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Prevalence Of Tuberculin Skin Test Positivity In Patients Of Early Rheumatoid Arthritis- Study from a tertiary care centre in North India.

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Objective: To assess the prevalence of tuberculin skin test (TST) positivity in early rheumatoid arthritis patients (< 6months disease duration) using Tuberculin sensitivity testing in a TB endemic country. **Method:** Included in this cross-sectional study were 200 patients of early rheumatoid arthritis divided into three groups- treatment naïve, patients on methotrexate only and methotrexate plus low dose corticosteroids. 1TU (0.1ml) of PPD RT-23 with tween 80 was injected intradermally over the left forearm and the induration measured after 72 hours. For interpretation, Induration >10mm was taken as positive, < 5mm as negative and 5-10mm as indeterminate. Healthy controls were taken for comparison. **Results:** 200 early RA patients and 60 healthy controls were included in this study. The median age of the study population was 43 years (IQR 33-51) with a mean disease duration of 3.4 ± 2.1 months. 54 patients (27%) with early RA and 22 healthy control (36.7%) had TST positive (p=0.1). The mean TST positivity inpatient cohort was 7.25±6.53(mm) and in the control population(mm) was 7.06±6.07.TST was positive in 26 (22.6%) treatment naïve patients (n= 115);22 (37.9%) patients on methotrexate(n=58) and 6 (22.2%) patients on methotrexate and low dose corticosteroids(n=27) (p=0.08). Prior BCG vaccination status, disease activity, a dose of methotrexate and rheumatoid factor seropositivity had no significant effect on TST positivity. **Conclusion:** Tuberculin positivity is low among patients with early RA as compared to the general population. The use of low dose steroids or methotrexate doesn't affect the tuberculin anergy. Further larger studies with augmented tuberculin doses are required to assess the factors affecting TST positivity in RA patients.

Keywords: BCG, Mantoux test, Tuberculin, PPD, RA, LTBI

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Introduction

Rheumatoid arthritis by its pathogenesis and treatment associated, is an immunosuppressive state [1]. The prevalence of latent tubercular infection (LTBI) in a healthy Indian population as reported from various studies ranges from 9-80% [2]. In tuberculosis (Tb) endemic country like India, this mandates essential screening for LTBI before initiating immunosuppression like biologicals [3]. Currently recommended test for LTBI screening are tuberculin skin test (TST), Interferon-gamma release assay (IGRA) and chest radiograph [2,3]. In developing countries, TST is more cost-effective than IGRA and the clinical utility of both in immunosuppressed patients is debatable [4,5]. In early untreated rheumatoid arthritis, due to abnormalities in circulating T cells, reaction to an antigenic stimulus is hampered which can affect TST [6]. Various studies have shown variable TST response in RA – naïve RA patients had smaller TST reading compared to treated patients [7]. Multiple studies had shown the effect of corticosteroids on TST reading in RA, however, other disease-modifying anti-rheumatic drugs (DMARDs) did not seem to possess any effect on the same [8,9,10]. This study was planned to assess the prevalence of TST positivity in naïve as well as treated RA patients in a Tb endemic population and correlate with various factors that affect it.

Materials and Methods

Setting: At a tertiary care centre in North India

Duration and type of study: Cross-sectional study conducted from January 2016 to July 2017

Sampling Methods: Simple random sampling

Sample size calculation: Assuming 95% confidence interval, with a margin of a error 5% and prevalence of RA being 15% in our rheumatology OPD (with annual rheumatology attendance of approx. 50,000 patients), the calculated sample for this study was 196 (rounded off to 200). For comparison, 60 age and sex-matched healthy controls were also recruited from the general population.

Inclusion criteria: Patients aged 18- 65 years who were classified as RA as per 2010 American College of Rheumatology (ACR) / European League Against Rheumatism (EULAR) criteria were assessed for eligibility. Those who had early RA (defined as disease duration less than 6 months from onset of symptoms) and gave written informed consent were enrolled in the study.

