

Evaluation of clinical and Para clinical findings, treatment response in RA patients: Data from a single center RA registry

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Rheumatoid arthritis (RA) is a chronic, inflammatory autoimmune disease characterized by the inflammatory arthritis rheumatoid factor (RF: An IgM produced against anti-immunoglobulin G) and anti-cyclic citrullinated peptide (anti-CCP) autoantibodies. In the present study, the aim was to register RA patients in Imam Khomeini Hospital, Tehran, Iran.

The study population of this research was RA patients referred to the rheumatology clinic in 2019 at Imam Khomeini Hospital in Tehran and had been diagnosed 5 years ago. Demographic, clinical, and laboratory information of patients at the beginning of referral at 3 months, and 1, 2, 3, and 4 years after referral, were carefully recorded in each patient questionnaire.

In the first visit, 79 RA patients were examined and in the other 5 visits, 73, 52, 33, 20, 13 patients, respectively, were examined totaling the 270 visits. RF and anti-CCP were positive in 58.22% and 62.02% of patients, respectively. The mean age of patients was 52.5±11.25 years. The results of the present study showed that the mean morning stiffness, DAS, arthritis, arthralgia, ESR, and CRP decreased from the second visit through the following five visits which indicated disease control.

Clinical and laboratory data showed considerable disease control, however, relapse of disease was seen due to drug discontinuation. Registering the disease makes it possible to record the necessary information of each patient, including demographic, clinical, and paraclinical findings as well as consultations, and gives the physician accurate access to patient information and unnecessary duplication of paraclinical examinations.

Keywords: Rheumatoid arthritis; Registry

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease with a prevalence of 0.1% to 1.9 % of the adult population that affects women 2-3 times more often than men and is characterized by synovial inflammation, cartilage, and bone destruction [1, 2]. Therapeutic approaches in RA include non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate, biologic agents such as TNF- α inhibitors, and corticosteroids [3].

Disease Registration is an organized system for collecting, storing and retrieving, analyzing, and disseminating information about a person with a specific disease or is exposed to the known or suspected adverse effects in a population and a certain geographical area [4]. One of the most important goals of the disease registration

program is to investigate the incidence and prevalence of the disease, as well as evaluation of the disease, quality of patient care services, measure and monitoring the safety and injury, and even promote research projects. The importance of registering diseases in research includes survival analysis and evaluation of clinical care outcome, etiological studies, production of descriptive information (incidence of mortality), economic and managerial analysis, and a suitable source for clinical trial, case, and cohort studies [5]. It should be noted that disease registration is considered as one of the practical pillars of public health [6]. Implementation of a registry system for RA disease can help to obtain accurate statistics of the incidence, type of treatment approach, and also reduce its complications. In Iran, Rheumatry is the Iranian

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rheumatology registry that was established in 2016. The rheumatry.com web site is an online registry system.

According to previous studies, implementation of a registry system for RA is useful to study the long-term effects of RA treatment and complications, the survival rate, and cause of death of RA patients. For example, the register of RA patients in France has shown that RA patients receiving biologics have a higher risk of infections and lymphomas [7]. Another study based on the RA patient registry in France showed that RA patients who are positive for anti-CCP respond better to Abatacept [8]. The important role of the disease registry in diagnosis, treatment, and follow-up of the patients is undeniable. Unfortunately, no study has been reported in Iran to register RA patients. In the present study, our aim was to report the clinical and paraclinical findings and treatment response in RA patients from a single center RA registry.

Materials and Methods

Study population

In this retrospective cross-sectional study, the study population included RA patients referred to the rheumatology outpatient clinic of Imam Khomeini Hospital, University of Medical Sciences, Tehran, Iran, who were diagnosed 5 years ago. Inclusion criteria was: Diagnosis of RA disease based on the 2010 criteria of American College Rheumatology (ACR) [9], informed consent of the patient for participation in the study, and adults over 18 years. Exclusion criteria were patient dissatisfaction of participation in the project.

