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Tuberculin Skin Reaction among Healthy People and Patients with Arthritis in the Southern Israeli Region*

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ABSTRACT

Introduction: Reactivation of latent tuberculosis is a major complication of tumor necrosis factor alpha (TNF-alpha) inhibitors. Therefore, screening for latent TB is recommended before initiation of this treatment. The aim of the study was to compare Tuberculosis skin test (TST) size reaction between healthy people and patients, with Rheumatoid arthritis (RA), Ankylosising spondylitis (AnS) and Psoriatic arthritis (PsA). **Patients and Methods:** Results of TST of 133 healthy subjects were compared with the results of TST of 79 patients, suffering from RA, AnS and PsA. A χ^2 test was used to compare the difference between the groups. A value of $p < 0.05$ was considered significant. Active tuberculosis (TB) was excluded by chest X-ray and through patient's history. The results of TST reaction were grouped according to the CDC's (Centers for Disease Control and prevention) recommendation, e.g. 0 - 4 mm, 5 - 9 mm, 10 - 15 mm and >15 mm. **Results:** Among RA patients 80% received Methotrexate (MTX), 50% Prednisone and 20% other DMARDs. 20% of patients suffering from AnS received MTX, 80%—NSAIDs, and among patients with PsA 70% received MTX, 30%—Salazopirin. There was no significant difference in history of bacilli Calmette-Guerine vaccination between the groups. There was no significant difference in TST reaction distribution between healthy subjects and patients with RA—$p > 0.5$. TST reaction distribution differed significantly between healthy people and AnS ($p < 0.05$) and PsA ($p < 0.001$) patients. The overall tendency in these two patients' groups was towards high positive TST, especially among PsA patients. **Conclusion:** Our results showed that RA patients may present TST reaction as healthy people. The high percent of our AnS and PsA patients that showed TST reaction above 15 mm need further exploration. We conclude that it may be not appropriate to use TST to recognize LTBI in our population.

Keywords: Latent Tuberculosis Infection; Tuberculosis Skin Test; Rheumatoid Arthritis; Ankylosing Spondylitis; Psoriatic Arthritis

1. Introduction

Tuberculosis (TB) remains a major cause of morbidity and mortality in the world. Almost 8 million new cases of TB infections occur annually, only 10% of these go on to develop an active disease [1]. The human immune response is highly effective in controlling primary infection resulting from exposure to Mycobacterium tuberculosis. However, all viable organisms might not be eliminated in some individuals. Thus, latency is established, a period during which the infected individual is asymptomatic, but harbors Mycobacterium organisms, which are capable of causing disease under special circumstances.

Tumor necrosis factor alpha (TNF-alpha) plays an important role in host defence against mycobacterium tuberculosis [2]. TNF-alpha is involved in the killing of mycobacteria by activating macrophages [3] and preventing the dissemination of infection by stimulation granuloma formation [4].

The introduction of tumor necrosis factor alpha inhibitors (TNF-i) in the treatment of Rheumatoid arthrtitis (RA), and other inflammatory arthritides such as Anky-

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losing Spondylitis (AnSp) and Psoriatic arthritis (PsA) represents a major advance of science in this area. However, an increase in active TB disease has been reported in association with this therapy [5].

Until the last 10 years, the tuberculin skin test (TST) was the only available test for the detection of LTBI.

According to Centers for Disease Control (CDC) and Prevention guidelines, an induration of >= 5 mm is classified as positive in the following groups: patients, who have HIV infection, patients, who have recent close contact with persons, who have TB, patients with organ transplants or immunosuppression (including immunosuppressive drugs such as TNF-i, methotrexate, prednisone, ciclosporin), and patients with fibrotic changes on chest radiographs consiostent with previous TB [6].

The poor specificity of the test, in presence of previous Bacille Calmette-Guerin vaccination, exposure to nontuberculous mycobacteria, or altered immune state among patients with rheumatic disease lead to difficulties in TST interpretation in these patients, with a growing number of reports demonstrating the low positive predictive values and low negative values of this test among patients with rheumatic disease [7,8].

