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CLINICAL PROFILE AND TREATMENT OUTCOMES OF PATIENTS WITH RHEUMATOID ARTHRITIS AT A TERTIARY CARE HOSPITAL OF PAKISTAN

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Abstract:

Objective: *To examine the clinical and laboratory features and to measure treatment outcomes after using different disease-modifying antirheumatic drugs in patients of rheumatoid arthritis.*

Methods: *The observational study was conducted at the Rheumatology Unit of Federal Government Polyclinic Hospital, Islamabad, Pakistan, from March 15, 2017, to September 14, 2018, and comprised rheumatoid arthritis patients of either gender diagnosed according to the American College of Rheumatology criteria. Disease activity score-28 and a thorough examination of the joints were employed to assess disease activity. Data was analyzed using SPSS 20.*

Results: *Of the 63 patients, 18(28.6%) were males and 45(71.4%) were females. The overall mean age was 43.09±13.03 years and mean duration of disease was 5.05±5.58 years. Seropositive disease was noted in 58(92.1%) patients and they had a higher level of erythrocyte sedimentation rate. Mean disease activity score-28 score at baseline was 5.52±0.99. At the end of 6 months, 44(69.8%) patients were in remission, 18(28.6%) had low disease activity and 1(1.6%) had moderate disease activity. The mean DAS score reduced to 3.11 0.77 at 6 months. Overall, 28(44.4%) patients had joint deformities.*

Conclusion: *Females had a higher incidence of rheumatoid arthritis compared to males, and, overall, there was a high prevalence of joint deformities.*

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INTRODUCTION:

Rheumatoid arthritis (RA) is the most frequently encountered autoimmune disease.[1] The prevalence of RA varies between 0.5% and 1% worldwide.[2] It has a reported incidence of 0.81% in the United Kingdom[3] and 0.75% in India.[4] It is a polyarticular disease with symmetric involvement of the joints. If left untreated, it can cause destruction of joints leading to disability.[1] Women are affected more often than men by RA, and women of childbearing age carry the most risk.[5]

The field of rheumatology is still developing in Pakistan. There are only a few hospitals in Pakistan with established rheumatology clinics and qualified rheumatologists. There are no national registries to keep account of different features of autoimmune diseases and their treatment outcomes. A few studies have been done on the local population which provide valuable insight into the details of these autoimmune diseases, including RA.[69] The current study was planned to look at the treatment outcomes using various drugs used for RA treatment.

PATIENTS AND METHODS:

The observational study was conducted at the Rheumatology Clinic of Federal Government Polyclinic
Hospital, Islamabad, Pakistan, from March 15, 2017, to September 14, 2018, which represented the first year of its inception. After approval from the institutional ethics committee, all patients who attended the Rheumatology Clinic were considered. These included both newlydiagnosed patients as well as those who were already diagnosed with RA but were attending this clinic for the first time. Those included were patients who fulfilled the American College of Rheumatology (ACR) criteria for RA.[10] Patients who had overlap of RA with other connective tissue diseases, like systemic lupus erythematosus (SLE) were also included in the study. The patients who came to the clinic regularly for the following six months for designated follow-ups made up the final sample. Those who showed poor compliance with the treatment or who were irregular in follow-up were excluded. After taking consent from each patient,epidemiological, clinical and laboratory data was collected on a pre-designed proforma. Detailed history about age, marital status, educational level, occupation, duration of disease and different clinical features of the disease was also taken. Patients with any formal education were classified as literate.

This was followed by a thorough examination of the joints to assess the disease activity using the Disease activity score-28 (DAS-28).[11] Thorough examination of other systems of the body was also done to look for systemic manifestations of the disease and also to rule out other co-morbid conditions. Routine blood tests, like blood complete picture (CP), erythrocyte sedimentation rate (ESR), liver and renal function tests along with fasting and random blood glucose levels were done. RA seropositivity was checked through either RA factor and/or anti-cyclic citrullinated peptide (Anti-CCP) antibodies. Radiographs of hands, feet and other involved joints of the patients were taken to look for subtle changes related to RA. Patients who had a disease duration <1 year and had low disease activity were not radiographed as their chances of having any positive findings on X-rays were very low. Xray chest was also done in all patients, but pulmonary function tests (PFTs) were ordered only in those who had a history of shortness of breath or dry cough. Those who were found to have abnormality on either X-ray chest or PFTs were advised to get their high-resolution computed tomography (HRCT) scan done to rule out the presence of interstitial lung disease (ILD) or any other RA manifestation in the lungs. Since all patients were to be started on disease-modifying anti-rheumatic drugs (DMARDs), hepatitis B and C status of all patients was also checked. Abnormality in lipid profile is commonly encountered in RA, and it was also tested along witha baseline electrocardiogram (ECG).