Demographic information of patients including age, sex, age of onset of disease, disease duration, coexistence of other diseases, and occupation was recorded for each patient. Laboratory findings were carefully recorded on the first visit, 3 to 6 months later, and then annually in each patient questionnaire including complete blood count (CBC), calcium, phosphorus, creatine, anti-nuclear antibody (ANA), florescent anti-nuclear antibody (FANA), rheumatoid factor (RF), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), anti-cyclic citrullinated peptide (anti-CCP), aspartate amino transferase (AST), alanine amino transferase (ALT),

creatine phosphokinase (CPK), and lactate dehydrogenase (LDH)), as well as clinical manifestations (morning stiffness, joint pain, joint thunder, and joint effusion), and of course, prognosis (response to treatment and the progression of the disease). Disease activity score 28 (DAS 28) was used to evaluate the disease activity, then, all data were entered on the rheumatry.ir¹ website. The protocol of the study was approved by the Ethical Committee of Tehran University of Medical Sciences (Code: IR.TUMS .IKHC.REC.1398.244).

Statistical Analysis

Data analysis was performed to describe the demographic and clinical status of patients using SPSS software (version 25) at both the descriptive and analytic levels. Quantitative variables were shown as mean \pm standard deviation and categorical variables were shown as percentage.

P value < 0.05 was considered as statistically significant.

Results

The present study included 79 RA patients for this research. In the first visit, 79 RA patients and on the other 5 visits, 73, 52, 33, 20, and 13 patients were evaluated, respectively. All 270 visits were evaluated. Female participants represented 51.9% and 48.1% were male. The mean age of all patients was 52.5 ± 11.25 years and was 52.26 ± 12.5 and 52.82 ± 10.1 years for men and women, respectively. The mean duration of the disease was 2.4 ± 1.47 years. In the present study, 8.9% of patients were smokers, of which 66.7% and 83.3% were positive for RF and anti-CCP. Of these patients 78.48% had undergraduate education and 43% of the patients lived in rural areas (Table 1).

The RA patients presented with polyarthritis (77.21%), oligoarthritis (15.18%), and monoarthritis (1.26%). Polyarthralgia was found in 6.32 % of the patients. Diabetes, hypertension, ischemic heart disease, and hyperlipidemia were observed in the patients at 15.18, 30.37, 15.18 and 17.72%, respectively (Table 1).

Table 1. Demographic and clinical features of RA patients

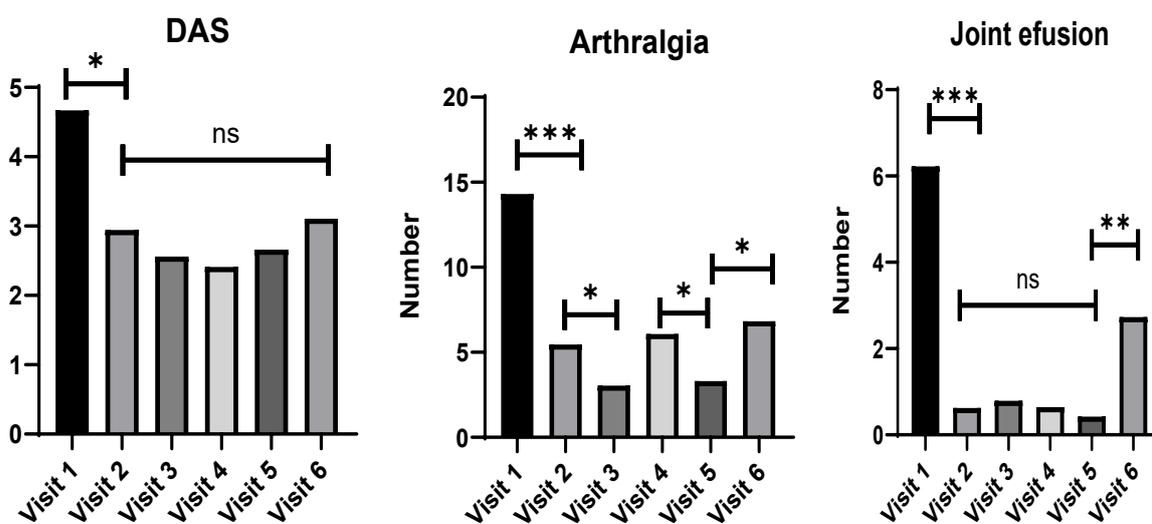
Parameter	N (%)
Sex	Male: 38 (48.1) Female: 41 (51.9)
Marriage	Married: 70 (88.4) Miss data: 9 (11.6)
Education	Under diploma: 62 (78.48) Diploma: 15 (18.98) Post graduate: 2 (2.53)

¹ Rheumatry.ir web site is under supervision of the Rheumatology Research Center in Shariati Hospital, Tehran Iran.