The aim of the study is to compare the distribution of TST reaction sizes among healthy people and patients, who suffer from Rheumatoid arthritis (RA), Ankylosisng spondylitis (AnS) and Psoriatic arthritis (PsA), who are candidates for TNF-i treatment and receiving the conventional treatment.

The primary end point of this study is to compare TST results distribution in the groups between healthy people and patients. The terms as “positive” or “negative” results were not considered.

2. Patients and Methods

The retrospective study was performed at the Rheumatology Unit in collaboration with Pulmonolgy Department, at the Barzilai Medical Centre, Israel. The study underwent institutional review board, for retrospective studies, approval. There was no need to obtain informed consent, because of design of the study.

Inclusion criteria were: results of TST of every consecutive patient, who underwent TST during the period of one year in 2010, were analyzed.

Overall exclusion criteria were active TB, known history of active TB, and recent immigrants (less then 5 years in Israel).

The results of TST of 133 healthy subjects (HS) were compared with the results of TST of 79 patients suffering from RA, PsA, AnS.

The TST was performed according to Mantoux method, using 5 tuberculin Units (TU) of Purified protein deprivate and maximal size of induration was measured after 72 hours, as recommended[9].

The results of TST reaction were grouped according CDC recommendations, e.g. 0 - 4 mm, 5 - 9 mm, 10 - 15 mm, and >15 mm.

Anergy was excluded by repeating the TST within two weeks for all subjects with TST = 0 mm on the first test and considering the second record results as definitive.

The socio-demographic and TB screening questionaires were obtained from medical charts and, current medical treatment was recorded.

All subjects underwent a chest radiograph, as a method to rule out active pulmonary TB as well as thorough medical history.

A χ^2 or Fisher’s exact test was used to compare the difference between groups. A value of $p < 0.05$ was considered significant.

3. Results

133 healthy subjects and 79 patients were enrolled into the study.

The mean age in the healthy control subject group was 35.3 years, while mean age of study group was 53.4 years ($p < 0.05$).

The study group had a gender distribution of 2 females: 1 male while the control group had a gender distribution of 5:3 male/female, and among the study group there were 41 patients with RA, 17 with AnS and 21 with PSA.

80% of the patients with RA were treated with Methotrexate (MTX), while 50% received Prednisone, and 20% other DMARDs.

19% of patients who suffered from AnS received MTX, 81%—NSAIDs, and among patients with PsA 71% received MTX, 29%—Salazopirin.

None of the patients were treated with TNF-i previously.

TST Assay

TST reaction < 5 mm was found in 60.9 % of healthy subjects, 61.0% among RA patients, 41.2% among AnS patients and 23.8% among PsA patients.TST reaction 5 - 9 mm was found in 19.5% of healthy subject, 17.1% RA patients, 23.5% AnS patients and 9.5% PsA patients.

TST reaction 10 - 14 mm was observed in 8.3% of healthy subjects, 3% of RA patients, 0% of AnS patients and 19% PsA patients

TST reaction > 15 mm was in 11.3% healthy subjects, 14.6% of RA patients, 35.3% AnS patients and 47.6% PsA patients.

There was no significant difference in TST reaction distribution between healthy subjects and patients with RA (RAxHS: $\chi^2 = 0.42$; $p > 0.5$). TST reaction distribution differed significantly between healthy people and AnS patients (AnSxHS: $\chi^2 = 8.7$; $p < 0.05$) and PsA

(PsAxHS: $\chi^2 = 22.4$; $p < 0.001$). The overall tendency in these two patient's group was towards high positive TST, especially among PsA patients.

4. Discussion

An accurate diagnosis of LTBI in patients before starting TNF-i treatment as well as the prophylactic treatment anti-TB treatment is crucial to prevent TB reactivation. The current screening strategy is based onTST, chest X-Ray and risk stratification questionnaire.