Exclusion criteria: Patients on concomitant disease-modifying antirheumatic drugs (DMARDs) like leflunomide and sulfasalazine were excluded however, use of hydroxychloroquine was permitted. Patients with other immunosuppressed states like Human Immunodeficiency Virus (HIV) infection, post organ transplant, diabetes, chronic kidney disease, previous treatment with steroids(>7.5mg/day), prior or current history of Tb, active viral infection and pregnancy were excluded. Patients who had any prior history of reactions to TST, received any live vaccine 4 weeks prior, received any biological DMARDS or had received BCG vaccination less than 15 years ago were also excluded.

Data collection procedure: The included cohort of early RA patients were studied under three groups- a) Early treatment naïve RA b) early RA patients on low dose corticosteroids (≤ 7.5mg /day) and methotrexate c) early RA patients only on methotrexate. 1 tuberculin unit (TU) or 0.1ml of purified protein derivative (PPD)-RT-23 with Tween 80 was used for TST. TST testing was done as per the recommended procedure and induration was read after 72 hours of PPD administration by trained personnel not involved in this study. For interpretation, induration > 10mm was taken as positive and < 5mm as negative. Patients with indeterminate TST (5-10 mm) underwent a clinical examination to rule out active TB signs. Also, a chest radiograph was obtained, findings of which were confirmed by a Contrast-enhanced computed tomography (CECT) chest and histopathology if required.

Ethics approval: Institutional Ethics committee gave ethical permission to conduct this study.

Statistical Analysis: The normality of quantitative data was checked by measures of Kolmogorov Smirnov tests of normality. If data were normally distributed unpaired student t-test was applied for the comparison of 2 groups. Mann-Whitney U-test was used for statistical analysis of skewed continuous variables. Proportions were compared using Chi-square or Fisher's exact test whichever was applicable. Wilcoxon Signed-Rank test was used for skewed data and comparison of non-parametric within-group comparison.

All the statistical tests were two-sided and α<.05 was considered significant. Analysis was conducted using IBM SPSS STATISTICS (version 22.0).

Results

200 patients with early RA and 60 healthy controls were included in this study. 115 (57.5%) patients were treatment naïve while 85(42.5%) were already on treatment. 58(29%) were on methotrexate alone and 27(13.5%) were on low dose corticosteroids plus methotrexate. The mean dose of methotrexate used in the methotrexate alone group(mg/week) was (12.5±3.50) and the methotrexate plus steroid group was (15±4.38). The mean dose of prednisolone (mg/day) used was (4.9±1.89).

Median (IQR) age of the study population was 43(33-51)years with 167 (83.5%) being female patients. Other baseline characteristics are as shown in Table-1. In the study population 54 patients (27%) were TST positive compared to 22 healthy controls (36.7%) (p= 0.1). Amongst the three treatment groups, TST was positive in 26 (22.6%) treatment naïve patients, 22 (37.9%) Patients on methotrexate and 6 (22.2%) patients on low dose steroids and methotrexate (p=0.08). TST positivity was also analysed between different doses of methotrexate which was not significant (p=0.56) (Supplementary Table- S1).

Prior BCG vaccination gives TST positivity, hence in the study population as well as healthy control TST positivity was assessed with a history of BCG vaccination. 53 (22%) RA patients with a history of BCG vaccination, 6 (32%) patients who were unvaccinated and 16 (40%) patients with unknown status had positive TST (p=0.39). In the healthy control group,18 (35.3%) with a history of BCG vaccination, 4 (50%) with unknown status and none who were unvaccinated had positive TST (p=0.54).

Seropositivity did not affect TST results in early RA patients. About 27 patients (28.5%) with RF positive as compared to 7 (31.8%) RF negative patients had positive TST (p=0.3). As for disease activity, 2 (67%) patients in remission, 7 (25%) patients with mild, 31(32.3%) with moderate and 14 (19.2%) with severe disease activity had TST positive (p=0.11).