Parameter	N (%)
Residence	Urban: 45 (57) Rural: 34 (43)
Smoking	Smoker: 7 (8.9) No smoker: 63 (79.7) Miss data: 9 (11.4)
History of rheumatism in first degree	RA: 9 (11.39) SLE: 2 (2.53)
Positive history of disease	Treated Tuberculosis: 1 (1.26) Treated Brucellosis: 1 (1.26) Cerebrovascular accident (CVA): 1 (1.26) Chronic kidney disease (CKD): 2 (2.53)
Type of arthritis	Poly arthritis: 61 (77.21) Oligo arthritis: 12 (15.18) Mono arthritis: 1 (1.26) Poly arthralgia: 5 (6.32)
Diabetes	12 (15.18)
Hypertension	24 (30.37)
Ischemic heart disease	12 (15.18)
Hyperlipidemia	14 (17.72)
Hypothyroid	9 (11.39)
Post-partum relapse	2 (2.53)
Knee arthroplasty	2 (2.53)

RF and anti-CCP was positive in RA patients at 58.22% and 62.02%, respectively. High titer of RF on the first visit and all visits, thereafter, was seen in the patients at 25.31% and 32.91%, respectively. High titer of anti-CCP on the first visit and total visits at 36.7% and 45.56%,

respectively, were seen in the patients. The mean of DAS, arthralgia, joint effusion, morning stiffness, joint tenderness, ESR, and CRP in the first to sixth visits are shown in [Figure 1](#).



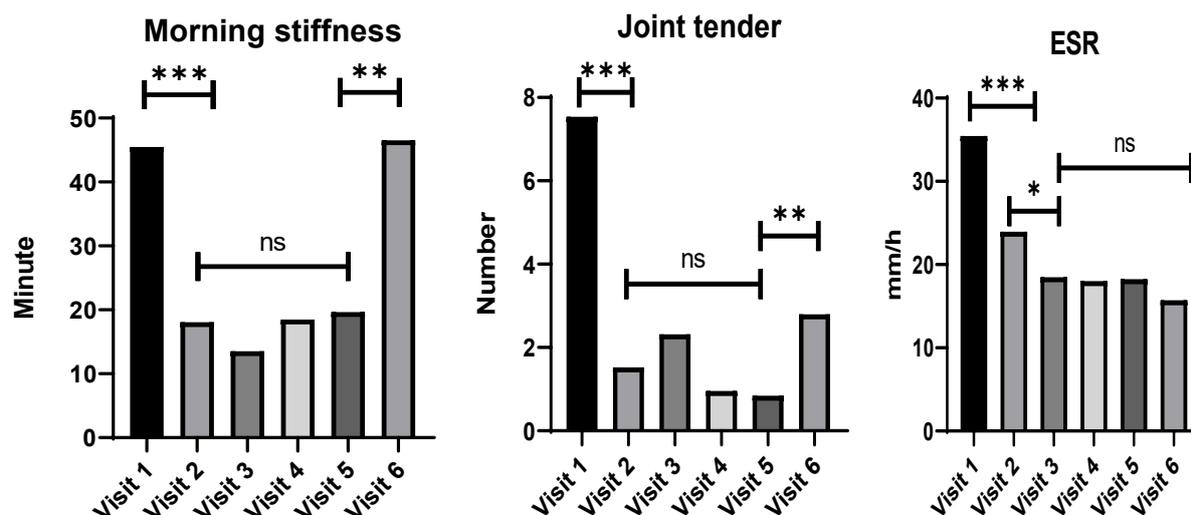


Figure 1. The mean of DAS, arthralgia, joint effusion, morning stiffness, joint tender, ESR and CRP in the first to sixth visits

The frequency of drugs used by patients on the first to sixth visits is shown in Table 2. Regarding extra-articular involvement, 10 cases (12.65 %) with pulmonary involvement were seen in one case of pleural effusion with positive anti-CCP, 4 cases of pulmonary fibrosis, and 5 cases of non-significant LAP (Table 3). Rheumatoid

nodule was seen in 3.7 % of the patients. Discontinuation of treatment due to drug side effects or arbitrary discontinuation is shown in Table 4. The most common cessation of treatment was due to the side effects of MTX, HCQ, and arbitrary discontinuation.

Table 2. Frequency of medications used by patients in the first to sixth visits.

