ORIGINAL ARTICLE

TUBERCULOSIS IN RHEUMATOID ARTHRITIS PATIENTS ON CONVENTIONAL AND BIOLOGICAL THERAPY

Mohamed AbdElgawad 1, Mohamed E. Abdalla 2, Mohamed Mosaad 3

1 Chest department, Faculty of Medicine, Zagazig University, 2 Chest department, Faculty of Medicine, Banha University, 3 Endemic and infectious diseases department, Faculty of Medicine, Suez Canal University

Correspondence to: Mohamed E. Abdalla, E-mail: mabdalla66@yahoo.com

ABSTRACT

Background: The long-term safety of therapeutic agents that neutralize tumor necrosis factor (TNF) is uncertain. Recent evidences show that treatment with tumor necrosis factor antagonists has been recognized as a risk factor for active tuberculosis (TB) in patients with rheumatoid arthritis (RA).

Aim of the work: The aim of this work was to assess the risk of active TB with other serious and non serious bacterial and viral infections in RA patients who are receiving conventional disease modifying anti rheumatic drugs (DMARDs) versus those who are receiving biological therapy.

Patients and methods: A prospective study conducted on (235) patients have rheumatoid arthritis RA, divided into two groups; group (A) included (105) RA patients receiving conventional disease modifying anti rheumatic drugs (DMARDs) with a mean age (51±12) and group (B) included (130) RA patients receiving biological therapy with a mean age (48±13) as (55) patients on infliximab, (32) patients on adalimumab, and (43) patients on etanercept. Assessment was done and included through medical history, clinical examination, chest x ray, HRCT chest, tuberculin skin test and sputum for acid fast bacilli (AFB). Those with latent TB were subjected for anti-tuberculosis Chemoprophylaxis.

Results: The prevalence of infectious complications was significantly more common in those who were receiving the biological therapy (39.2%) versus 15.2% for those who were receiving (DMARDs). Active TB was 2.5 times more in group (B). Other infections as respiratory tract infections, urinary tract infections, and herpes zoster were more common in those who were receiving biological therapy (29.2%, 4.6% and 3%), versus the other group (13.3, 0.9, and 0%) respectively.

Conclusion: From this study we concluded that the use of biological therapy in RA patients still raises a serious concern, namely the increased risk of infections, especially TB which demand specific and time-consuming measures before and during treatment. Chemoprophylaxis for patients on anti-TNF therapy was safe and partially prevents the reactivation of latent TB.

Key words: TB, anti-TNF therapy, Latent TB, Rheumatoid arthritis, Infliximab, Adalimumab, Etanercept, incidence.
INTRODUCTION

In the last decade, a new class of drugs referred to as biologics has been used successfully for treating patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and other inflammatory conditions. Infliximab alone has been used in more than 900,000 individuals worldwide (1). Drugs such as infliximab, adalimumab, and etanercept have been important treatment advancements because they allow the direct targeting of the inflammatory cytokine tumor necrosis factor alpha (TNF-α), which is elevated in the blood and the tissue of the patients (2). The FDA monitors the safety of newly licensed products, such as Infliximab, Adalimumab and etanercept. Infliximab (Remicade) is a mouse-human antibody against tumor necrosis factor alpha, intravenous infusion of infliximab can be administered in a single dose (5 mg/Kg), a monthly regimen, the loading regimen for all approved indications occurs at weeks 0, 2, and 6 then every 8 weeks at a clinic or hospital. The half-life time of infliximab is 10 days, and its biologic effect persists for up to 2 months. Infliximab is supplied as a sterile, white, lyophilized (freeze dried) powder 100 mg dose and must be reconstituted (3). Adalimumab, (HUMIRA, Abbott) is a fully human monoclonal antibody that binds to TNFα, preventing it from activating TNFα receptors. HUMIRA ("Human Monoclonal Antibody in Rheumatoid Arthritis") is marketed in both preloaded 0.8 mL syringes and also in preloaded pen devices (called Humira Pen), both injected subcutaneously, typically by the patient at home (4). Etanercept (Enbrel, Pfizer), is a fusion protein (TNF receptor-IgG fusion protein). Enbrel is marketed as a single-use 50 mg auto injector "pen" and used subcutaneously once weekly (5,6). Evidences about the benefits of these drugs are accumulating. However, they are not risk-free, and evidences of their risks primarily infections especially TB are mounting (5). The role of TNFα in the human immune response to Mycobacterium tuberculosis remains unclear (7). In animal models, it seems that TNFα has an important role in the host response against tuberculosis (8) including granuloma formation and containment of the disease (9). British Society for Rheumatology Biologics Register assessed the risk of serious infections in 11,798 TNF-inhibitor-treated patients and 3,598 patients receiving conventional DMARDs (10). Patients receiving TNF inhibitors had 4.2 serious infections per 100 patient-years as compared with 3.2 per 100 patient-years in those receiving conventional DMARDs. The risk was greatest during the first 6 months of therapy. So preventive actions are advised (10). French guidelines elicited in 2002, recommended anti-TB chemoprophylaxis before all anti-TNF therapy for patients presenting at least one of the following: tuberculin skin test (TST) diameter ≥ 5 mm in high-risk groups, abnormal chest radiography results with calcifications >1 cm, previous untreated exposure to TB, or episode of TB. A positive TST should be followed by medical assessment and chest radiography, as well as by other tests judged appropriate to identify active disease (11, 12). Correct chemoprophylaxis was defined as a 9-month treatment with isoniazid (13).

