, MTX: methotrexate, HCQ: hydroxychloroquine, LEF: leflunomide, AZA: azathioprine, MIN: minocycline

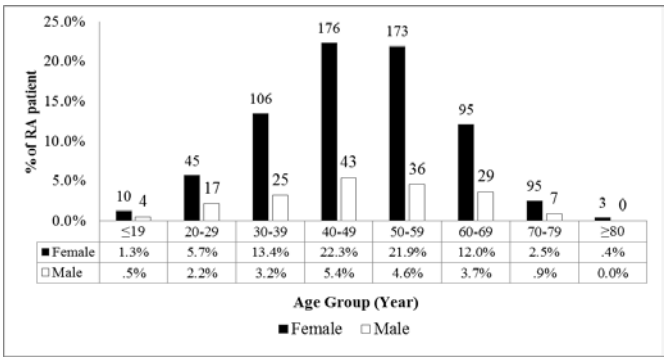

Fig. 1: Age-wise distribution of rheumatoid arthritis patients

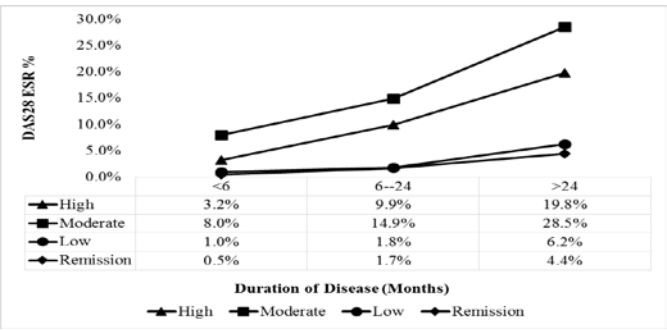

Fig. 2: DAS28 ESR vs. duration of disease

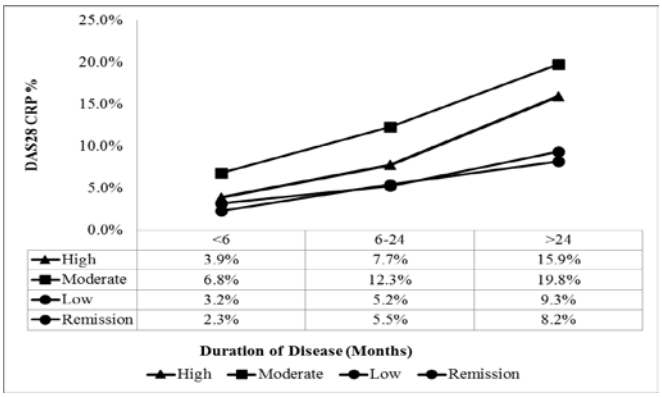

Fig. 3: DAS28 CRP vs. duration of disease

DISCUSSION

RA is the chronic autoimmune disease in developing countries like India, especially associated with disease-related complication, physical disability, and early mortality because of lack of awareness of patients regarding the disease or maybe noncompliance to the therapy which could be due to the high cost of management or temporary improvement of illness. Therefore, it is important to understand the magnitude of the problem of the disease especially in countries like India. The study analyzed demographic, clinical, comorbid, serological and treatment data on the patients with RA in the South region of India. This study revealed that prevalence of RA was more in female patients than male patients (79.6% vs. 20.4% respectively) which were almost similar to studies conducted by Al-Bishri *et al.* (78% vs. 22% respectively) [15] and Bajraktari *et al.* (76.8% vs. 23.2% respectively) [34]. In this research, we observed that male to female ratio was 1: 3.9 which was very close to 1: 4 ratio observed by Aletaha *et al.* [35] study and 1: 3.5 ratio reported by Al-Bishri *et al.* [15]. Whereas in a study conducted by Owino *et al.* [36] male to female ratio (1: 6.5) was higher than the ratio in this study. This higher ratio can be attributed to hormonal differences between female and male patients [37]. Our study showed that the peak prevalence of RA was in the age group of 40-49 followed by 50-59 in both the genders. In our study, the female was dominant over the male in number in all the age groups. A similar result was observed in Bajraktari *et al.* [34] study with respect to peak prevalence of RA distribution. But a study by Owino *et al.* [36] showed that the peak prevalence of RA was higher, especially in the younger age groups of 20-29 and 40-49. In our study, the vast majority of registered RA patients were housewives (66.4%) whereas, a study by Bajraktari *et al.* [34] showed the majority of patients were farmers followed by housewives (38% and 32.2% respectively). The higher prevalence of RA among the housewives or farmers was probably due to prolonged the duration of physical work with standing posture in the household work or agricultural field. We did not observe a correlation between RA prevalence and higher BMI although, it was reported that higher BMI has negative effects on the treatment of RA, Gremese *et al.* and Ajeganova *et al.* [38,39] emphasizing the need for weight control during the course of treatment. In this study, we observed much lower rates of smoking (2.8%) and almost similar alcohol consumption (1.9%) compared to the study by Bal *et al.* (16.2% and 2.0% respectively) [40]. This could be due to the uncommon practice of smoking and alcohol consumption especially in the female population in India. According to literature, smoking is known to be a risk factor for the development of RA [41, 42]. Also, smoking interferes with the course of treatment causing the poor outcome. Hence, this indicates the need for awareness among RA patients on the negative effect of smoking. Among most common symptoms of RA in our study multiple joint pain (76.3%) followed by morning stiffness (51.9%), fever (19.8%) and fatigue (15.7%) was observed considerably. It was found in our study that hypertension (21.5%) was the most common comorbidity followed by diabetes mellitus (17.7%) which was similar to the study conducted by Al-Bishri *et al.* [15]. There is also a report of peptic ulcer and diabetes as major comorbidity after hypertension in the East African study by Owino *et al.* [36] and Bal *et al.* [40]. ACD and IDA are the most common type of anemia in RA patients [43, 44]. IDA (10.6%) was the most prevalent anemia among our RA patients followed by ACD (2.5%). IDA may be caused due to prednisolone or NSAIDs leading to chronic blood loss by gastritis, peptic ulcer and gastroesophageal reflux [45]. In this study, serum RF was positive in 68.4% (mean 111.5±48.6 IU/ml), anti-CCP was positive in 75.7% (mean 133.3±70.9 u/ml) and CRP was positive in 89.3% (mean 37.1±46.4 mg/l). Positive serum RF was found to be similar to study by Bal *et al.