Visit	Patient (n)	PDN	HCQ	MTX	F.A	SSZ	LEF	Infliximab	Altebrel	Calcium-D
1	79	77	66	62	67	13	0	0	0	61
2	73	68	60	62	65	16	2	0	2	60
3	52	41	36	41	44	9	1	1	0	38
4	33	26	17	21	25	8	1	1	0	24
5	20	18	9	16	17	6	0	1	1	16
6	13	8	5	10	10	2	0	0	1	0

Visit	Patient (n)	Vitamin D3	Alendronat	Cinnopar	Zolendoronat	Denozomab	NSAID	Injection to joint
1	79	39	21	1	1	0	17	7
2	73	42	23	5	0	1	7	4
3	52	29	16	0	1	0	4	0
4	33	18	12	0	0	0	4	0
5	20	9	6	1	0	0	2	1
6	13	9	6	0	0	1	1	0

Table 3. Frequency of extra-articular involvement

Parameter		N (%)
Pulmonary	Exudative pleural effusion	1 (1.26)
	Pulmonary fibrosis	4 (5.06)
	Non-significant LAP	5 (6.32)
Rheumatoid nodule		3 (3.79)

Table 4. Discontinuation of treatment in RA patients

Parameter	N (%)
MTX discontinue due to pregnancy	3 (3.79)
MTX discontinue due to raise of creatinine	4 (5.06)
MTX discontinue due to raise of liver enzymes > 2 folds	4 (5.06)
Reduction of MTX dose due to raise of liver enzymes 1- 2 folds	4 (5.06)
MTX discontinue due to pulmonary involvement	3 (3.79)
SSZ discontinue due to gastrointestinal intolerance	3 (3.79)
Altebrel discontinue due to intolerance	2 (2.53)
HCQ discontinue due to ocular complications	7 (8.86)
HCQ discontinue due to Pigmentation	3 (3.79)
HCQ discontinue due to vertigo	1 (1.26)
Arbitrary discontinue due to breastfeeding	2 (2.53)
Arbitrary discontinue	16 (20.25)
Discontinue treatment under the supervision of a physician	2 (2.53)
No data	11 (13.92)

The frequency of osteoarthritis (OA), osteopenia and osteoporosis in RA patients is shown in [Table 5](#). [Table 6](#) shows the frequency of admission, and foot and ankle

arthritis. Evaluation of flare-up signs on the sixth visit of the RA patients was performed and the findings are presented in [Table 7](#).

Table 5. The frequency of osteoarthritis (OA), osteopenia and osteoporosis in RA patients.

Visit	Knee OA	Hand OA	Hip OA	Osteopenia	Osteoporosis
1	17	15	0	13	8
2	22	10	2	10	9
3	11	5	1	4	9
4	9	5	1	4	5
5	6	4	0	4	2
6	4	2	1	4	1
Total visit	34	19	3	21	18

Table 6. Frequency of admission, foot arthritis and ankle arthritis in RA patients.

Parameter	Frist visit	Total visits
Admission	14 (17.72)	1 (7.04)
Foot arthritis	6 (7.59)	10 (3.7)
Ankle arthritis	22 (27.4)	34 (12.59)

Table 7. Evaluation of flare signs in sixth visit of RA patients (N=13)

Parameter	N (%)
Raise of arthralgia	4 (30.77)
Joint effusion	3 (23.07)
Joint tenderness	3 (23.07)
Raise of morning stiffness	4 (30.77)

Discussion

The aim of this study was to register and evaluate the demographic, clinical, and laboratory information of RA patients referred to Imam Khomeini Hospital, Tehran, Iran. The results of the present study showed that the mean age of the patients is 52 years. The minimum and maximum age of the patients were 24 and 83 years, respectively, which is consistent with the age range of men and women in previous studies, that is, 55-64 and 74-84 years. In a similar study by Eri Kato et al. [10], the mean age of RA patients was 55.8 years, and similar to the present study, no significant age range difference was observed between the ages of the men or of the women.

The female/male ratio was 1.06. Although RA was more prevalent among women, it is not in full agreement with the literature that the incidence of women is 2 to 3 times higher than that of men. In a similar study by Shangyi et al., 80.6% of RA patients in a single registry in China were female [11]. About 78% of patients had undergraduate education. Given that according to previous studies the disability of RA is higher in people with lower education, the need for education in these patients is more emphasized [11, 12].