AIM OF THE WORK

The aim of this work was to assess the risk of active TB with other serious and non-serious bacterial and viral infections in RA patients who are receiving conventional disease modifying anti rheumatic drugs (DMARDs) versus those who are receiving biological therapy and to evaluate the effectiveness of an anti-tuberculosis chemoprophylaxis regimen in those with latent TB receiving biological therapy.

PATIENTS AND METHODS

Study design: A prospective study conducted on (235) patients have rheumatoid arthritis (RA), divided into two groups; group (A) included (105) RA patients on conventional disease modifying anti rheumatic drugs (DMARDs) with a mean age (51±12) and group (B) included (130) RA patients on biological therapy with a mean age (48±13) as (55) patients on infleximab, (32) patients on adalimumab, and (43) patients on etanercept. All patients were selected from Rheumatology outpatient clinic, King Fahd Hospital, Al Madina Al Monawarah, Kingdom Saudi Arabia during the period from 1/1/2010 to 1/10/2012. The study protocol was approved by the local ethics committee. Informed consent was obtained from the patients.

All patients underwent:
1. Full medical history.
2. Through clinical examination.
3. Postero-anterior chest X ray (CXR).
4. Tuberculin skin test (TST) by Mantoux method.
5. High resolution computed tomography (HRCT) Chest if CXR has any abnormality.
6. Sputum for acid fast bacilli (AFB) if the patient has any chronic chest complaint with sputum production.

Follow up monthly for:
1. Any medical complaint especially that suggestive TB infection and / or other bacterial or viral infection.
2. Full clinical examination including chest examination.
3. Sputum for AFB if the patient has any chest complaint with sputum production.
4. Other investigations as needed e.g. Fine needle aspiration (FNA) and excisional lymph node
biopsy and HRCT chest if chest X ray (CXR) has any abnormality.
5. The usual care and follow up in the rheumatology clinic was done.
6. An abnormal CXR suggesting latent TB and/or a positive TST (diameter ≥10 mm) were indications for anti-tuberculosis chemoprophylaxis.
7. Those with latent TB were given Isoniazed 5 mg /Kg body weight for 9 months starting 2 months before the biological therapy. While those developed active TB during treatment, received full anti-tuberculosis treatment and stopped the biological treatment.
8. Those with other infections received treatment according to the cause.
9. Exclusion criteria: Patients with active infection were excluded.
10. Statistical analysis: Results are expressed as mean and SD. Chi-square test for qualitative variables were used. All statistical analysis was performed using SPSS 17.0 for Windows (SPSS Inc, Chicago, IL, USA).

RESULTS
Table 1. Showed characters of the patient groups, there was no significant difference between two groups regarding to smoking, BCG vaccine and positive TST while active TB was more in (group B).
Table 2. showed infectious complications among two groups, there was significant increase in the incidence of total infectious complications among patients who were receiving biological therapy 39.2% (group B) versus patients who were receiving (DMARDs) 15.2% (group A). The incidence of active TB was 2.3% in group (B) versus 0.9% in group (A) with 2.5 more risk. Respiratory tract infection incidence was 29.2% in group (B) versus 13.3% in group (A). Incidence of urinary tract infection was 4.6% in group (B) versus 0.9% in group (A), and Herpes Zoster incidence was 3% in group (B) and 0% in group (A).
Table 3. Characteristics of patients with tuberculosis, 4 patients developed active TB during the follow up period, 3 of them had positive tuberculin test before starting therapy and the fourth has negative tuberculin test. One of the patients was under DMARDs for RA, with normal chest X-ray but with highly positive TST (about 22mm) and was given INH, 5 mg /Kg body weight for 9 months. 12 months after starting DMARDs, extra pulmonary tuberculosis (TB cervical lymphadenitis) was developed. The other three patients were on biological therapy for RA (2 patients on infliximab and one patient on adalimumab). The patient on adalimumab has normal chest x-ray, previously BCG vaccinated with positive tuberculin test, 5 months from starting medication he developed pulmonary tuberculosis. 2 male patients on infliximab had normal chest x-ray, previously BCG vaccine, moderate smokers, one patient has positive TST (about 24mm) so was given INH 5 mg /Kg body weight for 9 months. 6 months from starting medications, he developed extra pulmonary tuberculosis (TB cervical lymphadenitis) and the other patient has negative TST (4mm) and 4 weeks from starting medications, he developed pulmonary TB. All positive TST patients were given INH 5 mg /Kg body weight for 9 months. In all active pulmonary TB, the diagnosis was confirmed by +ve sputum for AFB. TB cervical lymphadenitis was confirmed by FNA and excisional lymph node biopsy. Patients with active TB received full anti TB treatment, and Anti-tumor necrosis factor agents were stopped.

