Section: Orthopaedics

Original Research Article

TO STUDY THE PROPORTION AND RISK OF LATENT TUBERCULOSIS IN PATIENTS DIAGNOSED WITH RHEUMATOID ARTHRITIS BEFORE STARTING DISEASE-MODIFYING ANTIRHEUMATIC DRUGS (DMARDS):

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Abstract

Background: Patients receiving treatment for rheumatoid arthritis with steroids and disease-modifying anti-rheumatic drugs (DMARDs) have a higher risk of reactivation of latent tuberculosis infection (LTBI) to active tuberculosis. We conducted this study was to evaluate and find the proportion and conversion of latent tuberculosis using the Quantiferon-TB Gold In-Tube (QFT) test for the diagnosis of LTBI in patients with rheumatoid arthritis receiving disease-modifying antirheumatic drugs (DMARDs) treatment. **Materials and Methods:** We included 33 patients starting from February 2021 to July 2022 patients with rheumatoid arthritis tested positive either with RA factor positive or anti-CCP positive. Screening tests for tuberculosis, such as tuberculin skin test (TST) and QFT assay were conducted. Positive QFT assay result regardless of TST results, were considered an indicator for the initiation of LTBI treatment. **Results:** Of 33 patients in the study, TST and QFT were positive in 39.4% (13 patients) and 51.5% (17 patients) respectively. During a follow-up period of 12 months, one patient (7.7%) developed tuberculosis after initiation disease-modifying antirheumatic drugs and steroid treatment from the other hospitals. TB did not occur in 16 patients who were QFT positive patients who received LTBI treatment. **Conclusion:** Due to non-availability of gold standard test to identify LTBI, we recommend the usage of tuberculin skin test and IGRA in order to prevent under or non-diagnosing latent tuberculosis infection, which in turn has the possibility to activate into fulminant TB in subjects with rheumatoid disease.

INTRODUCTION

Most of the people infected by Mycobacterium tuberculosis (Mtb) are asymptomatic and show no signs of the infection, a condition called latent Tuberculosis infection. The World Health Organization (WHO) estimates that there are 2 to 3 billion Mycobacterium tuberculosis infections globally, of which 5 to 15% will convert from latent to active disease over their lifespan. Most occurrences of active tuberculosis (TB) are caused by the reactivation of LTBI, making identification and treatment critical, especially in groups associated with high risk.[1-2]

Disease-modifying antirheumatic drugs (DMARDs) have been successfully tried in the management of inflammatory arthritis with one among them being rheumatoid arthritis (RA) in recent years.[3,4]

Compared to the general population, people with rheumatoid illnesses harboring latent tuberculosis infection are up to four times more likely to develop active tuberculosis. It was also discovered that individuals receiving biological therapy for underlying rheumatoid disorders had a risk of latent tuberculosis infection reactivation of up to 25%.[5,6]

Latent tuberculosis infection patients possess no signs or symptoms of active tuberculosis. Therefore, screening with tubercular skin test or QFT is recommended prior to beginning treatment that includes steroids and other biological agents that will change patient's immunological status. The patient may be more susceptible to developing an active tuberculosis infection due to the patient's weakened immune system.[7,8]

MATERIALS AND METHODS

The cross sectional study was conducted at the Department of Orthopedics after obtaining ethical clearance from Institute's ethical committee. Thirty three patients diagnosed with rheumatoid disease were included in the study from a study period of May 2020 till June 2022, after acquiring an informed, written consent. A detailed history regarding the condition was acquired followed by clinical examination and required laboratory investigations.

Past history of tuberculosis or any treatment history for the rheumatoid arthritis disease were obtained including the duration and dose of administration of steroids in the past 3 months were recorded. Detailed history of current symptoms of active tuberculosis infection were asked and if symptomatic they were screened with ZN staining for AFB and Chest X-ray and excluded from the study and managed appropriately. Enrolled patients with no symptoms were tested for latent tuberculosis infection with tuberculin skin testing (Mantoux) and Quantiferon GOLD (QFT), Patients with positive results were started on treatment of LTB infection.

TUBERCULIN SKIN TEST (TST).

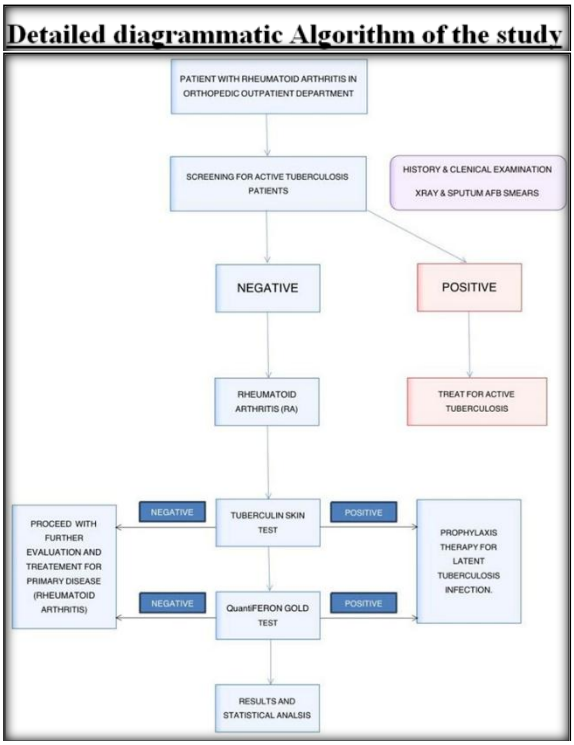
This test was carried out for 33 patients involved in the study. Test was carried out using 5 tubercular units (0.1 ml) of purified protein derivative intra-dermally at a 5–15-degree angle (26Gauze needle) over the left palmar surface of the forearm forming a bleb of about 4-6 mm. The site was circled, and the subjects were informed about the expected induration. The size of the induration was measured after 2 to 3 days.