Table 1: Baseline characteristics of the study population and healthy controls

Characteristics	Early rheumatoid arthritis patients (N=200)	Healthy controls (N=60)
Age(years); median(IQR)	43 (33-51)	36 (31-40) p=0.11
Sex, Female; n (%)	167 (83.5)	46 (76.6%) p=0.201
Disease duration (months); Mean ± SD	3.4 ± 2.1	
BCG vaccination status; n (%)		
Vaccinated Unvaccinated Unknown status	155 (77.5) 18 (9) 27 (13.5)	51 (85) p=0.027 1 (1.7) 8 (13.3)
RF positivity; n (%)	178 (89)	
Treatment received; n (%)		
Treatment naïve On methotrexate On methotrexate + low dose steroids (prednisolone equivalent ≤ 7.5 mg/day)	115 (57.5) 57 (28.5) 28 (14)	
DAS 28 CRP; median (IQR)	3.69 (2.9-4.49)	
Disease activity status; n (%)		
In remission Low disease activity Moderate disease activity High disease activity	3 (1.5) 28 (14) 96 (48) 73 (36.5)	

Table 2: Prevalence of TST positivity in RA patients from various studies

	Leon et al 17	Temborenea et al 18	Sezer et al 8	Koker et al 19	Greenberg et al 21	Malaviya et al 4	Present study
RA Cases	112	105	58 (35 treatment naïve, 23 on immunosuppressants)	94	61	44	200

Healthy Controls	96	-	69	126	42	General population data (40%)	60
Country	Peru	Argentina	Turkey	Brazil	USA	India	India
%PPD positive in RA	29.4%	12.4%	20% treatment naïve; 31% on treatment group	29.8%	14.3%	13.6%	27%
Prevalence	Low	Low	Low	Low	Low	Low	Low
TST cut off	>5mm	>5mm	>5mm	>10mm	>10mm	> 10mm	>10mm
Dose of PPD	5TU	2TU	5TU	5TU	5TU	1TU	5TU

Table 3 - TST positivity rate in the study group as per dosage of methotrexate

Dose category(mg/week)	No of pts	PPD positive	P value
0-7.5	17	30%	0.564
7.5-15	35	60%	
15-22.5	4	5%	
>22.5	1	5%	

Discussion

RA is an autoimmune disease whose pathogenesis involves complex interactions between T-cells, B-cells and various cytokines like IL-2, IL-6, IL-17 etc. Increased production of cytokines and chemokines occur as a result of this interaction, thus creating a network for added T-cell, macrophage and B-cell interactions. Macrophages when activated act as a further source of cytokines and chemokines, thus creating a continuous cascade of inflammation [11]. Increased risk of TB in patients of RA is a well-established fact with studies reporting its current prevalence being 2-4 times higher than in the general population.

However is it the disease itself or the various treatments including steroids, traditional, biological or target synthetic DMARDS that are predisposing the patients need to be answered [3,12,13]. Though there are studies regarding the response of TST in early RA; the exact mechanisms through which the disease modifies the response to TST are not very well elicited. According to Panayi et al a defect in the cellular immune function exists in RA. This leads to an inability to mount sufficient TST response [14]. Koetz et al stated that patients with Rheumatoid arthritis have abnormalities of circulating T cells, developing into early stages of the disease. Thus, the ability of our immune system to react to antigen stimulus might be decreased [15].

When we come across the pathobiology of TST in literature, it has been mentioned that injection of tuberculin antigen leads to migration followed by proliferation of the sensitized T-cells to the site of injection. These cells then release lymphokines leading to further attraction of monocytes and lymphocytes. This along with increased permeability of blood capillaries form an induration at the site of the test. The reaction to PPD is a measure of a person's immune responsiveness [16]. Various studies report that RA as a disease per se can alter the response to tuberculin antigen, but there are not enough studies in the literature citing the mechanisms that can cause the same. [17,18,19].

Findings in our study are in agreement with previous and recent ones reporting a low prevalence of positive TST among RA patients. As reported by Malviya et al [4]. LTBI prevalence measured by TST positivity rate in the general Indian population has been reported around 40% and similar results (36.7%) were found in our study. Confounding factors like treatment status, prior BCG vaccination, RF positivity and disease activity had no significant effect on TST positivity. TST positivity when compared across various treatment groups was statistically non-significant; also not varying with various doses of methotrexate used($p=0.564$).

Patients on methotrexate alone had numerically higher TST positivity compared to treatment naïve or combination of low dose steroids and methotrexate, but this was not statistically significant($p=0.065$). Another previous study in patients with different rheumatic diseases receiving methotrexate has shown false-positive TST in these patients [20]. The comparative analysis of various studies on TST positivity in RA is illustrated in table-2 [4,8,17,18,19,21]. A study in Brazil [22]. showed that TST positive rate among RA patients was comparable to the general population in their region which had an intermediate Tb burden.

