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REVIEW ARTICLE

Safety of tumor necrosis factor inhibitors use for rheumatoid arthritis and ankylosing spondylitis in Africa, the Middle East, and Asia: focus on severe infections and tuberculosis

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Abstract Multiple studies of patients in Western countries with rheumatoid arthritis (RA) and ankylosing spondylitis (AS) have indicated increased risk for active tuberculosis (TB) and other infections among these individuals. It has also been consistently reported that patients receiving tumor necrosis factor (TNF) inhibitors for these conditions have higher rates of active TB and other infections than RA or AS patients not receiving these medications. These issues have been studied less extensively in the Asia and Africa–Middle East regions, and information from these regions is important because of higher rates of TB in the general population. This paper reviews studies of RA and AS patients from Asia, Africa, and the Middle East who received TNF inhibitors. A literature search was conducted using http://www.ncbi.nlm.nih.gov/pubmed to collect and report these data. The years included in the PubMed literature search ranged from January 2000 to October 2011. Additionally, information from the China Hospital Knowledge Database was used to report data from Chinese patients with RA and AS treated with TNF inhibitors. Results from these studies indicate that the risk for active TB and other infections in AS and RA patients from Asia, Africa, and the Middle East are increased in patients receiving TNF inhibitors and that the risk is higher among those treated with monoclonal antibodies versus soluble TNF receptor.

Keywords Adalimumab · Ankylosing spondylitis · Etanercept · Infliximab · Rheumatoid · Tuberculosis

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Introduction

Rheumatoid arthritis (RA) is a common chronic inflammatory condition that has been estimated to affect about 1 to 2 % of individuals worldwide [1]. In China, the prevalence of RA ranges from 0.2 to 0.93 %, with the highest rate being reported from an urban area in Taiwan [2]. The prevalence of RA in Japan and Singapore is 0.31 % in men and 0.80 % in women. The combined values for the incidence of RA in Indonesia, Thailand, the Philippines, and Malaysia are 0.11 and 0.26 % for men and women, respectively. Values for

India and Pakistan combined are 0.16 and 0.38 % for men and women. In the Middle East and Africa, the combined prevalence in Egypt and Morocco of patients with RA in men and women is 0.14 % and 0.38 % and those for Jordan, Saudi Arabia, and Tunisia combined is 0.16 % and 0.37 % for men and women, respectively [3]. The prevalence of RA in Iraq has been reported to be 1 % in a sample of 6,999 subjects ≥16 years old [4]. Results from the Sultanate of Oman indicated a 0.84 % [5].

Ankylosing spondylitis (AS) is a less common condition that occurs in about 0.1 % of the population with regional differences that mirror the prevalence of human leukocyte antigen (HLA)-B27 seropositivity [6]. The estimated incidence of all types of spondyloarthropathies in the Japanese population is 0.48 per 100,000 patient-years [7]. Interestingly, AS has been reported as being virtually nonexistent in several African populations which could be reflective of the low prevalence of HLA-B27 in this region [8, 9]. However, in the Algerian and Moroccan populations where AS does occur, there is a weaker association between AS and HLA-B27 than reported for European patients (63 and 67 % in Algeria and Morocco, respectively, versus 80 to 90 % in Europe). These data suggest a possible influence of other genetic/environmental determinants in the studied population [10, 11].

Treatment with tumor necrosis factor (TNF) inhibitors has been repeatedly shown to slow radiologically demonstrable disease progression and decrease symptom severity and disability in patients with RA [12]. These agents have also been used effectively in the treatment of patients with AS [13]. Analysis of clinical trial results has also indicated that TNF inhibitors have safety risks, including an increased frequency of infections. Patients with autoimmune diseases, such as RA, are generally considered to have a compromised immune system, which makes them more susceptible to infections [14]. These patients also often suffer from comorbidities, such as diabetes, which also affect immune function [14]. These factors, in combination with the immunosuppressant effects of TNF inhibitors and corticosteroids, increase the risk for infection. Additionally, results from observational studies have also indicated significantly increased risk for serious infections, including tuberculosis (TB), in patients being treated with TNF inhibitors [15].

Safety assessments in controlled clinical trials may underestimate the frequency of uncommon adverse events [16]. Most clinical trials are not powered sufficiently to assess risk for rare events, and entry criteria may exclude high-risk patients likely to receive treatment in clinical practice. Most clinical studies also have short durations of follow-up [16]. Safety information obtained from patients who have been enrolled in registries is an important complement to those from clinical trials [16]. Registry studies accurately reflect the use of treatments both in the clinical setting and over the long-term. Registries can reveal the patterns and the relevance of serious infections, such as TB, resulting from TNF inhibitor use in a variety of patient populations (e.g., patients with particular background risks, patients with specific genetic backgrounds) [16–18]. The long-term safety data obtained from registries may allow physicians to better assess their treatment options to manage patients.

It is also important to note that risk of serious infection, notably TB as a result of treatment for RA or AS, may vary as a function of the prevalence of the disease in the population, which varies greatly from one region to another. In the USA, UK, France, and Germany, the 2009 prevalence of TB is 4.5, 15.0, 7.3, and 5.9 per 100,000 in the population, respectively. In China, Hong Kong, Korea, and the Philippines, the respective values are 138.0, 98.0, 114.0, and 520.0 per 100,000, respectively. In Algeria, Egypt, Jordan, and Morocco, they are 67.0, 30.0, 6.2, and 109.0 per 100,000, respectively [19].

