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Do Sero-Negative Patients Behave Differently Than Sero-Positive Patients In Rheumatoid Arthritis

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Abstract

Rheumatoid arthritis (RA) is known as a systemic inflammatory autoimmune disease which mainly affects women in comparison to male with a ratio of 3:1. Seronegative RA patients reveals more active disease at baseline, but showed a better retaliation to treatment compared with Seropositive RA patients. This study aimed to understand how sero-negative patients behave differently than sero-positive patients in Rheumatoid Arthritis.

Keywords: - Rheumatoid arthritis, Disease, Seronegative, Antibodies, Medicity.

INTRODUCTION

One of the systemic inflammatory autoimmune disease, Rheumatoid arthritis (RA) is affects mainly women as compared to male with a ratio of 3:1 (Markatseli et al., 2010). It is important to understand the pathogenesis of RA by timely diagnosis for proper treatment. Few studies indicated that a subpopulation of patients suffered with rheumatoid arthritis, diagnosed on clinical, radiologic and pragmatic grounds, but with negative rheumatoid factor tests, represent a clinical entity quite dissimilar to that of seropositive rheumatoid arthritis (Edelman et al., 1983). The frequency of hypertension and cardiovascular disease is much higher in older patients affected with RA than in general population. In addition, the rate of increase of hypertension and cardiovascular disease is also high (Mochizuki et al., 2019). Seronegative RA patients showed better response to treatment as compared to Seropositive RA patients in later stages (Choi et al., 2018). Anti-CCP test was found more specific than commonly used RF test (95% versus less than 90%) and has a better sensitivity (more than 70%). Testing for anti-CCP autoantibodies is widely accepted as an indispensable tool for diagnosis and early treatment in the management of rheumatoid arthritis patients (Venrooij et al., 2008).

This study aimed to understand how sero-negative patients behave differently than sero-positive patients in Rheumatoid Arthritis.

MATERIALS AND METHODS

This study was planned as a cross-sectional observational study, wherein 256 patients 18 years and above confirmed as RA, who reported for consultation at rheumatology department of Medanta –The Medicity hospital from August 2020 to February 2022 were enrolled. This study was based on patients diagnosed with RA and fulfils the American College of Rheumatology classification criteria (Panay et al., 1987) and/or the American College of Rheumatology/European League against Rheumatism criteria. The clinical profile of the patients studied appears in Table 1. Patients were excluded with presence of HIV 1 or 2, Hepatitis B or C viruses and VDRL; pregnant females, history of intake/administration of any investigational treatment within the last 12 weeks

in a clinical study prior to day of consultation. This study was initiated after approval of Medanta Institutional Ethics committee (MIEC). In total, 256 patients were enrolled for this study, wherein 245 (95.7%) patients were identified as Seropositive. Sero-positive RA was defined as RF and/or anti-CCP positive and sero-negative patients defined as both RF and anti-CCP negative. Medical records were mainly accessed from the Medanta's patient records i.e., Electronic hospital information system (eHIS). The study was conducted according to the IEC approved protocol, Site-SOPs, ICH GCP guidelines, ICMR guidelines and also followed the principles of Declaration of Helsinki and applicable regulatory requirements.

Data Collection

Data of confirmed RA patients was collected on the day of consultation. The data comprised of: a. Demographic data ; b. age at onset; c. Disease duration , d. ANA status & DAS 28 score , e. deformities & erosion, f. Treatment status and Comorbidities; g. extra articular manifestation such as nodules, eye, sicca, cardiac, ILD, vasculitis, neuropathy, Fibromyalgia, Osteoporosis and malignancy; & h. current and past Treatments with DMARDs, Biologicals & JAK inhibitors. Data related to patient's treatment with methotrexate (MTX), leflunomide, sulfasalazine and hydroxychloroquine (HCQs) was also collected.