Data was analysed using SPSS 20. Frequencies and percentages were calculated for qualitative variables. Means and standard deviations were calculated for quantitative variables. Patients were grouped according to their DAS-28 scores into mild, moderate and severe disease activity. The frequencies of all variables across these groups were compared, and $p<0.05$ was considered statistically significant.

RESULTS:

Of the 87 RA patients, 63(72.4%) met the inclusion criteria. Of them, 18(28.6%) were males and 45(71.4%) were females. The overall mean age was 43.09±13.03 years and mean duration of disease was 5.05±5.58 years. Seropositive disease was noted in 58(92.1%). RA factor was positive in 55(87.7%) patients and anti-CCP antibodies in 54(85%) (Table-1).

At presentation, 2(3.2%) patients had low disease activity, 17(26.9%) had moderate and 44(69.8%) had high disease activity on the basis of the DAS-28 score. The mean DAS28 score at presentation was 5.52±0.99. After 6 months,

Table-1: Baseline demographic characteristics.

Variables	Values (Percentage)
Age	43.09 ± 13.03
Duration of disease	5.05 ± 5.58
Gender	
Male	18 (28.6%) Female
45 (71.4%) **Education**	
Illiterate	19 (30.2%)
Literate	44 (69.8%) **Smoking**
Yes	10 (15.9%) No
53 (84.1%) **Extra-articular manifestations**	
None	58 (92.1%)
Yes	5 (7.9%)
Hypertension	
Yes	14 (22.2%) No
49 (77.8%)	
Diabetes	
Yes	9 (14.3%)
No	54 (85.7%) **Dyspepsia**
Yes	22 (34.9%) No
41 (65.1%)	
Osteoporosis	
No	6 (9.5%)
Osteopenia	11 (17.5%) Osteoporosis
16 (25.4%) NA	30 (47.6%)
Dyslipidaemia	
No	24 (38.1%) Yes
39 (61.9%) **Joint deformities**	
Yes	28 (44.4%) No
35 (55.6%) **Seropositivity**	
Seropositive	58 (92.1%)
Seronegative	5 (7.9%)
ESR	47.3 ± 21.5
Haemoglobin	12.18 ± 1.47
Platelets	301412 ± 94519

ESR: Erythrocyte Sedimentation Rate.

44(69.8%) patients were in remission, 18(28.6%) had low disease activity and 1(1.6%) had moderate disease activity. The mean DAS-28 score after 6 months was 3.11±0.77 (Tables-2-3).

Overall, 60(95%) patients received non-steroidal anti-inflammatory drugs (NSAIDs). Prednisolone was used in 58(90.5%) patients. The maximum dose of prednisolone used was 10mg per day. Of the 58 patients, 3(5%) managed to totally stop oral steroids after taper. The remaining 55(95%) patients continued

Table-2: Patient characteristics according to the isease activity score-28 (DAS 28) - Erythrocyte Sedimentation Rate (ESR) score at presentation.

Variables	DAS 28 at presentation		P value
	Low ≥2.6 - ≤3.2	Moderate >3.2 to ≤5.1	High >5.1
Gender			
Male			
1 (1.6%)	6 (9.5%)	11 (17.5%)	0.96
Female	1 (1.6%)	11 (17.5%)	33 (69.8%)
Education			
Illiterate	1 (1.6%)	5 (7.9%)	13 (20.6%)
0.81			
Literate	1 (1.6%)	12 (19%)	31 (49.2%)
Smoking			
Yes			
0	4 (6.3%)	6 (9.5%)	0.66
No	2 (3.2%)	13 (20.6%)	38 (60.3%)
Extra-articular manifestations			
None	1 (1.6%)	15 (23.8%)	42 (66.7%)
0.53			
Yes	1 (1.6%)	2 (3.2%)	2 (3.2%)
Hypertension			
Yes	0	5 (7.9%)	9 (14.3%)
0.57			
No	2 (3.2%)	12 (19%)	35 (55.6%)
Diabetes			
Yes	0	4 (6.3%)	5 (7.9%)
0.41			
No	2 (3.2%)	13 (20.6%)	39 (61.9%)
Dyspepsia			
Yes	0	7 (11.1%)	15 (23.8%)
0.51			
No	2 (3.2%)	10 (15.9%)	29 (46%)
Osteoporosis			
No			
0	3 (4.8%)	3 (4.8%)	0.78
Osteopenia			
0	2 (3.2%)		9 (14.3%)
Osteoporosis			
1 (1.6%)	4 (6.3%)		11 (17.5%)
NA			1 (1.6%)
8 (12.7%)			21 (33.3%)
Dyslipidemia			
No			
1 (1.6%)	9 (14.3%)	14 (22.2%)	0.26