Table 1. Characteristics of the patient groups.

<table>
<thead>
<tr>
<th>Age: Mean±SD</th>
<th>Group A (105)</th>
<th>Group B (130)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>No</td>
<td>%</td>
</tr>
<tr>
<td>male</td>
<td>58</td>
<td>55.2</td>
</tr>
<tr>
<td>female</td>
<td>47</td>
<td>44.8</td>
</tr>
<tr>
<td>Smoking</td>
<td>76</td>
<td>72.4</td>
</tr>
<tr>
<td>BCG vaccine</td>
<td>105</td>
<td>100</td>
</tr>
<tr>
<td>+ve TST</td>
<td>13</td>
<td>12.4</td>
</tr>
<tr>
<td>Active TB cases</td>
<td>1</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Table 2. Infectious complications among the two groups.

| No | % | No | % |
| Upper respiratory tract infection | 14 | 13.3 | 38 | 29.2 |
| Urinary tract infection | 1 | 0.9 | 6 | 4.6 |
| Herpes zoster | - | 0% | 4 | 3 |
| Active TB cases | 1 | 0.9 | 3 | 2.3 |
| Total infections | 16 | 15.2 | 51 | 39.2 |
| Upper respiratory tract infection | 14 | 13.3 | 38 | 29.2 |

Table 3. Characteristics of patients with tuberculosis (TB):

<table>
<thead>
<tr>
<th>No</th>
<th>Age</th>
<th>sex</th>
<th>Smoking</th>
<th>BCG vaccine</th>
<th>TST results</th>
<th>CXR</th>
<th>Prophylaxis</th>
<th>treatment</th>
<th>TB location</th>
<th>TB onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>46</td>
<td>F</td>
<td>Non</td>
<td>yes</td>
<td>22mm</td>
<td>normal</td>
<td>INH 300 mg/9 m</td>
<td>DMARDs</td>
<td>Pulmonary</td>
<td>12 m*</td>
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<tr>
<td>2</td>
<td>53</td>
<td>M</td>
<td>mild</td>
<td>yes</td>
<td>18mm</td>
<td>normal</td>
<td>INH 300 mg/9 m</td>
<td>adalimumab</td>
<td>Lymph node</td>
<td>5 m*</td>
</tr>
<tr>
<td>3</td>
<td>51</td>
<td>M</td>
<td>Moderate</td>
<td>yes</td>
<td>4 mm</td>
<td>normal</td>
<td>No</td>
<td>infliximab</td>
<td>Pulmonary</td>
<td>4 w*</td>
</tr>
<tr>
<td>4</td>
<td>39</td>
<td>M</td>
<td>moderate</td>
<td>yes</td>
<td>24mm</td>
<td>normal</td>
<td>INH 300 mg/9 m</td>
<td>infliximab</td>
<td>Lymph node</td>
<td>6 m*</td>
</tr>
</tbody>
</table>

TST = Tuberculin Skin Test;*from initiation of therapy to diagnosis of active TB.
DISCUSSION
Epidemiological studies have shown that patients with RA are at increased risk of certain infections compared with the general population (14) and infections have long been recognized as a major cause of morbidity and mortality in RA (15). Assessing the impact of biological therapies on the risk of TB also needs to take into account the fact that patients with rheumatoid arthritis have increased risk of getting TB (16), more importantly we must consider the incidence of TB in the general population. In our study when we compare two groups from the same community, with no significant differences in socio-demographic data, we can say comfortably that treatment with biological therapy in RA arthritis patients has increased risk of total infection 2.5 times more than those treated with (DMARDs) and the ratio of active TB between group B and group A was 3:1.

