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ORIGINAL ARTICLE

Tuberculosis chemoprophylaxis in rheumatoid arthritic patients receiving tumor necrosis factor inhibitors or conventional therapy

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Abstract *Introduction:* Patients with rheumatoid arthritis (RA) have increased susceptibility to infection. The risk of acquiring infection including tuberculosis (TB) in RA may be increased in patients receiving any immuno-suppressive medication including anti-TNF therapy, which is used successfully for treating patients with rheumatoid arthritis. The aim of this work was to assess the risk of TB in RA patients on anti-TNF therapy compared to conventional disease modifying anti rheumatic drugs when screening for latent TB and TB chemoprophylaxis was applied.

Patients and methods: This study conducted on (235) RA patients indicated for either conventional therapy or anti-TNF therapy from 1-1-2010 to 1-10-2013. Assessment was done before RA treatment and included medical history, clinical examination, plain chest X-ray, HRCT chest QuantiFERON®-TB Gold in-tube (QFT-GIT) test and microbiologic investigations for tuberculosis when indicated. All patients with positive QFT-GIT received chemoprophylactic treatment for TB.

Results: The studied rheumatoid arthritic patients were divided into two groups; group (A) included (105) RA patients on conventional disease modifying anti rheumatic drugs (DMARDs) with mean age (51 ± 12) and group (B) included (130) RA patients on anti-TNF therapy with mean age (48 ± 13). This study showed no significant increase of tuberculosis among patients on anti-TNF therapy (group B) compared to patients on (DMARDs) (group A). Chemo-prophylaxis in patients on anti-TNF therapy leads to prevention of reactivation of latent TB.

Conclusion: There was no significant increased risk for tuberculosis among RA patients receiving anti-TNF therapy when screening and chemoprophylaxis was applied, so screening of RA patients before anti-TNF therapy for latent tuberculosis and TB chemoprophylaxis should be done.

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Introduction

Patients with rheumatoid arthritis (RA) are reported to have an increased susceptibility to infection [1]. Studies of a specific

susceptibility to tuberculosis (TB) in patients with RA have produced contrasting results. For example in the USA, an increased incidence of TB in patients with RA was not observed [2]. In contrast, a substantial increase in the risk of acquiring TB in RA has been reported in Europe and Asia [3,4]. The risk of acquiring TB in RA may be increased in patients receiving oral glucocorticoid therapy or the use of therapeutic agents that neutralize tumor necrosis factor (TNF) [5,6].

A new study shows that tuberculosis infection (TB) is 10 times more common among male patients who have rheumatoid arthritis than it is in the general population, and that risk appears to be elevated by treatment with any immunosuppressive medication, including anti-TNF therapy, which was used successfully for treating patients with rheumatoid arthritis. 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 tissue of RA patients [7]. The FDA monitors the safety of newly licensed products, such as infliximab, adalimumab and etanercept. Infliximab (Remicade) is a mouse-human (chimeric) 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 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 [8]. Adalimumab, (HUMIRA, Abbott) is a fully human monoclonal antibody that binds to TNFα, preventing it from activating TNF 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 [9]. Etanercept (Enbrel, Pfizer), is a TNF receptor-IgG fusion protein. A single-use 50 mg auto injector "pen" was used subcutaneously once weekly [10,11]. Evidence about the benefits of these drugs is accumulating. However, they are not risk-free, and evidence of their risks primarily infection especially TB is also mounting so preventive actions are advised [12].

The aim of this work was to assess the risk of TB associated with the use of anti-TNF therapy compared to disease modifying anti rheumatic drugs (DMARDs) in RA patients when screening for latent TB with TB chemoprophylaxis was applied.

Patients and methods

Study design

A prospective study conducted on (235) rheumatoid arthritic patients indicated for either conventional therapy or anti-TNF therapy from 1/1/2010 to 1/10/2013 at the King Fahd Hospital in Al Madenha Almonoura, Kingdom of Saudi Arabia and Dallah and Nagd hospitals. RA was diagnosed according to established classification criteria [7] by rheumatologists.

The studied patients were divided into two groups; group (A) included (105) rheumatoid arthritic patients on conventional disease modifying anti rheumatic drugs (DMARDs) with mean age (51 ± 12) and group (B) included (130) rheumatoid arthritic patients on biological therapy with mean age (48 ± 13) as(55) patients on infliximab, (32) patients on adalimumab, and (43) patients on etanercept.