Statistical Method

The analysis included profiling of patients on different demographic, clinical, duration of disease, disease activity measures, and medications. A detailed analysis was taken up on patients with Seropositive and Seronegative group. Descriptive analysis of quantitative parameters were conveyed as means with standard deviation and median with inter quartile range (IQR). Categorical data were expressed as absolute number and percentage. Independent Student t – test/ Wilcoxon rank sum tests was used for testing of mean/median difference between the two independent groups. Cross tables were generated and Chi square test was also applied for testing of associations. P-value < 0.05 is considered statistically significant. All analysis was done using SPSS software, version 24.0.

RESULTS

The study included 256 patients of RA. Seropositivity rate was 95.7% (n = 245).

Table 1: Patients Characteristics with respect to study groups

	Seropositive (n = 245)	Seronegative (n = 11)	Total (n = 256)	p-value
Gender, n (%)				
Female	213 (86.9%)	10 (90.9%)	223 (87.1%)	0.701
Male	32 (13.1%)	1 (9.1%)	33 (12.9%)	
Age (Years), n (%)				
≤ 40	25 (10.2%)	0 (0.0%)	25 (9.8%)	0.551
41 – 50	50 (20.4%)	2 (18.2%)	52 (20.3%)	
51 – 60	79 (32.2%)	3 (27.3%)	82 (32.0%)	
61 – 70	61 (24.9%)	5 (45.5%)	66 (25.8%)	
> 70	30 (12.2%)	1 (9.1%)	31 (12.1%)	
Mean ± SD	56.5 ± 11.4	59.2 ± 8.4	56.6 ± 11.3	0.438
Age of Onset (Years), n (%)				
≤ 35	92 (37.6%)	3 (27.3%)	95 (37.1%)	0.617
35 - 60	143 (58.4%)	7 (63.6%)	150 (58.6%)	
> 60	10 (4.1%)	1 (9.1%)	11 (4.3%)	
Mean ± SD	40.2 ± 12.3	43.0 ± 9.6	40.4 ± 12.2	0.460
Disease Duration (Years), n (%)				
≤ 2	10 (4.1%)	1 (9.1%)	11 (4.3%)	0.803
2 – 5	8 (3.3%)	0 (0%)	8 (3.1%)	
5 - 10	42 (17.1%)	2 (18.2%)	44 (17.2%)	
> 10	185 (75.5%)	8 (72.7%)	193 (75.4%)	
Median (IQR)	15.2 (10.1 - 21)	12.2 (6.6 - 22)	15.2 (10.1 - 21)	0.801

***p – value < 0.05, statistically significant; SD – Standard Deviation, IQR – Inter Quartile Range,**

Most of the patients were female – 223 (87.1%) with mean age of 56.6 ± 11.3 years (Range: 29 – 88 years). Gender and age were comparable between seropositive and seronegative groups (p > 0.05). The onset age of RA for Seropositive and seronegative groups were 40.2 ± 12.3 years and 43.0 ± 9.6 years respectively. The median disease duration for Seropositive and Seronegative groups were 15.2 years (IQR: 10.1 – 21.0 Years) vs 12.2 years (IQR: 6.6 – 22) years (Table 1).

Table 2: Comorbidities

Comorbidities	Seropositive (n = 245)	Seronegative (n = 11)	Total (n = 256)	p-value
Hypertension	69 (28.2%)	3 (27.3%)	72 (28.1%)	0.949
Hypothyroid	61 (24.9%)	0 (0%)	61 (23.8%)	0.058
Diabetes M	28 (11.4%)	0 (0%)	28 (10.9%)	0.235
CAD	22 (9%)	0 (0%)	22 (8.6%)	0.299
H/O TB	13 (5.3%)	1 (9.1%)	14 (5.5%)	0.589
Asthma	4 (1.6%)	0 (0%)	4 (1.6%)	0.669
Chronic Kidney Disease	2 (0.8%)	0 (0%)	2 (0.8%)	0.764

***p – value < 0.05, statistically significant**

In seropositive group, about 25% patients had hypertension and hypothyroid whereas about 10% patient had history of diabetes and CAD. TB was reported by 5.3% patients and Asthma and CKD were less than 2%. In seronegative group, only hypertension and TB were reported by 3 (27.3%) and one patient respectively (Table 2).

