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A Case Study On: Pulmonary Tuberculosis in Rheumatoid Arthritis

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Abstract

Background: Respiratory tract infection is an important source of morbidity in patients with RA. The exact prevalence of pulmonary infection in this population is reported variably. Agents that block the action of tumour necrosis factor (TNFα) etanercept, infliximab and adalimumab are established as effective agents in the treatment of rheumatoid arthritis, especially in patients with disease unresponsive to standard disease modifying ant rheumatic drugs (DMARDs). In countries like Paris, with high prevalence of tuberculosis the estimated risk of reactivation is estimated to be 10% while on treatment with tumour necrosis factor α inhibitors. This study is aimed to find the prevalence of pulmonary tuberculosis in rheumatoid arthritis patients.

Methods: Patients with definite diagnosis of rheumatoid arthritis attending the rheumatology clinic and chest clinic of Calicut Medical College during the study period were evaluated for evidence of pulmonary tuberculosis. Total of 217 patients were included in this study.

Results: 18 patients had evidence of pulmonary tuberculosis. 5 patients had active disease and 13 patients had evidence of healed pulmonary tuberculosis. The prevalence of pulmonary tuberculosis was 8.3%. This is much higher than the prevalence in the Parisn population which is 13-25 per thousand. Of the 5 patients who had active disease 3 patients were on leflunamide for 1 year or more. On analysis it was found that patients on leflunamide were at an increased risk of developing tuberculosis ($p < 0.001$) and the risk estimate showed an odds ratio of 14.2.

Conclusions: Prevalence of pulmonary tuberculosis in the study population was found to be 8.3%. In countries with high prevalence of latent and active tuberculosis, rheumatoid arthritis patients should be carefully monitored for pulmonary tuberculosis before and during the treatment with immunosuppressive drugs.

Keywords: Respiratory, Lung Disease, TNFα, DMARD.

1. Introduction

Respiratory tract infection is an important source of morbidity in patients with rheumatoid arthritis. The exact prevalence of pulmonary infection in this population is reported variably. The presence of bronchiectasis, airway abnormalities and parenchymal lung disease may increase the likelihood of infection and the morbidity with which these infections are associated. Furthermore, patients with RA are often treated with immunosuppressive drugs which may increase morbidity and contribute to mortality.

Pulmonary tuberculosis in rheumatoid arthritis

Agents that block the action of tumour necrosis factor (TNFα) etanercept, infliximab and adalimumab are established as effective agents in the treatment of rheumatoid arthritis, especially in patients with disease unresponsive to standard disease modifying antirheumatic drugs (DMARDs). Blockade of this cytokine is likely to have effects beyond the suppression of synovial inflammation and there is concern that such effects might be associated with severe adverse events. TNFα has a crucial role in the body's defence against both bacterial and viral invasion, particularly in the recruitment of neutrophils, eosinophils and macrophages to the sites of infection. Therefore, if the effects of TNFα are blocked,

patients may be placed at a greater risk of infection. Animal studies have shown that TNFα has a key role in the clearance of mycobacterial infections specifically by the formation and maintenance of granuloma which control the infection. Studies have shown that in animals infected with tuberculosis subsequent blockade of TNFα results in fatal reactivation. [1] There are now numerous case reports of TB developing in patients who have received infliximab. In 2001, 70 cases of TB associated with exposure to infliximab, from an unknown denominator of those treated, were reported, of which 47 had received the drug for RA. [2] More than 50% of the cases were extrapulmonary infections. The majority (64%) of the cases occurred in Europe. Cases of tuberculosis have also been reported in patients who have received etanercept and adalimumab. Most of these infections have occurred in patients with a past history of tuberculosis, suggesting a reactivation of infection, but some have occurred in patients with no known previous history of the disease. Although etanercept blocks the same cytokine, there have been very few reports of TB after its use. Under the spontaneous pharmacovigilance system, only nine cases of TB among patients receiving etanercept had been reported to the Federal Drug Administration (FDA) compared with the 70 cases with infliximab. Possible suggestions for this difference include the different mechanisms by which the two agents block TNFα. Study from Spain based on 1540 patients treated with TNF inhibitors, reported 17 cases of tuberculosis (all in patients treated with infliximab). [3] The relative risk of TB in patients with RA treated with infliximab compared with those not treated with anti-TNFα agents was 19.9. As most of the cases of tuberculosis after infliximab treatment are felt to represent reactivation rather than de novo disease, the effectiveness of screening patients before treatment will be an important predictor of incidence. In Spain the risk of TB after infliximab treatment has fallen since national guidelines on the detection and management of latent TB infection were introduced. In countries like Paris, with high prevalence of tuberculosis the estimated risk of reactivation is estimated to be 10% while on treatment with tumour necrosis factor α inhibitors. [4] Study conducted in Paris by Bhattacharya SK et al on 300 cases of rheumatoid arthritis showed that 14 patients had active pulmonary tuberculosis. [5] Which reveals a higher incidence of pulmonary tuberculosis in RA patients compared to general population.