Cases of active tuberculosis have been reported worldwide with the use of therapeutic agents that inhibit tumor necrosis factor alpha (TNF-α) and accordingly, reinfection or reactivation of acquired infection should be expected with the use of anti-TNF agents (17). The risk of tuberculosis due to biological therapy has been investigated using data from a Swedish registry from 1999 to 2001 (18). Patients with RA who were treated with TNF inhibitors had a 4-fold increased risk of tuberculosis compared with those who were not treated with TNF inhibitors. The risk of developing tuberculosis among patients being treated for RA with TNF inhibitors has also been investigated using registries established in Korea (19) and Spain (20). Compared with the general Korean population, the risk of tuberculosis was 8.9-fold higher for patients with RA and 30.1-fold higher for patients with RA treated with infliximab. Etanercept use was not associated with any increased risk of tuberculosis above that seen in the general RA population (19). Data from the Spanish databases also showed an estimated incidence of tuberculosis among RA patients receiving infliximab of 1893 cases/100,000 patients in 2000 and 1113/100,000 in 2001, compared with a background incidence of tuberculosis in Spain in 2000, which were 21 cases/100,000 patients (20). All go with our results.

However, though we used Tuberculin skin testing (TST) before starting the biological therapy, the possibility of false-negative reactions in immune-compromised populations must be borne in mind (21). The effectiveness of screening by TST can be affected by many factors as treatment with immunosuppressive, which lead to high prevalence of anergy to the tuberculin skin test in such patients so a negative TST result is an unreliable indicator for TB exposure in such patients. We have 4 cases with TB, 3 of which were TST positive and one was negative. The screening also in the present study revealed that about 11.5% of patients who are candidates for anti-TNF therapy have latent TB (27 out of total 235) and according to Zalevsky et al. TST retest is required to identify such patients (6). However we started prophylaxis INH 5 mg /Kg body weight for 9 months, and only 3 out of 27 with latent TB get active infection (11%) which means incomplete prevention as mentioned in some studies that Anti-tuberculosis chemoprophylaxis was only of partial preventive success of active TB in patients receiving anti-TNF drug therapy (21,22). Carmona et al., 2005 concluded that Strategies to treat latent TB infection that are tailored to the at-risk population can effectively and safely lessen the likelihood of active TB in patients treated with TNF antagonists (23).

The efficacy of screening and anti-TB chemoprophylaxis may explain why the median time from the beginning of anti-TNF therapy to TB onset is much higher (5-6 months) in our study than that in the other study describing TB in patients treated with infliximab (14 weeks), when no screening for TB was done (24). Tubach et al (2009) found increased risk for TB infection with early anti-TNF treatment and absence of correct chemoprophylaxis treatment that favor the reactivation of latent TB (25). In the present study, we observed both patterns of TB infection; reactivation of a latent TB infection which will never be avoided with pre-treatment screening and new infection occurring during follow-up.

Regarding to the type of drugs used in the treatment of patients with RA showed active TB; we found 2 cases with active TB were receiving infliximab, while the 3rd one was receiving adalemumab. We cannot conclude that any drug have more or less risk for active TB affection, but this raising the issue that this is not only a class effect but individual drug effects also occur (21, 22). Another important point is that, we get only small numbers of active cases which can’t determine the effects of each drug alone.

Our study also showed that BCG vaccination status had no significant influence on the TST response. Serial TST testing in patients receiving TNF is indicated to identify patients with reactivation of latent tuberculosis infection or those exposed to mycobacterium (26). The pattern of TB in the present study showed atypical presentation among patients who are receiving anti-TNF therapy, 2 extra-pulmonary tuberculosis (lymph nodes) versus one pulmonary TB in group B. This was in accordance with Keane et al, 2001 who found that the pattern of TB disease was unusual. The majority of the patients (56 percent) had extra pulmonary tuberculosis (27, 22).

One of our patients, who had negative TST, had developed pulmonary tuberculosis 4 weeks after starting infliximab. So, according to Mow et al, 2004 evaluation for TB risks should include not only a TST, but also a detailed history of travel, TB exposures, and such symptoms as chronic cough and weight loss, a
chest X-ray should be considered (28) and other tests such as a Quantiferon-TB Gold assay may be helpful for individuals vaccinated with BCG, but it is still controversial for persons taking immune-suppressants because of the high number of false-negatives in this group according to Ferrara et al, 2005 (29).

Conclusion: From this study we concluded that there was an increasing risk of developing active tuberculosis among patients who are receiving anti-TNF therapy. Screening of patients before anti-TNF therapy for latent tuberculosis with TST should be done which proved to be effective, and has partially decreased the risk of developing active TB. TST retest should be considered if the initial TST is negative. Proper TB chemoprophylaxis treatment for patients with latent TB on anti-TNF therapy was safe and partially prevents the reactivation of latent TB.

REFERENCES