Table 3: Extra Articular Manifestation

Extra Articular Manifestation	Seropositive (n = 245)	Seronegative (n = 11)	Total (n = 256)	p-value
Sicca Symptoms	126 (51.4%)	6 (54.5%)	132 (51.6%)	0.840
ILD	39 (15.9%)	1 (9.1%)	40 (15.6%)	0.542
Osteoporosis	36 (14.7%)	1 (9.1%)	37 (14.5%)	0.605
Nodules	25 (10.2%)	1 (9.1%)	26 (10.2%)	0.905
Fibromyalgia	21 (8.6%)	1 (9.1%)	22 (8.6%)	0.952
Neuropathy	8 (3.3%)	0 (0%)	8 (3.1%)	0.543
Malignancy	3 (1.2%)	0 (0%)	3 (1.2%)	0.712
Vasculitis	3 (1.2%)	0 (0%)	3 (1.2%)	0.712

*p – value < 0.05, statistically significant

In seropositive group, about 50% patients had symptom of sicca. About 15% patients had ILD and Osteoporosis. Nodules and Fibromyalgia were reported by about 10% patients. Neuropathy, Malignancy and Vasculitis were less than 3%. Out of 11 seronegative patients, 6 had symptom of sicca. One case of each ILD, osteoporosis, nodules and fibromyalgia were reported (Table 3).

Table 4: ANA and Das 28 ESR Results

	Seropositive (n = 245)	Seronegative (n = 11)	Total (n = 256)	p-value
ANA, n (%)				
Positive	49 (50.5%)	2 (28.6%)	51 (49%)	0.262
Negative	48 (49.5%)	5 (71.4%)	53 (51%)	
Das 28 ESR, n (%)				
Remission	36 (16.3%)	3 (30%)	39 (16.9%)	0.656
Low Disease Activity	42 (19%)	1 (10%)	43 (18.6%)	
Moderate Disease Activity	104 (47.1%)	4 (40%)	108 (46.8%)	
High Disease Activity	39 (17.6%)	2 (20%)	41 (17.7%)	

***p – value < 0.05, statistically significant**

ANA positivity rate was higher (50.5%) for seropositive as compared to seronegative (28.6%), however the difference was not statistically significant. Das 28 ESR was not statistically different between the seropositive and seronegative patients (p = 0.656) (Table 4).

Table 5: Deformities and Erosions

	Seropositive (n = 245)	Seronegative (n = 11)	Total (n = 256)	p-value
Deformities, n (%)				
Yes	245 (100%)	11 (100%)	256 (100%)	-
No	0 (0%)	0 (0%)	0 (0%)	
Erosions, n (%)				
Yes	108 (44.1%)	4 (36.4%)	112 (43.8%)	0.614
No	137 (55.9%)	7 (63.6%)	144 (56.2%)	

***p – value < 0.05, statistically significant**

All 256 patients had deformities. Erosions were reported higher among seropositivity patients (44.1%) as compared to seronegative patients (36.4%), however difference was not statistically significant (Table 5).

