The risk of tuberculosis infection in 410 Saudi patients receiving adalimumab therapy

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BACKGROUND: Adalimumab is a fully humanized monoclonal anti-body inhibitor of tumor necrosis factor-a used to treat various autoimmune disorders. Adalimumab poses a risk for tuberculosis (TB) infection, especially in countries where TB is endemic.

OBJECTIVE: Determine the rate of TB infection after adalimumab therapy in Saudi Arabia.

DESIGN: Medical record review.

SETTINGS: Tertiary care center in Riyadh.

PATIENTS AND METHODS: Demographic and clinical data were retrieved from the electronic healthcare records of all patients who received adalimumab treatment from 2015 to 2019.

MAIN OUTCOME MEASURES: Occurrence of TB after adalimumab therapy.

SAMPLE SIZE: 410 patients (median [IQR] age, 37 [28], range 4-81 years), 40% males

RESULTS: Rheumatoid arthritis was the most frequent indication (n=153, 37%). The patients were followed for a mean of 36 (8.9) months. No case of TB infection or reactivation was observed. An interferon-gamma release assay (IGRA) was requested in 353/391 (90.3%) patients, prior to initiating therapy. The IGRA was positive in 26 cases (6.6%). The IGRA-positive patients received isoniazid prophylactically. Bacterial infectious complications of adalimumab therapy occurred in 12 (2.9%) patients. Urinary tract infection was the most frequent complication (culture requested in 48 patients, positive in 8).

CONCLUSION: Adalimumab treatment was not associated with a risk of TB disease or TB reactivation in our cohort over the follow-up observation period. No TB reactivation occurred with adalimumab therapy when TB prophylaxis was used. The positive IGRA rate in patients on adalimumab treatment was low (7%).

LIMITATIONS: Single center and one geographical area in Saudi Arabia.

CONFLICT OF INTEREST: None.
The introduction of tumor necrosis factor alpha (TNF-α) monoclonal antibodies like infliximab, adalimumab, certolizumab pegol and soluble TNF-α receptors like etanercept have made it possible to control the progression of many immune-mediated inflammatory disorders like rheumatoid arthritis and inflammatory bowel disease and others. However, TNF inhibitors also block key cytokines crucial for host defense against many infections, including infections due to an intracellular organism such as Mycobacterium tuberculosis. The relative risk of TB reactivation in patients receiving anti-TNF-α treatment is 1.5- to 17-fold higher than the average community risk, depending on the agent used. Anti-TNF-α monoclonal antibodies like infliximab and adalimumab pose the highest risk as compared to soluble TNF-α receptors. The median time to TB infection or reactivation after treatment varies between 17 and 79 weeks, depending on the agent used. Other risk factors for TB reactivation include immunosuppression, steroid use and living in an endemic TB area. Saudi Arabia is a moderate risk country for TB with a reported prevalence of 15.8/100,000 population. Effective TB screening and adequate treatment of latent TB infection (LTBI) reduces the TB reactivation frequency by 85%, especially in countries with a high prevalence of TB infection.

The risk of TB reactivation linked to biological drugs including monoclonal TNF-α inhibitors and others used in the treatment of immune-mediated diseases has been reported in Saudi Arabia. Dewedar et al reported on 112 patients treated with different TNF inhibitors (56 receiving infliximab, 36 patients receiving adalimumab and 20 patients receiving etanercept) with no TB disease occurring in any of the treatment arms during 5 years of follow up. Latent TB was diagnosed in 1.8% of the cases during therapy. Al-Kadi et al, in a retrospective cohort study with 60 patients receiving rituximab for RA, concluded that rituximab has a very low risk of TB reactivation. The follow-up period was short however. The current study evaluated the risk of TB infection/reactivation from a fully humanized monoclonal TNF-α inhibitor, adalimumab, which is increasingly used in the treatment of patients with rheumatic disorders, including RA, psoriatic arthritis, and ankylosing spondylitis in Saudi Arabia.