TST RESULTS

- ≤ 5 mm considered negative.
- ≥ 10 mm considered intermediate.
- ≥ 15 mm considered positive.

Quantiferon GOLD (QFT)

1 milliliter of blood was taken into 3 blood collection tubes each: one tube having only heparin (as negative control), the second tube having the T-cell mitogen Phyto-hemagglutinin (as a positive control), and the third tube with ESAT-6, CFP-10 and TB 7.7 (Tubercular antigens) peptides which are dried on the inner aspect of the tube. After mixing, the tubes were incubated upright for approximately 20 hours at 37°C before plasma before harvesting it for further analysis. The amount and concentration of IFN-γ present in each tube were estimated using the QFT ELISA. IFN-γ release in the control tube(Nil) with normal saline will be deducted from the TB antigen and PHA-stimulated sample tubes. After stimulation with M. tuberculosis-specific antigens, samples with greater than 0.35 IU/ml of IFN-γ will be deemed positive, whereas samples with lesser than 0.35 IU/ml of IFN-γ will be deemed negative. If the concentration of IFN-γ is lower than 0.35 IU/ml for tubercular antigens and lower than 0.5 IU/ml for the positive control, the QFT test result will be deemed inconclusive.



WHO recommendation for the treatment of LTBI.

Drug Regimen	Dose per Kg body weight	Maximum Dose
Isoniazid alone, daily for 6 or 9 months	Adults, 5 mg Children, 10 mg (range, 7–15 mg)	300 mg
Daily rifampicin alone for 3–4 months	Adults, 10 mg Children, 15 mg (range, 10–20 mg)	600 mg
Daily isoniazid plus rifampicin for 3–4 months	Isoniazid: Adults, 5 mg Children, 10 mg (range, 7–15 mg) Rifampicin Adults, 10 mg Children, 15 mg (range, 10–20 mg)	Isoniazid, 300 mg Rifampicin, 600 mg
Weekly Rifapentine plus isoniazid for 3 months (12 doses)	Individuals aged ≥ 12 years: Isoniazid: 15 mg Individuals aged 2–11 years: isoniazid: 25 mg Rifapentine: 10.0–14.0 kg = 300 mg 14.1–25.0 kg = 450 mg 25.1–32.0 kg = 600 mg 32.1–50.0 kg = 750 mg > 50 kg = 900 mg	Isoniazid, 900 mg Rifapentine, 900 mg

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RESULTS

Table 1: Sex distribution of subjects. In the study total number of cases were 33. majority of subjects were females, 72.7% and 27.3% were males

Sex distribution of subjects		Count	percentage
Sex	Female	24	72.7%
	Male	9	27.3%
	Total	33	100.0%

Table 2: Diagnosis of Rheumatoid arthritis

Diagnosis of Rheumatoid arthritis		Count	percentage
RA Factor	Negative	6	18.2%
	Positive	27	81.8%
Anti CCP	Not done	27	81.8%
	Positive	6	18.2%

In the study 81.8% were positive for RA factor and 18.2% were negative for RA factor.

Table 3: QFT Results distribution

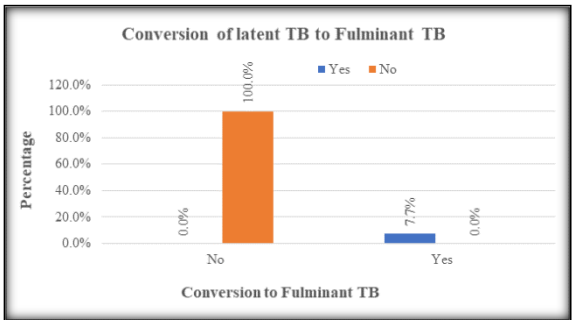
QFT Results distribution		Count	percentage
QFT Results	Positive	17	51.5%
	Negative	16	48.5%
	Total	33	100.0%

In the study proportion of Latent TB based on QFT Results 17 (51.5%) patients were positive.