Table 6: Medications

Treatment, n (%)	Seropositive (n = 245)	Seronegative (n = 11)	Total (n = 256)	p-value
Methotrexate	229 (93.5%)	11 (100%)	240 (93.8%)	0.381
Lefno	202 (82.4%)	10 (90.9%)	212 (82.8%)	0.467
HCQS	126 (51.4%)	4 (36.4%)	130 (50.8%)	0.328
Saaz	62 (25.3%)	1 (9.1%)	63 (24.6%)	0.222
Tofacitinib	21 (8.6%)	0 (0%)	21 (8.2%)	0.311
Rutaximab	17 (6.9%)	0 (0%)	17 (6.6%)	0.632
Tocilizumab	5 (2%)	0 (0%)	5 (2%)	0.366

*p – value < 0.05, statistically significant

Methotrexate, lefno, HCQS and tofacitinib were common medications for sero posiive and negative patients. Along these medications, tofacitinib, rutaximab and tocilizumab were given to less than 10% of seropositive patients (Table 6).

DISCUSSION

The age of patients, age of onset of disease and disease duration showed minor difference between the groups, which was insignificant to suggest any direct or indirect correlation with the seropisitivity. This is well in agreement with the results of previous study (Bland et al., 1964). Occurrence of Lung disease in seropositive patients was slightly higher in seropositive group, but not significant to form a correlation. This is similar to previous study findings (Meka et al., 2010). Another study reported the association of RA with ILD (Patel et al., 2008). The study conducted by Wisnieski et al. suggested a relation between presence of rheumatoid nodules with RF factor (Wisnieski et al., 1964) while another study described a high incidence of rheumatoid nodules in seropositive patients (Panay et al., 1987). There was no significant difference found in presence of rheumatoid nodules in both the groups, in our study, which is quite similar to the findings of study conducted by Vjollca Sahatçiu-Meka et al. There was slightly higher incidence of neuropathy in seropositive patients but it is insufficient to form a direct correlation, which is similar to previous study findings (Meka et al., 2010). Presence of vasculitis was only noted in seropositive patients which points towards a relation between the two factors. This is aligned with the results of a previous study (Nordberg et al., 2018). Seropositive patients were found to have severe disease course, which is in accordance to previous study results. The radiographic damage was higher in seropositive patients, which is in contrast with a previous study finding (Syversen et al., 2010). Although in various other studies which have reported similar findings (Hecht, 2015; Rönnelid, 2005; Nell, 2005; Broek, 2012; Katchamart, 2015). Patients achieving remission was slightly higher in seropositive patients. There were mixed results for patients with LDA, MDA and HAD, insufficient to suggest a relation between the groups. There has been mixed results in previous studies as well, where some suggested fewer seropositive patients achieving remission (Nell, 2005; Kastbom, 2004) and some studies with conflicting results (Choi, 2018; Barra, 2014).

CONCLUSION

The majority of the patients were female in this study. ANA positivity rate was higher for seropositive as compared to seronegative, however the difference was not statistically significant. There was no significant association was observed between the study groups in terms of gender, mean

age, mean age of onset, and median disease duration. No association was observed between the groups with respect to comorbidities, extra articular manifestation, deformities, erosions, and treatment. These findings could specify a difference in clinical presentation or perception of patients with RA who are seropositive. It is recommended to conduct studies to understand how sero-negative patients behave differently than sero-positive patients in Rheumatoid Arthritis.

REFERENCES

[1]. Barra, L., Pope, J. E., & Orav, J. E. et al. (2014). Prognosis of seronegative patients in a large prospective cohort of patients with early inflammatory arthritis. J Rheumatol., 41, 2361–2369.

[2]. Bland, J. H., MD, F. A. C. P., & Brown, B. S. E. W. (1964). Seronegative and Seropositive Rheumatoid Arthritis. Annals of internal Medicine, 60(1), 88-94.

[3]. Choi, S. T, & Lee, K. H. (2018). Clinical management of seronegative and seropositive rheumatoid arthritis: A comparative study. PLoS ONE, 13(4), e0195550.

[4]. Edelman, J., & Russell, A. S. (1983). A comparison of patients with seropositive and seronegative rheumatoid arthritis. Rheumatology International, 3, 47–48.