**PATIENTS AND METHODS**

In this retrospective study, we included all patients who received adalimumab treatment at King Abdulaziz Medical City (KAMC) in Riyadh, from 2015 to 2019. The hospital is a major referral hospital for the whole of Saudi Arabia, with a total bed capacity of 1000 and more than 600,000 annual outpatient clinic visits in all subspecialties. The data were retrieved from the electronic healthcare records, including demographic data (gender and age), primary diagnosis, adalimumab (Humira, AbbVie) treatment (dose used, frequency, total cumulative dose), the tuberculin skin test, and interferon-gamma release assays (IGRA) results. Adalimumab is given as a subcutaneous injection 40 mg every other week for adults. QuantiFERON-TB Gold is the commercial IGRA assay used in the hospital since 2009. In addition, data related to steroid treatment, radiological studies, infectious disease consultations before adalimumab therapy, documentation of BCG scar, follow-up visits, indications for admissions to hospital during adalimumab therapy, infectious complications, the results of cultures and latent TB treatment regimens when prescribed, were retrieved. All data were collected by physician data collectors and reviewed by the study coordinator for consistency. The study was approved by the Institutional Review Board of King Abdullah International Medical Research Center. No consent was required due to the retrospective nature of the study.

We wanted a sample size to detect TB incidence compared to similar patient groups. The sample size was calculated using the Raosoft online calculator; the required sample size with margin of error 5% and 95% CI was 410 patients. Categorical variables are presented as frequency and percentage with continuous variables as mean and standard deviation. Categorical variables were compared using the chi-square test or Fisher exact test, as appropriate. All tests were two-tailed and significance was accepted at a P value <.05. Statistical testing was performed using SPSS for Windows (version 20.0; IBM, Armonk, NY, USA).

**RESULTS**

From 2015 to 2019, 410 patients received adalimumab at KAMC. Rheumatoid arthritis followed by inflammatory bowel disease was the most frequent indication for adalimumab therapy (Table 1). The mean (SD) age was 38.4 years (17.7) (median 37, range 4 to 81 years), and 166 (40.5%) were male. The sample included 50 patients younger than 18 years of age. Nineteen (4.6%) patients were lost to follow up; none due to death. The 19 patients were either followed up in another hospital or were “no shows” at the clinic. All losses to follow-up occurred in the first 12 months after drug administration (Figure 1). The median total dose of adalimumab was 2240 mg (Figure 2).

No case of TB disease was reported after a mean (standard deviation) follow-up of 36 (8.9) months. Latent TB was diagnosed in one patient during treat-
Table 1. Characteristics of patients receiving adalimumab (n=391).

| Parameter                                      | Male | Female |
|-----------------------------------------------|------|--------|
| Parameter                                    | 161  | 230    |
| Male                                         | 41.2 | 58.8   |
| >18 years                                    | 141  | 200    |
| Female                                       | 87.5 | 87.0   |
| >18 years                                    |      |        |
| Age                                           | 38.4 |        |
| Saudi                                         | 373  |        |
| Comorbidities                                 |      |        |
| Diabetes mellitus                            | 54   |        |
| Chronic liver disease                        | 4    |        |
| Chronic renal disease                        | 3    |        |
| Chronic obstructive pulmonary disease         | 2    |        |
| Indication for adalimumab                    |      |        |
| Rheumatoid arthritis                         | 146  |        |
| Inflammatory bowel disease                   | 99   |        |
| Psoriasis                                    | 65   |        |
| Juvenile arthritis                           | 27   |        |
| Ankylosing spondylitis                       | 23   |        |
| Connective tissue disease                    | 1    |        |
| Hidradenitis suppurativa                     | 6    |        |
| Sacroiliitis                                 | 3    |        |
| Uveitis                                      | 6    |        |
| Vasculitis                                   | 2    |        |
| Others                                       | 17   |        |
| Mean adalimumab dose (mg)                    |      |        |
| IGRA Positive                                | 2116.9| 1224.7|
| IGRA Negative                                | 2215.8| 1219.8|
| ID evaluation prior to therapy               |      |        |
| No                                           | 379  |        |
| Yes                                          | 12   |        |
| Interferon-gamma release assays (IGRA)        |      |        |
| Documented                                   | 353  |        |
| Positive                                     | 26   |        |
| Negative                                     | 327  |        |
| Not documented                               | 38   |        |
| Mean steroid dose                            |      |        |
| IGRA Positive                                | 1661.7| 2244.1|
| IGRA Negative                                | 2803.3| 6871.1|

Data are number (%) or mean (standard deviation).

ment with adalimumab (7 months after initiating adalimumab). One patient had a history of pulmonary TB disease, treated more than 10 years prior to the adalimumab therapy.

