Original Research Article

Study of clinical, laboratory profile and outcome with DMARDs on extra-articular manifestations of rheumatoid arthritis

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Abstract

Rheumatoid Arthritis is a chronic systemic inflammatory symmetrical polyarthritis. Extra articular manifestations (EXRAs) are common with RA. In the present article we have studied EXRA(Extra-articular manifestations of RA) which are associated with disease duration, in patients attending teaching medical institute attached to tertiary referral centre.

Key Word: Rheumatoid Arthritis (RA), Extra articular manifestations of RA (EXRAs), Disease Activity Score of 28 joints (DAS 28), Anti Citrullinated Peptide Test (Anti CCP) Disease modifying anti rheumatic drugs (DMARDs).

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INTRODUCTION

Rheumatoid arthritis (RA) is a systemic inflammatory polyarthritis that primarily affects small di-arthrodial joints of hands and feet in symmetrical pattern. It is a heterogeneous disease with variable severity, unpredictable course, and variable response to drug treatment[1]. In India, the prevalence of RA is 0.5% to 0.75%. The peak age of onset is in the fourth and fifth decade of life with more than 75% patients develop disease between 30 and 50 years of age. 40% of patients are considered to have extra articular manifestations (EXRA). Extra-articular manifestations are seen with severe active disease and with increased mortality. Predominant EXRAs involve exocrine glands, lungs, blood vessels, nerves, skin, eyes and heart. Fatigue and weight loss indicate disease activity. Anaemia, pure red cell aplasia (PRCA), multiple myeloma have been reported[2]. Patients with EXRAs with severe disease with higher mortality[3]. The EXRAs with high mortality are vasculitis, pericarditis, pleuritis, ILD, amyloidosis, Felty's syndrome[1,3]. Extra-articular involvement is more likely in those who have Rheumatoid Factor (RF) positive and or are HLA DR4 positive. Occasionally there are also systemic manifestations such as vasculitis, visceral nodules, Sjogren's syndrome or pulmonary fibrosis. Sjogren's syndrome, anaemia of chronic disease and pulmonary manifestations are relatively common in 6-10% in early disease and related to worse outcome. Occurrence of these systemic manifestations is a major predictor of mortality in patients with RA[3]. Both RA and EXRAs show a geographic trend, with higher prevalence in northern latitudes and low prevalence in developing countries. Indian patients are considered to have low incidence of EXRAs[4]. Assessment is done by Disease Activity Score of 28 swollen and tender joints (DAS 28) and classifies patients as high, moderate or low disease activity The objective of our study was to find how prevalent EXRAs with RA in our study group and outcome with Disease modifying anti rheumatic drugs (DMARDs).

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MATERIALS AND METHODS

100 RA patients were included in this study and investigated for EXRAs. Patients with spondyloarthropathies were excluded. A questionnaire was used to gather data prospectively. Demographic data on age, sex, age of onset of symptoms of RA and EXRAs were recorded. Patients were enrolled as per ACR 2010 EULAR criteria for RA. Laboratory data including complete blood count, erythrocyte sedimentation rate (ESR), C - reactive protein (CRP), liver function test, Anti Citrullinated Peptide Test (Anti CCP) , 2DEcho,CT chest were recorded in case record form. Eye examination was done by ophthalmologist. Disease activity was calculated of RA patients using DAS 28. DAS 28 was calculated at the beginning and at the end of 6 months of study to evaluate outcome with DMARDs in a tertiary care centre. Patients were grouped into remission group (DAS < 2.6), low disease activity group (DAS 2.7 to 3.1), Moderate disease activity group (DAS 3.2 to 5.1) and high disease activity group (DAS >5.1).