* (69.2%) [40] but lower than the study by Owino *et al.* and Inoue *et al.* (78.9% and 77.3% respectively) [36, 46]. The mean value of DAS28 ESR (4.6±1.6) was higher than the mean value of DAS28 CRP (4.0±1.5). We observed that as the disease duration increased the severity of the disease activity scores also increased. Patients with longer duration disease (>24 mo and 6-24 mo) had the highest number of disease severity index belonged to either moderate or high disease activity. In our study, we observed that non-biological DMARDs (87.7%) was prescribed most commonly followed by NSAIDs (64.4%). Among the non-biological DMARDs, hydroxychloroquine (63.5%) prescribed more commonly followed by methotrexate (62.4%) and sulphasalazine (28.1%). Only one patient received biological DMARDs (etanercept) (0.1%) during the study period. Whereas in a study by Bal *et al.* [40] hydroxychloroquine was prescribed only to 15.8% of RA patients. However, we could not find any prescription of cyclosporine, gold, thiomalate and D-penicillamine drugs in our hospital record most of which are associated with higher incidence of adverse drug reactions (ADRs) and availability of safer drugs with better efficacy for the treatment of RA patients. In a study by Al-Bishri *et al.* [15], prednisolone (80.8%) was prescribed the most commonly followed by methotrexate (74.4%).

Moreover, 7.6% patients received biological DMARDs (etanercept). A study by Almeida *et al.* [47] showed that the treatment of RA patients most frequently included methotrexate (39.8%) followed by antimalarial (30.6%) and prednisolone (30.6%) with anti-TNF alpha (3.06%) least in number. It indicates that the non-biological DMARDs drugs are frequently prescribed compared to biological DMARDs [48-50]. In our study, most patients received dual DMARDs (52.3%) in combination followed by monotherapy DMARDs (26.0%). DAS28 ESR score was calculated to obtain the severity of the disease and compared with the duration of disease along with DMARDs combinations. It was observed that the majority of patients were prescribed with the DMARDs in the late stage of the disease. Among the DMARDs combinations, Methotrexate plus Hydroxy-chloroquine (35.4%) was prescribed to the majority of the patients with all stages of severity. However, the number of patients who received methotrexate plus hydroxychloroquine increased as the disease duration and severity of disease activity increased.

CONCLUSION

This study mainly focused on the demographical details, clinical characteristics and treatment pattern in RA patients in South India. We observed female was dominant over the male in number and the majority of the patients had the later stage of the disease probably

due to lack of medical facility or financial problems in the lower income groups. The end stage of the disease was always associated with poor prognosis with multiple drug therapy. In our study, we observed methotrexate plus hydroxychloroquine were the major combinations which was most effectively used in both high and moderate disease severity groups probably due to a better outcome and least side effects. The use of steroids was limited compared to non-biological DMARDs and there were used if there was any relapse or poor prognosis.

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ABBREVIATION

ACD: anemia of chronic disease, ACR: american college of rheumatology, ADRs: adverse drug reactions, Alb: albumin, Anti-CCP: anti-cyclic citrullinated peptide, BMI: body mass index, CRF: case record form, CRP: C-reactive protein, DAS: disease activity score, DMARDs: disease-modifying antirheumatic drugs, ESR: erythrocyte sedimentation rate, Hb: hemoglobin, HCQ: hydroxychloroquine, IDA: iron deficiency anemia, IEC: institutional ethical committee, MRD: medical record department, MTX: methotrexate, NSAIDs: nonsteroidal anti-inflammatory drugs, RA: rheumatoid arthritis, RF: rheumatoid factor, TIBC: total iron binding capacity.

CONFLICT OF INTERESTS

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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