The IGRA test was documented in 353 patients prior to starting therapy (Table 2). We were not able to find a record of IGRA or TST in 38 patients (9.7%), many of whom were referrals from other hospitals and some had a history of treatment with TNF inhibitors or other biological drugs.

All positive IGRA tests were documented prior to adalimumab therapy except one patient who became IGRA positive 7 months after initiating adalimumab treatment. No positive IGRA results were recorded for the group less than 18 years of age. About half of the positive IGRA cases were in patients with rheumatoid arthritis. Rheumatologic disease overall accounted for 72% of all IGRA positive cases.

Patients with inflammatory bowel disease accounted for 15.3% of the positive IGRA cases (4/26). Of the 153 patients with rheumatoid arthritis, 13 were IGRA positive (9.8%) while 4 patients of 99 with inflammatory bowel disease were IGRA positive (4.5%). The mean age of the IGRA-positive group was 47.9 (19.2) years vs. 37.7 (17.5) years in the IGRA-negative group. Positive IGRA was significantly associated with age more than 30 years (P= .023).

The mean (SD) total adalimumab dose in the IGRA-positive group was 2116.9 (1224.7) mg vs. 2215.8 (1219.8) mg in the IGRA-negative group. The mean (SD) total steroid dose (prednisolone) in the IGRA-negative group was 2803.34 (6871.1) mg vs. 1661.73 (2244.1) mg in the IGRA-positive group. The cumulative steroid dose was not significantly associated with IGRA result (P= .936). For patients with a negative IGRA, the test was done only once in 147 patients while 180 patients had more frequent testing during therapy. Testing was
done annually in the majority of patients with more than one testing.

A new chest x-ray prior to initiating adalimumab (within 4 weeks) was requested in 75 patients, of whom 6 were in IGRA positive and 67 were IGRA negative. Evidence of old granulomatous disease was reported in one patient in the IGRA-positive group and three patients in the IGRA-negative group. However, many had an older chest x-ray.

Isoniazid was prescribed for all IGRA-positive pa-
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patients prior to adalimumab therapy, and the duration of therapy was set at 9 months. Adalimumab therapy was initiated within 2 weeks of INH therapy in most of the patients. However, concomitant treatment occurred in a few patients.

Hospital admission was required for 91 cases during adalimumab therapy; admission was for infection in 13 patients (14.3%). One patient was admitted with hypotension and arrested in the emergency room. A diagnosis of intra-abdominal sepsis was made as a cause of death based on the history and physical findings. Another patient was admitted, labeled as septic shock and died as a no code. Both blood cultures were negative. Urinary tract infection was the most frequent infectious complication. Urinary analysis and culture were requested for 48 patients (12.3%); culture was positive for 8 patients. Escherichia coli was isolated in 7 patients including patients who died as a no code. A blood culture was positive in three of 32 cases screened (Group D Salmonella species, Candida albicans, E coli). One patient had a positive respiratory culture of 18 cases screened (Staphylococcus aureus).

DISCUSSION

In the current study, there were no cases of TB disease or reactivation in the 391 patients treated with adalimumab after being followed-up for 3 years. One patient developed LTBI while on adalimumab therapy. The reported rate of TB in patients treated with adalimumab varies worldwide. A national study, based on the Spanish Rheumatology Society Biological Products Database, reported that of 5198 patients treated with biotherapy, only one case of TB disease occurred after adalimumab therapy.

Similarly, only 0.12% of 7009 patients treated with adalimumab in 21 randomized clinical trials developed TB disease. The median time to TB reactivation ranges from 12 to 80 weeks from the first drug dose of a TNF inhibitor, depending on the drug used. The median time for TB reactivation with adalimumab was 18.5 months. The follow-up in the cohort was adequate to identify TB infection and reactivation cases.