Yes 3 (4.8%)	8 (12.7%)	30 (47.6%)
Joint deformities Yes 1 (1.6%) 0.7	9 (14.3%)	18 (28.6%)
No 1 (1.6%)	8 (12.7%)	26 (41.3%)
Seropositivity Seropositive 2 (3.2%) 0.85	16 (25.4%)	40 (63.5%)
Seronegative 0	1 (1.6%)	4 (6.3%)
ESR 16.5±9.19 0.03	41.7±20.2	50.8±21.06
Platelets 240500±55861 0.04	258882±85166	320613±94519

taking prednisolone during the whole study period. Of them, 24(44%) patients were taking prednisolone >5mg per day, 22(40%) 5mg per day, and 9(16%) were taking 2.5mg or less per day. Of the total patients, 21(34%) received intra-articular steroid injections. While all patients received DMARDs, a single DMARD was used in 53(84.1%) patients, 2 in 9(14.3%) and 3 in 1(1.6%) patients. Of the 53 patients who were on single DMARD, 42(79.2%) were on methotrexate, 6(11.3%) leflunomide, 3(5.6%) sulfasalazine and 1(1.6%) was on hydroxychloroquine. Adverse effects were seen in 8(12.7%) patients taking methotrexate, 1(1.6%) taking leflunomide and 1(1.6%) patient taking

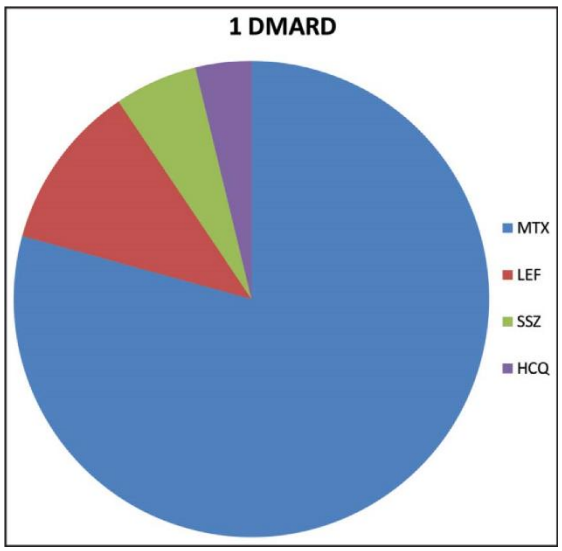
sulfasalazine. None of the patients received biologic therapy. Also, 22(34.9%) patients were on bisphosphonates, with 7(11.1%) on alendronate and 15(23.8%) on ibandronate.

The patients had a mean ESR of 47.33±21.5, haemoglobin (Hb) 12.18±1.47 and platelet count 301412±94519). Urinalysis showed proteinuria in 1 (1.6%) patient. This patient with proteinuria also had SLE and had nephritis secondary to SLE. Dual-energy X-ray absorptiometry (DEXA) scan was performed on 32(50.8%) patients, which showed normal result in 4(6.3%), osteopaenia in 12(19%) and osteoporosis in 16 (25.4%).

Table-3: Patient characteristics according to the disease activity score-28 (DAS 28) - Erythrocyte Sedimentation Rate (ESR) score at 6 months.

Variables	DAS 28 at 6 months		
P value			
Remission	Low	Moderate	
Gender			
Male	15 (23.8%)	3 (4.8%)	
0	0.33		
Female	29 (46%)	15 (23.8%)	
1 (1.6%)	**Education**		
Illiterate	14 (22.2%)	4 (6.3%)	
1 (1.6%)	0.47		
Literate	30 (47.62%)	14 (22.2%)	
0	**Smoking**		
Yes	8 (12.7%)	2 (3.17%)	
0	0.71		
No	36 (57.1%)	16 (25.4%)	
1 (1.6%)	**Extra-articular manifestations**		
None	40 (63.5%)	17 (27%)	
1 (1.6%)	0.86		
Yes	4 (6.3%)	1 (1.6%)	
0	**Hypertension**		
Yes	8 (12.7%)	6 (9.5%)	
0	0.38		
No	36 (57.1%)	12 (19%)	
1 (1.6%)	**Diabetes**		
Yes	4 (6.3%)	5 (7.9%)	
0	0.15		
No	40 (63.5%)	13 (20.6%)	
1 (1.6%)	**Dyspepsia**		
Yes	15 (23.8%)	7 (11.1%)	
0	0.72		
No	29 (46%)	11 (17.5%)	
1 (1.6%)	**Osteoporosis**		
No	6 (9.5%)	0	
0	0.68		
Osteopenia	6 (9.5%)	5 (7.9%)	
0			
Osteoporosis	10 (15.9%)	6 (9.5%)	
0			
NA	22 (34.9%)	7 (11.1%)	
1 (1.6%)	**Dyslipidaemia**		
No	21 (33.3%)	3 (4.8%)	
0	0.04		
Yes	23 (36.5%)	15 (23.8%)	
1 (1.6%)	**Joint deformities**		
Yes	18 (28.6%)	9 (14.3%)	
1 (1.6%)	0.44		
No	26 (41.3%)	9 (14.3%)	
0	**Seropositivity**		
Seropositive	40 (63.5%)	17 (27%)	
1 (1.6%)	0.86 Seronegative	4 (6.3%)	
1 (1.6%)	0		