In our study as well, no statistically significant difference was found between the TST positivity rate of RA patients and healthy controls. Treatment with higher doses of steroids has shown anergy to TST in previous studies [9,23]. however, in our study we had an anergic response even with the use of prednisolone in doses<7.5 mg/day.

A possible explanation for this can be immunosuppression occurring at even lower doses which need to be studied in a larger cohort of rheumatoid arthritis patients on daily steroids. Another important factor presumed to affect TST positivity is the history of prior BCG vaccination [24,25].

In our study we had excluded patients with such a history of fewer than 15 years based on observation by Wang et al [24]. who had suggested that chances of TST being falsely positive are higher if the duration of vaccination is less than 15 years. Similar to findings by Hizel et al [26]. history of BCG vaccination did not affect TST positivity rate in our early RA cohort. Malaviya et al [27]. A study concluded that recommended dose of PPD of 5 TU is low to detect TST positivity in RA patients.

They have suggested using an augmented PPD (RT 23 with Tween-80) dose of 10 TU combined with Quantiferon Tb-Gold (QFTG) test to detect RA patients with LTBI comparable to the general population. A similar idea on a combination of TST and QFTG to detect LTBI in RA patients on adalimumab therapy was given by other studies [28,29,30].

As our study was conducted before the one by Malaviya et al, we used PPD of 1 TU without augmentation. Further confirmation with QFTG was withheld because of the then-existing Ministry of Health and Family Welfare (MOHFW) guidelines. This study had limitations in terms of sample size and disproportionate treatment groups. QFTG was not done to detect or confirm further patients with LTBI infections.

Patients with negative and indeterminate testing couldn't be confirmed further by augmented TST testing which would have influenced the final results. The dose of PPD used could have affected the results, although comparative studies suggesting the same in literature are very few.

Conclusion

This study implies that as suggested by newer studies in TB endemic nations a combination of TST and QFTB should be ideally used to detect LTBI in RA patients. Further studies comparing TST doses and various cut-offs will provide more information regarding TST positivity in RA patients.

Similarly effect of biological DMARDs and other approved drugs for RA treatment like Janus kinase Inhibitors on TST positivity needs to be addressed in future studies.

What does the study add to existing knowledge?

- This is one of the few studies on TST positivity in early RA, which shows that patients with early RA, irrespective of their treatment with low dose steroids or methotrexate, have a TST positivity rate same as the general population.
- Prior BCG vaccination status, disease activity state and RF seropositivity also did not affect TST positivity in early RA patients

Author contributions

KK, NS and SS collected the data and conducted this study. KK, DM and SJ did data analysis. KK and DM did manuscript drafting. All authors were involved in revising and approved the final version of the manuscript.

Reference

01. Palit J, Chattopadhyay C, Malaviya AN, Uberoi S, Kumar R. Some immunological parameters in rheumatoid arthritis from India. Biomedicine. 1977 Mar;27(2)70-3.
[Crossref]

02. Handa R, Rao UR, Lewis JF, Rambhad G, Shiff S, Ghia CJ. Literature review of rheumatoid arthritis in India. Int J Rheum Dis. 2016 May;19(5)440-51.
doi: 10.1111/1756-185X.12621 [Crossref]

03. Handa R, Upadhyaya S, Kapoor S, Jois R, Pandey BD, Bhatnagar AK, Khanna A, Goyal V, Kumar K. Tuberculosis and biologics in rheumatology- A special situation. Int J Rheum Dis. 2017 Oct;20(10)1313-1325.
doi: 10.1111/1756-185X.13129 [Crossref]

04. Malaviya AN, Thakaran R, Rawat R, Kapoor S, Garg S, Baghel SS, Messi C, Vivekananda, Zaheer Q. Real life experience of a screening strategy for latent tuberculosis before treatment with biologicals in Indian patients with rheumatic diseases. Indian J Rheumatol. 2018;13(4)233-9.
Doi: 10.4103/injr.injr_66_18 [Crossref]

05. Sharma SK, Vashishtha R, Chauhan LS, Sreenivas V, Seth D. Comparison of TST and IGRA in Diagnosis of Latent Tuberculosis Infection in a High TB-Burden Setting. PLoS One. 2017 Jan 6;12(1)e0169539.
doi: 10.1371/journal.pone.0169539 [Crossref]