This accepted strategy has significantly reduced the rate of TB reactivation under TNF-i therapy [9]. Despite this success, the correct approach to LTBI diagnosis is still under discussion, and the main issue is correct interpretation of TST among patients with inflammatory arthritis [10].

The TST is recall response to soluble antigens previously encountered during tuberculosis infection. After intradermal injection of purifed protein derivate (PPD), a crude mixture of more than 200 M. tuberculosis proteins, a sensitized individual antigen specific T cells are activated to secrete cytokines that mediate a hypersensitivity reaction. TST is classic delayed type hypersensitivity (DTH) reaction [11]. This reaction has been shown to be absolutely dependent on the presence of memory T cells. Both the CD4+ and CD8+ fractions of cells have been shown to modulate a response. Contemporary debate regarding the reaction is focused on the role of the Th1 and Th2 cells, originally discovered by Mosmann. It has been postulated that the Th1 cell is the "inducer" of a DTH response since it secretes interferon gamma (IFN-gamma), a potent stimulator of macrophages, while the Th2 cell is either not involved or acts as a downregulator of the cell mediated immune response [12].

In immune modulated inflammatory disease (IMID) immune disregulation is observed rather than immune deficiency. In Rheumatoid Arthritis patients, a type 1 cytokine predominance (IFN-gamma) is found in synovial membrane, synovial fluid and blood [13], in patients with psoriasis a type 1 cytokine reaction activity even is more prominent with IFN-gamma high production and up regulation of keratinocytes [14].

The data presented in this study, indicate, that patients with IMID have different TST response within the different disease groups, while in comparison with healthy people the TST reaction size distribution may be the same, or even more pronounced toward larger size of induration reaction.

Our RA patients showed the same distribution of TST reaction as healthy people, although most were receiving immune-supression treatment such as Methotrexate and Prednisone.

The results of TST reaction among RA patients in literature are contradictory. The current accepted opinion is that RA patients have an attenuated test reaction, as was shown in several studies [8,15], while other studies documented the same TST reaction in RA patients as among healthy people [16,17].

PsA patients in our study showed more prominent TST reaction in comparison to healthy pupulation, despite the fact, that most PsA patients treated with immunosuppressive treatment. The results are in accordance with other studies, among patients with PsA and also with psoriasis [18-20]. The phenomenon may be explained by the specific skin reaction to antigens among patients with psoriasis, that is an augmented type 1 cytokine activity with prominent IFN-gamma production, explaining the prominent TST reaction.

Patients with AnS showed a tendency to higher TST reaction in comparison to healthy controls and RA patients, although no significant statistical difference was observed. The same results among patients with AS were shown in another work. Thus, in the work of Pamik *et al*. the mean size of induration of TST reaction was 12.1 mm, which is higher than in their RA patients and Lupus Erythematosus patients [21]. Inanc N *et al*., while analysing agreement between Quantiferon test and TST, showed, that 82% of AS patients had induration more, than 10 mm [22]. These interesting results confirm the similarities in the immune processes in the whole group of spondyloarthropaties, which may differ from those in RA patients.

In conclusion, the evidence presented here suggests that adherence to the accepted TST-based recommendations for the diagnosis of LTBI, may lead to overestimation of positive results and, overdiagnosis of LTBI.

The presented data raise the suggestion of revision of algoritms of LTBI, particulary among non-endemic population.

Our study has obvious limitations. First, it included a small number of subjects, paticulary in AnS group, which may have influence on our capacity to approach to statistical significance. Second, we did not analyse correlation between TST results and disease activity, and could not provide the BCG status, although the age of all examined persons suggested their previous vaccination.

Our group of patients was significantly older, than group of health controls, which may lead to lower results of TST in the patient group compared with health control.

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List of Abbreviations

TST—Tuberculosis skin test
TNF-alpha—Tumor necrosis factor alpha
TNF-I—Tumor necrosis factor alpha-inhibitors
RA—Rheumatoid Arthritis
AnS—Ankylosing Spondylitis
LTBI—Latent Tuberculosis Infection
MTX—Methotrexate