RESULTS

Prevalence of females with RA was 70% in our study. Extra articular manifestations were seen in our study were 48%. We added anaemia and dyslipidaemia as EXRAs in our study. The mean age at diagnosis in our study was 46.7 years. RA factor is positive in 78 out of our 100 patients (78%). Females with EXRA in our study were 36 out of 70 (51.4%). In patients with EXRA, 42 out of 78(53.8%) has RA factor positive, p value is 0.027, which is significant. In our study 66 patients are Anti CCP positive and 38 out of 66(58%) patients with EXRA, (P=0.014 significant), which shows correlation between Anti CCP and EXRA (**Table 1**). Commonest extra articular manifestations were anaemia (22%), ILD (12%), dyslipidaemia (8%), dry eyes (7%) and pulmonary hypertension (5%) (**Table 2**). In our study, DAS 28 was calculated at presentation and at follow up of 6 months. Patients with EXRA have high DAS suggestive of high disease activity (p= 0.003). We found that 74% patients were in remission of low disease activity group and 42% patients in remission of moderate to high disease activity group, with DMARDs, at the end of 6 months follow up (p=0.0169), which is significant.

Table 1: Comparisons between RA with EXRA and RA without EXRA.

N=100	With EXRA	Without EXRA	p value
	48	52	0.407(NS)
Age			0.069(NS)
Age <40(N=26)	8(30.76%)	40(54.04%)	
Age >40(N=34)	40(54.04%)	34(45.96%)	
Sex			
Males (N=30)	12(40%)	18(60%)	
Females (N=70)	36(51.4%)	34(48.6%)	
Disease Duration			**0.001(S)**
< 2 yrs (N=43)	12(27.9%)	36(63.15%)	
>2 yrs (N= 57)	36(63.15%)	21(36.85%)	
RA Factor Positive(N=78)	42(53.8%)	36(46.15%)	**0.027(S)**
Anti CCP Positive (N=66)	38(58%)	28(42%)	**0.014(S)**
DAS 28			**0.003(S)**
1.<2.6(Remission)	1(2.08%)	7(13.46%)	
2.7-3.1(Low)	19(38.58%)	31(59.61%)	
3.2-5.1(Moderate)	22(45.83%)	13(25%)	
4.>5.1(High)	6(12.5%)	1(1.92%)	

Table 2: EXRA in our study

SR.NO	System	Total	Male	Female
		48	**12**	**36**
1	Haematological	28(58.3%)	10(83.33%)	18(50%)
	A. **Anaemia**	**22**(45.83%)	8(66.66%)	14(38.8%)
	a. Anaemia of chronic disease	17(35.41%)	8(66.66%)	9(25%)
	b.Fe deficiency anaemia	5(10.41%)	0	5(13.8%)
	B.Leucopenia	0	0	0
	C. Thrombocytopenia	6(12.5%)	2(16.66%)	4(11.11%)
	D. Eosinophilia	0	0	0
2.	Pulmonary	14(29.16%)	3(25%)	11(30.55%)
	A.**ILD**	**12**(25%)	2(16.66%)	10(27.77%)
	B.Pleural effusion	2(4.16%)	1(8.33%)	1(2.77%)

3.	Cardiac	14(29.16%)	3(25%)	11(30.55%)
	A.**Dyslipidemia**	**8**(16.66%)	1(2.08%)	7(14.58%)
	B.**Pulmonary hypertension**	**5** (10.41%)	1(2.08%)	4(11.11%)
	C. IHD	1(2.08%)	1(2.08%)	0
4.	Ocular	11(22.91%)	2(16.6%)	9(25%)
	A.Scleritis	1(2.08%)	0	1(2.77%)
	B.Episcleritis	1(2.08%)	0	1(2.77%)
	C.Sjogren's syndrome	2(4.16%)	0	2(5.55%)
	D. **Dry eyes**	**7**(14.58%)	2(16.66%)	5(13.88%)
5	Renal	3	3	0
	Proteinuria	3(6.25%)	0	3(8.33%)
	Amyloidosis	0	0	0
6	Skin	3(6.25%)	0	3(8.33%)
7	Neurological	0	0	0