06. Auguste P, Tsertsvadze A, Pink J, Court R, McCarthy N, Sutcliffe P, et al. Comparing interferon-gamma release assays with tuberculin skin test for identifying latent tuberculosis infection that progresses to active tuberculosis- systematic review and meta-analysis. BMC Infect Dis. 2017 Mar 9;17(1)200.
doi: 10.1186/s12879-017-2301-4 [Crossref]

07. Mehta B, Zapantis E, Petryna O, Efthimiou P. Screening Optimization of Latent Tuberculosis Infection in Rheumatoid Arthritis Patients. Arthritis. 2015;569620.
doi: 10.1155/2015/569620 [Crossref]

08. Sezer I, Kocabas H, Melikoglu MA, Arman M. Positiveness of purified protein derivatives in rheumatoid arthritis patients who are not receiving immunosuppressive therapy. Clin Rheumatol. 2009 Jan;28(1)53-7.
doi: 10.1007/s10067-008-0982-1 [Crossref]

09. Agarwal S, Das SK, Agarwal GG, Srivastava R. Steroids Decrease Prevalence of Positive Tuberculin Skin Test in Rheumatoid Arthritis-Implications on Anti-TNF Therapies. Interdiscip Perspect Infect Dis. 2014;430134.
doi: 10.1155/2014/430134 [Crossref]

10. Bélard E, Semb S, Ruhwald M, Werlinrud AM, Soborg B, Jensen FK, et al. Prednisolone treatment affects the performance of the Quanti FERON gold in-tube test and the tuberculin skin test in patients with autoimmune disorders screened for latent tuberculosis infection. Inflamm Bowel Dis. 2011 Nov;17(11)2340-9.
doi: 10.1002/ibd.21605 [Crossref]

11. Scherer HU, Häupl T, Burmester GR. The etiology of rheumatoid arthritis. J Autoimmun. 2020 Jun;110;102400.
doi: 10.1016/j.jaut.2019.102400 [Crossref]

12. Carmona L, Hernández-García C, Vadillo C, Pato E, Balsa A, González-Alvaro I, et al. Increased risk of tuberculosis in patients with rheumatoid arthritis. J Rheumatol. 2003 Jul;30(7)1436-9.
[Crossref]

13. Lim CH, Chen HH, Chen YH, Chen DY, Huang WN, Tsai JJ, et al. The risk of tuberculosis disease in rheumatoid arthritis patients on biologics and targeted therapy- A 15-year real world experience in Taiwan. PLoS One. 2017 Jun 1;12(6)e0178035.
doi: 10.1371/journal.pone.0178035 [Crossref]

14. Panayi GS, Corrigall VM, Pitzalis C. Pathogenesis of rheumatoid arthritis, The role of T cells and other beasts. Rheum Dis Clin North Am. 2001 May;27(2)317-34.
doi: 10.1016/s0889-857x(05)70204-0 [Crossref]

15. Koetz K, Bryl E, Spickschen K, O'Fallon WM, Goronzy JJ, Weyand CM. T cell homeostasis in patients with rheumatoid arthritis. Proc Natl Acad Sci U S A. 2000 Aug 1;97(16)9203-8.
doi: 10.1073/pnas.97.16.9203 [Crossref]

16. Nayak S, Acharjya B. Mantoux test and its interpretation. Indian Dermatol Online J. 2012 Jan;3(1)2-6.
doi: 10.4103/2229-5178.93479 [Crossref]

17. Ponce de León D, Acevedo-Vásquez E, Sánchez-Torres A, Cucho M, Alfaro J, Perich R, et al. Attenuated response to purified protein derivative in patients with rheumatoid arthritis-study in a population with a high prevalence of tuberculosis. Ann Rheum Dis. 2005;64(9)1360-1. doi: 10.1136/ard.2004.029041 [Crossref]

18. Tamborenea MN, Tate G, Mysler E, Debonis J, Schijedman A. Prevalence of positive ppd in a cohort of rheumatoid arthritis patients. Rheumatol Int. 2010 Mar;30(5)613-6.
doi: 10.1007/s00296-009-1027-z [Crossref]