The risk of tuberculosis infection is higher in patients with rheumatologic diseases as compared to healthy individuals. LTBI prevalence is variable depending on type of rheumatologic disease and how endemic TB is in the region; TB ranges between 13% to 22% depending on the screening test with the highest observed in psoriatic arthritis. There is a 2- to 10-fold increase in the risk of TB disease in patients with rheumatoid arthritis. In Saudi Arabia, Alamoudi et al reported TB pneumonia in 12% of 108 patient with rheumatoid arthritis who had pleuropulmonary manifestations. TB disease occurred in 7% of 116 patients and was the cause of death in 3 of 19 patients in a study from the western region of Saudi Arabia. A history of TB disease pre-dated the diagnosis of rheumatoid arthritis in 4% of patients.

Use of TNF inhibitors in the treatment of rheumatologic disease is associated with an increased risk of TB infection and reactivation. Arkema et al observed an overall reduction in the hazard ratio for TB disease in a biologically exposed rheumatoid arthritis population compared with biological naïve. Two previous studies and our study showed no increase risk of TB disease with the use of TNF inhibitors although the overall number of treated cases was relativity small.

Guidelines on the use of TNF inhibitors recommend medical evaluation and screening for TB with IGRA when available or TST prior to starting therapy. Chest x-ray is also recommended for patients with a positive IGRA or if medical evaluation indicates an x-ray. Compliance with the TB screening recommendation guidelines significantly reduced the risk of TB reactivation in patients receiving TNF inhibitors, particularly in patients with RA. The screening programs are considered as a performance measure, especially in countries with a high TB burden. In our cohort, 38 patients (9.7%) had no documentation in our hospital of any screening for LTBI prior to adalimumab therapy. IGRA became the standard screening test for LTBI in all National Guard hospitals in 2009 and TST was used prior to that. Our search for TB screening included both electronic health records and 5 years of preceding medical files. Those patients may have had their LTB screen earlier than that, had their TB screen performed in another hospital before referral and a physician decided that there was no need for a repeat IGRA, or could represent poor adherence to recommendations. Chest x-ray at the time of a positive IGRA was requested in less than 50% of patients. However, most of the patients had a chest x-ray within the last 6 months before treatment initiation. Adherence to guidelines should be carefully evaluated in future studies.

The positive IGRA rate in the Saudi population is variable depending on the assessed population. For healthcare workers a rate of 19% to 25% has been reported. However, healthcare workers as a population have many non-Saudi nationals from high-TB endemic countries and the rate in this population does not represent the true rate among Saudis. In hemodialysis patients, a positive IGRA rate as high as 45% has been reported. The positive IGRA rate in our study was 7.8%. Balkhy et al reported an overall IGRA posi-
Activity rate of 9% in a Saudi population-based survey done from 2010 to 2013. The rate in the 15 to 44 year age group was 7.6%, but 17.6% in the 44 to 64 year age group. A lower rate of positive IGRA (4%) in patients with rheumatoid arthritis was also reported from the western region. The use of steroids and other immunosuppressive medication is high in patients with rheumatologic and inflammatory bowel diseases and has been previously linked to high indeterminate IGRA results. However, the use of steroids in our cohort was not associated with IGRA results.

Other infectious complications can occur with TNF inhibitors including life threatening infections. Adalimumab is associated with a modest risk of serious infectious complications when compared to other anti-TNF-α-like agents, certolizumab pegol, for example. Two patients in our cohort were diagnosed with presumed septic shock and died although all cultures were negative. Both were being treated with adalimumab. Other infectious complications were mostly related to simple urinary tract infections.

The low risk of TB infection/reactivation and the low IGRA positivity rate, especially in the younger patients in this study and in another previous study, suggests that routine screening for latent TB before adalimumab therapy may not be cost effective in Saudi Arabia. If the findings of this study are further consolidated by studies from different parts of the country, modification of the current guidelines adopted in Saudi Arabia of routine TB screening prior to adalimumab may be required. A more individualized risk stratification and cost-effective approach are more appropriate.

In conclusion, treatment with adalimumab in this cohort of patients was not associated with a risk of TB. Patients with a positive IGRA who received INH treatment had no TB reactivation during the follow up. The study was limited to a single center and one geographical area in Saudi Arabia. Results need to be supported by studies with a larger sample size and other geographical areas of the country.
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