[5]. Hecht, C., Englbrecht, M., & Rech, J., et al. (2015). Additive effect of anticitrullinated protein antibodies and rheumatoid factor on bone erosions in patients with RA. Ann Rheum Dis., 74, 2151–2156.

[6]. Kastbom, A., Strandberg, G., & Lindroos, A., et al. (2004). Anti-CCP antibody test predicts the disease course during 3 years in early rheumatoid arthritis (the Swedish TIRA project). Ann Rheum Dis., 63, 1085–1089.

[7]. Katchamart, W., Koolvisoot, A., & Aromdee, E., et al. (2015). Associations of rheumatoid factor and anti-citrullinated peptide antibody with disease progression and treatment outcomes in patients with rheumatoid arthritis. Rheumatol Int., 35, 1693–1699.

[8]. Markatseli, T. E., Papagoras, C., & Drosos, A. A. (2010). Prognostic factors for erosive rheumatoid arthritis. Clin Exp Rheumatol., 28(1), 114-123.

[9]. Meka, V. S., Rexhepi, S., Kërliu, S. M., & Rexhepi, M. (2010). Extra-articular manifestations of seronegative and seropositive rheumatoid arthritis. Bosn J Basic Med Sci., 10(1), 26–31.

[10]. Mochizuki, T., Ikari, K., Yano, K., & Okazaki, K. (2019). Five-year incidence of common comorbidities, such as hypertension, dyslipidemia, diabetes mellitus, cardiovascular disease, cerebrovascular disease and cancer, in older Japanese patients with rheumatoid arthritis. Geriatr Gerontol Int., 19(7), 577-581.

[11]. Nell, V. P., Machold, K. P., & Stamm, T. A., et al. (2005). Autoantibody profiling as early diagnostic and prognostic tool for rheumatoid arthritis. Ann Rheum Dis., 64, 1731–1736.

[12]. Nordberg, L. B., Lillegraven, S., Aga, A. B., Sexton, J., & Olsen, I. C., et al. (2018). Comparing the disease course of patients with seronegative and seropositive rheumatoid arthritis fulfilling the 2010 ACR/EULAR classification criteria in a treat-to-target setting: 2-year data from the ARCTIC trial. RMD Open, 16(2), e000752.

[13]. Panay, G. S., Celinska, E., & Emery, P., et al. (1987). Seronegative and seropositive rheumatoid arthritis: similar diseases. Br J Rheumatol., 26(3), 172-180.

[14]. Patel, R. R., Ryu, J. H., & Vassallo, R. (2008). Cigarette smoking and diff use lung disease. Drugs, 68(11), 1511-1527.

[15]. Rönnelid, J., Wick, M. C., & Lampa, J., et al. (2005). Longitudinal analysis of citrullinated protein/peptide antibodies (anti-CP) during 5 year follow up in early rheumatoid arthritis: anti-CP status predicts worse disease activity and greater radiological progression. Ann Rheum Dis., 64, 1744–1749.

[16]. Syversen, S. W., Goll, G. L., & Heijde, V. D. D., et al. (2010). Prediction of radiographic progression in rheumatoid arthritis and the role of antibodies against mutated citrullinated vimentin: results from a 10- year prospective study. Ann Rheum Dis., 69, 345–351.

[17]. van den Broek, M., Dirven, L., & Klarenbeek, N. B., et al. (2012). The association of reatment response and joint damage with ACPA-status in recentonset RA: a subanalysis of the 8-year follow-up of the best study. Ann Rheum Dis., 71, 245–248.

[18]. Venrooij, W. J. V., Beers, J. J. B. C. V., & Pruijn, G. J. M. (2008). Anti-CCP Antibody, a Marker for the Early Detection of Rheumatoid Arthritis. Annals of the New York Academy of Sciences, 1143(1), 268-285.

[19]. Wisnieski, J. J., & Askari, A. D. (1981). Rheumatoid nodulosis. A relatively benign rheumatoid variant. Arch Intern Med., 141(5), 615-619.