19. Köker IH, Pamuk ON, Karlikaya C, Tunçbilek N, Cakir N. A low prevalance of purified protein derivative test positivity in Turkish patients with rheumatoid arthritis, Association with clinical features and HRCT findings. Clin Exp Rheumatol. 2007 Jan-Feb;25(1)54-9.
[Crossref]

20. Arias-Guillén M, Sánchez Menéndez MM, Alperi M, Riestra S, González Budiño MT, García-Clemente MM, et al. High rates of tuberculin skin test positivity due to methotrexate therapy: False positive results?. Semin Arthritis Rheum. 2018 Dec;48(3)538-546.
doi: 10.1016/j.semarthrit.2018.03.018 [Crossref]

21. Greenberg JD, Reddy SM, Schloss SG, Kurucz OS, Bartlett SJ, Abramson SB, et al. Bingham CO 3rd, Comparison of an in vitro tuberculosis interferon-gamma assay with delayed-type hypersensitivity testing for detection of latent Mycobacterium tuberculosis- a pilot study in rheumatoid arthritis. J Rheumatol. 2008 May;35(5)770-5.
[Crossref]

22. Tannus Silva DG, Silva BD, Torres PP, Santana PJ Jr, Junqueira-Kipnis AP, Rabahi MF. Latent tuberculosis in rheumatoid arthritis- evaluating cellular response and high-resolution computed tomography. Arch Bronconeumol. 2012 May;48(5)144-9.
doi: 10.1016/j.arbres.2011.12.013 [Crossref]

23. Schatz M, Patterson R, Kloner R, Falk J. The prevalence of tuberculosis and positive tuberculin skin tests in a steroid-treated asthmatic population. Ann Intern Med. 1976 Mar;84(3)261-5.
doi: 10.7326/0003-4819-84-3-261 [Crossref]

24. Wang L, Turner MO, Elwood RK, Schulzer M, FitzGerald JM. A meta-analysis of the effect of Bacille Calmette Guérin vaccination on tuberculin skin test measurements. Thorax. 2002 Sep;57(9)804-9.
doi: 10.1136/thorax.57.9.804 [Crossref]

25. Cohn DL. The effect of BCG vaccination on tuberculin skin testing- Does it matter?. Am J Respir Crit Care Med. 2001;164(6)915-6.
doi: 10.1164/ajrccm.164.6.2107090c [Crossref]

26. Hizel K, Maral I, Karakus R, Aktas F. The influence of BCG immunisation on tuberculin reactivity and booster effect in adults in a country with a high prevalence of tuberculosis. Clin Microbiol Infect. 2004 Nov;10(11)980-3.
doi: 10.1111/j.1469-0691.2004.00970.x [Crossref]

27. Malaviya AN, Aggarwal VK, Rawat R, Baghel S, Thakran R, Zaheer Q, et al. Screening for latent tuberculosis infection among patients with rheumatoid arthritis in the era of biologics and targeted synthetic disease-modifying anti-rheumatic drugs in India, a high-burden TB country- The importance of Mantoux and Quantiferon-TB Gold tests. Int J Rheum Dis. 2018 Aug;21(8)1563-1571.
doi: 10.1111/1756-185X.13261 [Crossref]

28. Sargın G, Şentürk T, Ceylan E, Telli M, Çildağ S, Doğan H TST, Quanti FERON-TB Gold test and T-SPOT. TB test for detecting latent tuberculosis infection in patients with rheumatic disease prior to anti-TNF therapy. Tuberk Toraks. 2018 Jun;66(2)136-143.
doi: 10.5578/tt.66444 [Crossref]

29. Chen DY, Shen GH, Hsieh TY, Hsieh CW, Lan JL. Effectiveness of the combination of a whole-blood interferon-gamma assay and the tuberculin skin test in detecting latent tuberculosis infection in rheumatoid arthritis patients receiving adalimumab therapy. Arthritis Rheum. 2008 Jun 15;59(6)800-6.
doi: 10.1002/art.23705 [Crossref]

30. Lalvani A, Millington KA. Screening for tuberculosis infection prior to initiation of anti-TNF therapy. Autoimmun Rev. 2008 Dec;8(2)147-52.
doi: 10.1016/j.autrev.2008.07.011 [Crossref]