Approximately 8.9% of the patients were smokers. The relative risk of RA is about 1.5 to 3.5 times higher in smokers, especially in women. The risks in smoking are exclusively related to RF and Anti-CCP positivity [13]. In the patients of the present study, about 66% and 83% of smokers were positive for RF and anti-CCP.

Cardiovascular risk factors in our patients were hypertension (30%), hyperlipidemia (17%) and diabetes (15%), respectively, which reminds us to pay special attention to the appropriate treatment of these cases. Similar to these findings, in a study reported by Helga Radner et al., the prevalence of hypertension, hyperlipidemia, and diabetes in RA patients was 18.6%, 6.2%, and 9.9%, respectively [14]. Given that

cardiovascular causes are one of the most common causes of death in RA patients, control of RA disease, which causes a systemic inflammation and ultimately a risk factor for heart disease and control of other risk factors, is essential [12, 15].

Fifty-eight percent and 62% of the patients were RF and anti-CCP positive and 32.91 and 45.56% of RF and anti-CCP patients had high titers. Considering that RF and anti-CCP are progressive predictor factors in the patients and are related to the prognosis of the disease, so it is necessary to pay more attention to these cases [12, 16, 17]. In this regard, a similar study by Emil Rydell et al. [18] was performed on 223 RA patients. The results of this study showed that smoking, RF, and anti-CCP significantly increased the risk of disease progression.

The mean ESR based on literature in RA patients is 50, which was an average of 35 in our patients. Subsequent visits show a decrease in ESR, which may indicate disease control along with other findings, including clinical examinations [17]. DAS-ESR was used to evaluate the activity of the disease, which averaged 4.6 at the initial visit and decreased to 2.6 at the fourth visit, which is defined as remission. However, there is an increase in DAS in visits 5 and 6, which can be due to a flare-up of RA. Despite the increase in DAS, it was still less than 3.2, which is defined as low disease activity [19, 20]. Kuriya B et al. [21] studied the DAS-ESR and DAS-CRP thresholds in 995 RA patients. Results of their study showed that the threshold values of DAS, based on CRP, are lower than DAS-ESR and the values of 2.5, 2.9 and 4.6 are considered as remission, low disease activity, and high disease activity, respectively.

Regarding extra-articular involvement, 10 cases (12.65%) with pulmonary involvement were seen in one case of pleural effusion with positive anti-CCP, 4 cases of pulmonary fibrosis and 5 cases of non-significant LAP. In a study by Koduri et al. on 1,400 RA patients, the incidence of pulmonary involvement was 52 in 1,400 (3.71%) in

these patients [22]. Rheumatoid nodules were observed in 3.8 % of the RA patients. In a study on 214 RA patients, Mirjana Ziemer et al. reported a prevalence of rheumatoid nodules of 27.5% [23]. Other extra-articular involvement, including ocular and cardiovascular involvement, was not seen in the patients in the present study.

HCQ discontinuation was seen in 8.8% of patients due to ocular complications. According to sources, the probability of retinal toxicity in the presence of risk factors such as consumption for more than ten years, doses higher than 6 mg/kg, and renal failure of stage three and higher is about 7.5% in the first ten years of use and lack of risk factor is less than 2% [12]. In 3.79% of the cases skin pigmentation was observed due to HCQ complications. Rash and hyperpigmentation are common complications of HCQ that lead to discontinuation of treatment [12, 24].

An increase in liver enzymes more than two-fold was seen in 5% of the patients, which led to discontinuation of MTX treatment, and in about 5% of the patients there was an increase between 1-2 times normal, which was eliminated by reducing the dose of the drug. According to similar studies, the increase in liver enzymes above one-fold normal is about 22% and more than twice is 1-2%, which is more likely in the presence of other risk factors

such as diabetes and obesity and the use of other hepatotoxic drugs [12, 25].

This study has potential limitations that should be noted. We had limited time to do research and collect data and lack of trained personnel for registration of RA was another limitation. Implementation of the registry system for rheumatic diseases in all rheumatology clinics in Iran is strongly suggested.

Conclusion

Clinical and laboratory data showed considerable disease control, however, relapse of disease was seen due to drug discontinuation. Disease registry makes it possible to record the necessary information of each patient, including demographic, clinical, paraclinical findings, and consultations giving the physician accurate access to patient information and unnecessary duplication of paraclinical examinations.

Conflict of interest

The authors report that they have no conflicts of interest to declare.

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