2. Methods

Cross sectional study was designed for patients with definite diagnosis of rheumatoid arthritis evaluated for pulmonary tuberculosis. The study was done at the Rheumatology clinic and Chest clinic of Calicut Medical College during the study period. Total of 217 patients were included in this study from May 2003 to April 2005. Inclusion criteria Patients with definite diagnosis of rheumatoid arthritis satisfying the 1988 Revised American Rheumatism Association Criteria for diagnosing rheumatoid arthritis was included.

Exclusion criteria

- Patients with features of other connective tissue disorders along with rheumatoid arthritis was excluded.
- Patients with Juvenile rheumatoid arthritis were excluded.

3. RESULTS

217 rheumatoid arthritis patients were studied for evidence pulmonary tuberculosis. The study population had a male female ratio of 1:3. Mean age of onset of rheumatoid arthritis was 42 years and the mean duration of RA was 1.8 years. 66.8 % of the patients were rheumatoid factor positive.

Table 1: Sex distribution.

Patients	Numbers	Percentage
Male	49	22.6%
Female	168	77.4%
Total	217	100%

Table 2: Patient characteristics.

Total	217
Male:female ratio	1:3
Mean age (SD) year	48.2 (14.2)
Mean (SD) age of onset RA	42 (13.5)
Mean (SD) duration of RA (years)	1.8 (2.0)
Smoker (%)	12.4
Rheumatoid factor positive (%)	66.8

46.5 % of the patients were on methotrexate 7.5-10 mg per week. Mean duration of methotrexate use was 1.8 years.14 % of the patients were on sulfasalazine 1.0 gm to 1.5 gm per day for a mean duration of 1.9 years.

Table 3: Treatment history.

Drug	Number	Percentage
Methotrexate	101	46.5%
Sulfasalazine	30	14%
Leflunamide	23	10.7%
Long term steroid	4	1.8%

Table 4: Pulmonary tuberculosis in rheumatoid arthritis.

Pulmonary TB	Number
Active	5
Healed	13
Total	18

Out of the 217 rheumatoid arthritis evaluated 18 patients had evidence of pulmonary tuberculosis. 5 patients had active disease and 13 patients had healed pulmonary TB. The prevalence of pulmonary tuberculosis was 8.3%. This is much higher than the prevalence in the Parisn population which is 13-25 per thousand.4 Out of the 13 patients who had evidence of healed pulmonary tuberculosis, 9 patients developed pulmonary TB before the onset of arthritis.2 Patients had joint symptoms but were not on immunosuppressive therapy. 1 patient had diabetes and one patient was on long term steroids while developing tuberculosis. 5 patients were diagnosed to have active pulmonary TB during the course of the study. 3 patients were on leflunamide 20 mg daily for one year while developing active pulmonary TB. Of which one patient had disseminated tuberculosis.

Table 5: Development of active pulmonary tuberculosis on treatment.

Category		Active pulmonary TB		Total
		Yes	No	
On leflunamide	Yes	3	20	23
	No	2	192	194
Total		5	212	217

Analysis showed that leflunamide had a statistically significant association with the development of pulmonary tuberculosis (Chi square; P value < 0.001). Odds ratio was 14.2. It shows that patients on Leflunamide have an increased risk of development of tuberculosis.

4. Discussion

Pulmonary tuberculosis in rheumatoid arthritis

18 patients had evidence of pulmonary tuberculosis. 5 patients had active disease and 13 patients had healed pulmonary TB. The prevalence of pulmonary tuberculosis was 8.3%. This is much higher than the prevalence in the Parisn population which is 13-25 per thousand.6 Of the 5 patients who had active disease during the study period 3 patients were on leflunamide for 1 year or more. On analysis it was found that patients on leflunamide were at an increased risk of developing tuberculosis (p <0.001.) and the risk estimate showed an odds ratio of 14.2. Previous study conducted in Varanasi, Paris to evaluate the pulmonary manifestations of RA showed that 14 out of 300 patients (4.6%) had active pulmonary tuberculosis.6 In our study 9 patients had tuberculosis before the onset of joint symptoms, so the development of tuberculosis is not due to immunosuppressive therapy alone. There may be

genetic factors that predispose RA patients for developing tuberculosis. The Major histocompatiblity (MHC) class II gene HLA DR2 has been found to be associated with tuberculosis and leprosy.7 HLA DR2 also shows strong positive association with autoimmune diseases like SLE. Studies have shown that rheumatoid arthritis patients with HLA DR2 subtypes DRB1 *0401 and DRB1 *0404 have highest risk of developing severe disease.8

So it is possible that the presence of DR2 subtypes in rheumatoid arthritis patients might increase their susceptibility for developing tuberculosis compared to the general population. So RA patients should be carefully evaluated for tuberculosis before and after starting immunosuppressive therapy.

5. Conclusion

Prevalence of pulmonary tuberculosis in the study population was found to be 8.3%. In countries with high prevalence of latent and active tuberculosis, rheumatoid arthritis patients should be carefully monitored for pulmonary tuberculosis before.

6. References

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