Table 4: Conversion of latent TB to Fulminant TB among steroids users in subjects with QFT Positive results

		Steroids Usage			
		Yes		No	
		Count	percentage	Count	percentage
Conversion to Fulminant TB	No	12	92.3%	4	100.0%
	Yes	1	7.7%	0	0.0%
a. QFT Results = Positive					

In the study among 17 QFT positive subjects, 13 subjects who were using steroids, 7.7% converted to Fulminant TB and 92.3% did not convert to Fulminant TB. Among 4 subjects who were not using Steroids, 0% converted to Fulminant. There was no significant association between Steroid use and conversion to Fulminant TB.



Bar diagram showing Conversion of latent TB to Fulminant TB among steroids users in subjects with QFT Positive results.

DISCUSSION

According to the WHO, roughly 2 to 3 billion individuals across the world are known to be infected with Mycobacterium tuberculosis, and 5-15% of the infected population progresses from latent tuberculosis infection (LTBI) to symptomatic active disease over the course of their lifetime. In populations associated with high risk, such as those with rheumatoid arthritis, identification and treatment are particularly important due to the LTBI's reactivation, which has greatly increased the number of people with active tuberculosis.

The correlation between subjects of rheumatoid arthritis & latent tuberculosis were well documented by a cohort study conducted by Mehta et al.[10] Furthermore, TB testing before the commencement of DMARDS lowers the likelihood of reactivation of latent TB infection by about 85%. [11]

Objective was to obtain proportion of LTB infection in patients diagnosed with Rheumatoid Arthritis, with the total of 33 (9 males and 24 females) patients by using Interferon-Gamma-Release Assay (IGRA) and Tuberculin -Sensitivity Test (TST,).

TST has a number of drawbacks; it necessitates two visits to a healthcare facility and is prone to have human errors as one tries to interpret the results. Additionally, it might be altered due to a prior BCG vaccination and the immunological condition of the test subject. Due to the immune-mediated pathophysiology of RA or the immunomodulators employed in its treatment, its sensitivity may be reduced in RA patients. Also cross-reactivity with non tuberculous mycobacterial infection could affect its specificity.[12]

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TST and IGRAs have been compared in numerous studies. Because of the higher sensitivity and lack of the confounding effect of preceding BCG vaccination, some researchers have arrived at the conclusion that IGRAs are more beneficial than TSTs.[13]

Although TST was used in the current investigation, the QFT assay was used as standard test for LTBI diagnosis instead of TST.

Moreover, a study by Malaviya et al. inferred that 267 (36.6%) of the 730 patients who were considered for biological DMARDS 265 with rheumatoid arthritis, 400 with axial spondylo-arthritis, 34 with psoriatic arthritis and 31 others were positive for LTBI.[14]

The prevalence of LTBI was discovered to be 43% in a different study by the same researcher using QFT and TST in a cohort study of 144 Rheumatoid arthritis patients, which was approximately 40% in the usual population.[15]

In our study, we found that the proportion of latent TB based on QFT Results was 51.5% and with TST results was 39.4%.

If even one of these tests was positive, the patient was treated with antimicrobial medications in accordance with the LTBI treatment protocol. DMARDS can then be started when the treating practitioner feels it necessary. In the event that both tests are negative, DMARDS may be started, with a repeat test being conducted once a year during follow-up sessions.

The second objective was to find the risk of latent tuberculosis converting into fulminant tuberculosis by the use of steroids for the treatment of rheumatoid arthritis.

According to the World Health Organization, 5 to 15% of the infected population convert from LTBI to symptomatic disease during their life time.[16] Follow-up period, one patient who was tested QFT positive i.e. 7.7% converted to Fulminant TB, developed into active TB in months after initiation of steroids from the previous hospital prescriptions also was tested sputum positive with changes in the chest x-ray.

The patient was put on tuberculosis regimen by the pulmonologist. LTBI prophylaxis helps in greatly reducing the number of TB cases and their apt management. Even though few studies conducted in low-TB-prevalence regions showed a greater specificity with IGRAs than with the TST, neither approach provided a good enough predictive value for active tuberculosis infection. Both of these tests are used to screen for latent infection of tuberculosis. Future research should focus on a screening technique having a higher predictive value. Due to the patients having high-risk factors (such as Immunodeficiency, organ transplantation, silicosis, TNF-a blockers consumption, close contacts of TB patients, and kidney dialysis) significantly increase the rate at which TB reactivates, patients with high-risk factors in nations with low TB prevalence should be screened for LTBI and managed accordingly. As a result, screening for LTBI in rheumatoid arthritis patients is highly advised, especially prior to beginning anti-Tumour Necrosis Factor therapy.

CONCLUSION

In our study, we infer that the proportion of latent tuberculosis in patients associated with high risk like rheumatoid arthritis diagnosed cases is 51.5% and 7.7% converted to Fulminant TB among the total of 33 (9 males and 24 females) patients. Due to the unavailability of a gold standard test to check for latent tuberculosis infection, we recommend the usage of tuberculin skin test(TST) and IGRA in order to prevent under or non-diagnosing LTB infection, which in turn has the possibility to activate into fulminant TB in subjects with rheumatoid disease.

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