Table 3: Comparison of our study with other studies

Sr. No		Our Study N=100	Bharadwaj *et al* N=140	Turessan *et al* N=424
1	Prevalence of EXRA	48%	36(25.7%)	169(39.8%)
2	Females	70%	81.43%	76.43%
3	Females with EXRAs	75%	80.50%	69.2%
4	Age at diagnosis	46.32yrs	46yrs	57.8yrs
5	Mean duration of disease to develop EXRAs	2.7yrs	4yrs	5.9 yrs
6	Positive RA Factor	78%		
7	RA Factor positive with EXRAs	87.5%		
8	Anti CCP positive	66%		
9	Anti CCP positive with EXRAs	79%		
10	EXRAs			
	1.Anaemia	22(45.83%)	0	0
	2. ILD	12(12%)	13(9.2%)	25(5.8%)
	3.Dyslipidemia	8(8%)	0	0
	4. Dry Eyes	7(7%)	4(2.85%)	41(9.6%)
	5. PAH	5(5%)	0	0
	6. Pericarditis	0	0	4.2%
	7.Neuropathy	0	12(8.57%)	8(1.8%)
	8. Vasculitis	0	3(2.14%)	14(3.3%)
	9. Scleritis	1(1%)	3(2.14%)	3(0.7%)
	10.Episcleritis	1(1%)	1(0.7%)	3(0.7%)
	11. Rheumatoid Nodule	2(2%)	4(8.5%)	114(26.85%)
	12.Panniculitis	3(6.25%)	0	0
	13. Felty's syndrome	0	0	9(2.1%)
	14. Pleuritis	2(2%)	0	19(4.5%)

DISCUSSION

Aim of the present study was to find prevalence, clinical and laboratory profile of extra articular manifestations of Rheumatoid arthritis patients and correlation with RA Factor, Anti CCP positivity and outcome with DMARDs with disease activity measured by DAS 28. The data was compared with 2 studies i.e. Turesson *et al* [3] and Bharadwaj *et al* [5]. Percentage of females is 81.43% in Bharadwaj and 76.43% in Turesson *et al* studies and 70% in our study. Mean age at diagnosis, 46 years was in Bharadwaj study and 57.8 years in Turesson and 46.32 in our study. The mean duration of disease was 4 years in Bharadwaj and 5.9 years in Turesson studies and 2.75 in our study. RA factor positive in 78 out of 100 patients (78%). Extra articular manifestations were 25.7% in Bharadwaj and 39.8% in Turesson. The reason for this could be due to addition of anaemia and dyslipidaemia in our study, which were not considered in both those studies. (**Table 3**). Females with EXRA in our study were 75%, in Bharadwaj study 80.50%, in Turesson study 69.2%. Patients with disease duration more than 2 years were more prevalent with EXRA than patients with disease duration less than 2 years (p = 0.001) which is comparable with data of Bharadwaj and Turessan. Disease duration more than 2 years had more EXRA in our study which is similar with other 2 studies (p = 0.001). RA factor positive in 78 out of 100 patients (78%) and in patients with EXRA 42 out of 48(87.5%) ,p value

is 0.027, which is significant and similar findings are also seen in Turesson *et al* study. 45.83 % patients had anaemia in our study. In Bharadwaj study ,EXRAs were, ILD 13 (9.29%), neuropathy was 12 (8.57%), dry eyes 4 (2.85%), vasculitis 3 (2.14%), scleritis 3 (2.14%) and in Turesson study, EXRAs were rheumatoid nodule 114 (26.85%), pleuritis 19(4.5%), pericarditis 18 (4.2%) , vasculitis 14 (3.3%), Felty's syndrome 9 (2.15%), dry eyes 4(9.6%),scleritis and episcleritis 3 (0.7%) and amyloidosis 3 (0.7%).Study conducted by Chanakya had found 56% patients of RA with anaemia [6]. In study conducted by Omar Sharif Mullick *et al*, lipid profile was studied as a marker of endothelial dysfunction with detailed lipid profile and brachial artery flow mediated vasodilatation which showed that patient of RA showed atherogenic lipid profile [7]. PAH was 5% in absence of heart disease and ILD. Study by Carlos *et al* showed high incidence of PAH in RA patients [8]. Study done by Cengiz *et al* showed 39% patients having Anti CCP positive having EXRA with insignificant correlation between Anti CCP and EXRA [9].In study done by Prasanta parida *et al*, DAS was more than 5.1 in 50% patients with EXRA [10].

CONCLUSIONS

The prevalence of EXRA manifestations in RA is 48%. Occurrence of EXRAs increases with disease duration. Anaemia, interstitial lung disease, dyslipidaemia and pulmonary hypertension are the commonest EXRAs. EXRAs more common in RA and anti CCP positive. High DAS 28 associated with increased probability of EXRA. DMARDs beneficial in controlling disease activity in RA with EXRAs.

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