Before starting treatment for RA patients they underwent:

(1) Complete medical history.
(2) Clinical examination.
(3) Routine laboratory investigations.
(4) Plain chest X-ray (CXR).
(5) QuantiFERON®-TB Gold in-tube (QFT-GIT; Cellestis Limited, Carnegie, Australia) done according to the manufacturer instructions.
(6) High resolution computed tomography (HRCT) chest if chest X-ray (CXR) has any abnormality.
(7) Microbiological investigations to exclude active pulmonary tuberculosis in clinically suspected cases (AFB smear, mycobacterial Tuberculosis culture, and real time polymerase chain reaction).
(8) All patients with positive QFT-GIT received chemoprophylactic treatment for TB with INH 5 mg/kg body weight for 9 months [13] (after excluding active TB by medical assessment, chest radiography, as well as by other tests judged appropriate to identify active disease.

Follow up done monthly for:

(1) Any medical complaint especially suggestive of TB affection.
(2) Clinical examination: general and chest examination.
(3) Radiological and laboratory investigations for TB if the patient had new symptoms or signs suggestive of TB.
(4) Other investigations as needed e.g. excisional lymph node biopsy.

A patient was classified as a TB case when bacteriological confirmation of TB was done from any specimen obtained from a patient with an appropriate clinical picture [14].

Patients with active TB received anti TB medication, and Anti-tumor necrosis factor agents were stopped [15].

Exclusion criteria

Patients with active infection and patients with other immunosuppressive diseases were excluded.

Statistical analysis

All statistical analysis was performed using SPSS 12.0 for Windows. Results are expressed as mean and SD. Chi-square test for qualitative variables were used.

Results

This study was conducted on (235) rheumatoid arthritic patients. Patients were divided into two groups; group (A) included (105) RA patients on conventional disease modifying anti rheumatic drugs with mean age (51 ± 12) and group (B) included (130) RA patients on biological therapy with mean

age (48 ± 13) as (55) patients on infliximab, (32) patients on adalimumab, and (43) patients on etanercept.

Table 1 shows characteristics of the studied patient groups, there was no significant difference between two groups regarding age, sex, smoking, BCG vaccine and positivity of QFT-GIT.

Table 2 shows infectious complications among two groups, there was a significant increase of respiratory infectious complications among patients on biological therapy (group B) than patients on DMARDs (group A) as in group (A) the number of patients who developed respiratory infectious complications was14 (13.3%) while it was 38 (29.2%) in group (B).

Table 3 Characteristics of patients who developed active tuberculosis, 4 patients developed TB, one female patient under DMARDs for RA, with normal chest X-ray and negative QFT-GIT before starting treatment for RA, 12 months after starting DMARDs developed pulmonary tuberculosis. The other three patients were on biological therapy for RA (2 patients on infliximab and one patient on adalimumab), a male patient on adalimumab had a normal chest X-ray, previously was BCG vaccined and had a negative QFT-GIT and 5 months from starting medication developed extra pulmonary tuberculosis (TB cervical lymphadenitis). 2 male patients on infliximab had normal chest X-rays, were previously BCG vaccinated and moderate smokers and had a negative QFT-GIT and one patient after 6 months from starting medication developed extra pulmonary tuberculosis. (TB cervical lymphadenitis).The other patient after 4 weeks from starting medication developed pulmonary TB.

Discussion

Rheumatoid arthritis (RA) is a chronic, progressive inflammatory condition that can lead to a significant disability and joint pain. The cytokine tumor necrosis factor α (TNFα) plays a key role in its pathogenesis [16]. Introduction of the anti-TNF therapies has dramatically improved the outcome of severe RA. While TNFα is a central cytokine in the synovial inflammation of RA, it also has an important role in host defense mechanisms. This may be particularly important with regard to intracellular infections. Anti-TNF therapies in RA patients, therefore, have the potential to lead to an increased rate of infection [17].

From the published reports of clinical trials, there has been no consistent pattern of serious infection risk associated with anti-TNF therapy. Some studies show no increased risk in active treatment groups compared with placebo groups [18,19], some suggest a possible increased risk [20,21]. The aim of this work was to assess the risk of TB associated with the use of anti-TNF therapy compared to DMARDS in RA patients when screening for latent TB with TB chemoprophylaxis was applied.