Patients with a more active disease were more likely to have a raised ESR (p=0.03) and a raised platelet count (p=0.04). Patients with higher age were more likely to have extra-articular manifestations (p=0.01), hypertension (p=0.04), osteoporosis (p<0.01), dyslipidaemia (p=0.04) and joint deformities (p=0.04). Patients with dyslipidaemia had a more active disease after 6 months of treatment (p=0.04). Smokers were more likely to have joint deformities (p=0.045). Patients with extra-articular manifestations were more likely to have a higher DAS-28 score at presentation (p=0.014) but not at 6 months (p=0.51). Patients with anti-CCP antibodies were more likely to have joint deformities (p=0.001). Patients with a higher platelet count were more likely to have osteoporosis (p=0.02) and higher DAS-28 score at presentation (p=0.04).



MTX - Methotrexate, LEF - Leflunomide, SSZ - Sulfasalazine, HCQ - Hydroxychloquin.

Zigure-1: Disease-modifying antirheumatic drugs (DMARDs) used in the patients.

DISCUSSION

The field of rheumatology is still in its nascent phase in Pakistan, and the current study was planned to fill the gap in locally-produced literature. The male-female ratio was 2.5:1 which is comparable to a recent study in Karachi.[6]

Overall, 58(92.1%) patients had a seropositive disease which is considered a bad prognostic marker.[12] RA factor was positive in 55(87.7%) while Anti-CCP antibodies were detected in 54(85%) patients. This is comparable to a recent study in Lahore.[9] RA is considered a multisystem disease and can involve skin, lungs, heart, eyes etc.[13] Presence of these extra-articular features is considered a bad prognostic factor.[14] International studies show that almost 40% patients show extra-articular manifestations of the disease.[15] In the current study, only 5(7.8%) patients had them, and ILD was the most common manifestation.

The study showed that 28(44.4%) patients had some sort of joint deformity. This is quite a high figure and signifies the amount of time lost by the patients before they were properly seen by a rheumatologist and the treatment started. In Western countries, doctors now rarely come across these deformities because of prompt diagnosis and treatment of the disease. This shows how badly we need more qualified rheumatologists and rheumatology centres in the country. Figures from other part of Pakistan show radiological erosions in 40% patients and visible deformities in 4.4%[8].

Patients in our study were also checked for the presence of any co-morbid conditions. Dyslipidaemia was the most commonly observed keeping with the earlier studies.[16] These patients have an elevated risk of cardiovascular disease, with the risk of myocardial infarction increased by 1.63 times compared to the general population.[17] Dyspepsia was the second most commonly observed co-morbid condition in 22 (34.9%) patients. Osteoporosis was next in line seen in 16(25.4%) patients, but it should be noted that women in their child-bearing age were not screened for osteoporosis so the actual figure might be even higher. DEXA scan was done to screen for the presence of osteoporosis. Hypertension and diabetes were noted in 14(22.2%) and 9(14.3%) patients respectively.

Further, the final mean DAS score in the current study is comparable to that reported in a study from a tertiary care hospital in Lahore.[9] The other study had a 24-month duration.

Traditionally, methotrexate has been used as the first-line drug with good results.[18] In our population, intolerance to

condition found in 39(61.9%) patients. It was also noted that patients who had an active disease were more likely to have dyslipidaemia which is in methotrexatewas noted in 8(12.7%) patients. These patients on MTX achieved DAS-28 score of 3.16±0.39 at the end of 6 months, showing that it is a very welltolerated and effective drug. Overall, 44(69.8%) patients achieved remission and an additional 18(28.6%) achieved low disease activity state. However, whether patients managed to maintain this response over the next 6-12 months was not measured in this study. This shows that achieving remission or low disease activity is an achievable target. This is termed "treat to target approach" and is now a regular feature of treatment guidelines for RA.[19,20] It has also been noted that this approach is associated with fewer joint deformities and joint destruction.

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