This study conducted on (235) patients has RA, is divided into two groups; group (A) included (105) RA patients on conventional disease modifying anti rheumatic drugs (DMARDs) with mean age (51 ± 12) and group (B) included (130) RA patients on anti-TNF therapy with mean age (48 ± 13) as (55) patients on infliximab, (32) patients on adalimumab, and (43) patients on etanercept.

Based on previous studies that showed a reduced performance of the tuberculin skin test (TST) in immunosuppressed rheumatoid arthritic subjects [22] and to avoid false positive TST as all the studied patients were BCG vaccinated, so in this study QFT-GIT was used instead of TST for screening for latent TB.

This study showed that among the studied 235 RA patients 25 patients had positive QFT-GIT (10.6%) (Table 1) this finding agrees with previous studies [2,3].

In this study there was significant increase of respiratory infectious complications among patients on biological therapy (group B) than patients on DMARDs (group A), as in group (A) the number of patients who developed respiratory infectious complications was 14 (13.3%) while it was 38 (29.2%) in group (B) this finding agrees with previous findings of Andrea Kane (2013) [23].

In the studied patients there was non-significant difference in the number of patients who developed active tuberculosis between RA patients on DMARDs and patients on anti-TNF therapies. This finding does not agree with the study of Askling et al. (2005) [24] which showed that in RA patients TNF antagonist treatment was associated with an increased risk of TB, up to 4-fold in magnitude. This difference in result may be attributed to the efficacy of chemotherapy in these study patient groups which decreased the activation of latent tuberculosis.

In this study the efficacy of screening and anti-TB chemoprophylaxis may explain why the time from the beginning of anti-TNF therapy to TB onset is much higher (5–6 months) in the present study than in a previous study [25] that found the median time to develop TB from the beginning of anti-TNF therapy in patients treated with infliximab was 14 weeks, when no screening nor TB chemoprophylaxis was done.

Tubach et al. (2009) found an increased risk of TB infection with early anti-TNF treatment and absence of correct chemoprophylactic treatment that favor the reactivation of latent TB [26]. In the present study, all the patients who developed TB were new TB cases and no patients with latent TB who received chemoprophylaxis developed TB reactivation.

Table 1 Characteristics of the studied patient groups.

	Group A (105)		Group B (130)		t/X^2	s
Age: M ± SD	(51 ± 12)		(48 ± 13)		1.5	0.07
Sex	No.	%	No.	%		
Male	57	54.2	70	53.8	0.005	0.9
Female	48	45.8	60	46.2		
Smoking	76	72.4	89	70.8	0.018	0.89
BCG vaccine	105	100	130	100	0.0	1
+ve QFT-GIT	12	11.4	13	10	0.09	0.76

Table 2 Infectious complications among two groups.

	Group A (105)		Group B (130)		X^2	P	X^2	P
	No.	%	No.	%				
Upper and lower resp. tract infection	14	13.3	38	29.2	6.09	0.01	3.4	0.3
Urinary tract infection	–	0	6	4.6	2.9	0.09		
Herpes zoster	–	0	4	3.07	1.3	0.23		
Active TB	1	.95	3	2.30	0.6	0.42		

Table 3 Characteristics of patients who developed active tuberculosis (TB).

No.	Age	Sex	Smoking	BCG vaccine	QFT-GIT	CXR	Prophylaxis	Treatment	TB location	TB onset
1	46	F	Non	Yes	−ve	Normal	INH 300 mg/9 m	DMARDs	Pulmonary	12 m[*]
2	53	M	Mild	Yes	−ve	Normal	INH 300 mg/9 m	Adalimumab	Lymph node	5 m[*]
3	51	M	Moderate	Yes	−ve	Normal	No	Infliximab	Pulmonary	4 w[*]
4	39	M	Moderate	Yes	−ve	Normal	INH 300 mg/9 m	Infliximab	Lymph node	6 m[*]

[*] From initiation of therapy to diagnosis of active TB.

Conclusion

This study concluded that TB chemoprophylaxis for RA patients with latent TB who received anti-TNF therapy is efficient for minimizing reactivation of latent TB, so screening of these patients before anti-TNF therapy for latent tuberculosis should be done.

Conflict of interest

These authors declare no conflict of interest.

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