This paper reviews the risk for serious infections in patients with either RA or AS who have been or are being treated with TNF inhibitors from Asia, Africa, and the Middle East. To report these data, a literature search was conducted using http://www.ncbi.nlm.nih.gov/pubmed (years included ranged from January 2000 to October 2011). Additionally, information from the China Hospital Database was used to collect and report data from Chinese patients with RA and AS treated with TNF inhibitors. These data, summarized in Table 1, are important for rheumatologists and other physicians who prescribe biologic therapies because these areas have a high background incidence of TB and other infections.

Risk of TB and serious infection in RA and AS patients

The Asia Pacific Region

Japan

Postmarketing surveillance for 5,000 RA patients receiving infliximab with ≥6 months of follow-up indicated that 0.3 % developed TB [20]. In this study, 64 % of the patients were female and had no history of TB, and comorbidities were present more frequently in those who developed TB versus those who did not. A second study from Japan compared the infection risk for RA patients receiving TNF inhibitors versus nonbiologic agents [21]. The analysis included 1,144 patients, 646 of whom were treated with either infliximab or etanercept and were followed for up to 1 year. In patients not exposed to TNF inhibitors, the incidence rate for serious infections was 2.64 per 100 patient-years. In those treated with TNF inhibitors, the rate for serious infections is 6.42 per 100 patient-years (p=0.026) [21].

Table 1 Summary of the incidence of TB and other infections

Country	Disease state	Number of patients	Study description (treatment)	Incidence of infections
Japan	RA	5,000	Infliximab	TB: 0.3 % patients [22]
	RA	1,144 (646 treated, 498 TNF inhibitor naive)	Infliximab	Serious infections [23]
				6.42/100 patient-years (treated)
				2.64/100 patient-years (TNF inhibitor naive)
China	RA	101	Etanercept	TB: 0 [25]
	RA	87	Infliximab	TB: 1/87 patients, pneumonia: 2/87 patients [26]
	RA	67	Infliximab	TB: 1/67 patients [27]
	RA	242	Adalimumab	TB: 3/242 patients [28]
	AS	63	Infliximab, etanercept	TB: 0 (both infliximab and etanercept) [30]
	AS	74	Infliximab	TB: 0 [27]
	AS	95	Etanercept	TB: 0 [30]
Taiwan	RA	35	Adalimumab	TB: 1/35 patients, sinusitis: 1/35 patients, pneumonia: 1/35 patients [31]
	RA	43	QFT-G + TST prior to adalimumab treatment	18.6 % positive TST—no TB in 2 years (patients treated with INHP prior to adalimumab)
				81.4 % negative TST—4 TB cases (9.3 %) [32]
Philippines	RA	64	Infliximab	Pneumonia: 1/64 patients [34]
	AS	64	Infliximab	Pneumonia: 1/64 patients [34]
Korea	RA	1,285 untreated 193 treated	1,285 TNF inhibitor naive	TB [35]
			90 infliximab	TNF inhibitor naive: 9/1,285 patients
			103 etanercept	Infliximab: 2/90 patients
				Etanercept: 0
	AS	919 untreated 354 treated	919 TNF inhibitor naive	TB [36]
			66 adalimumab	TNF inhibitor naive: 308/100,000 patient-years
			78 infliximab	Adalimumab: 490/100,000 patient-years
			210 etanercept	Infliximab: 540/100,000 patient-years
				Etanercept: 0
Thailand	RA or AS	100	Etanercept or infliximab	TB and hepatitis B [37]
				Etanercept: 2 cases
				Herpes zoster [37]
				Infliximab: 2/23 patients
India	RA	12	Etanercept	TB: 5 % patients [38]
	AS	147	Infliximab	TB: 10.6 % patients [38]
Morocco	RA	494	Untreated	TB: 3,640/100,000 persons [39]
Algeria	General	N/A	Untreated	TB: 88/100,000 persons [41]
Iraq	General	N/A	Untreated	TB: 64/100,000 persons [41]
Bahrain	General	N/A	Untreated	TB: 29/100,000 persons [41]
Qatar	General	N/A	Untreated	TB: 43/100,000 persons [41]
Turkey	General	N/A	Untreated	TB: 29/100,000 persons [41]
Tunisia	General	N/A	Untreated	TB: 24/100,000 persons [41]
Oman	General	N/A	Untreated	TB: 14/100,000 persons [41]
Jordan	General	N/A	Untreated	TB: 6/100,000 persons [41]
The United Arab Emirates	General	N/A	Untreated	TB: 3/100,000 persons [41]

TB tuberculosis, *RA* rheumatoid arthritis, *TNF* tumor necrosis factor, *AS* ankylosing spondylitis, *QFT-G* QuantiFERON-TB Gold, *TST* tuberculin skin test, *INHP* isoniazid prophylaxis, *N/A* not applicable

China and Hong Kong

The prevalence of TB is high in China. Results from a survey published in 2002 that included information from 365,097 individuals indicated that the prevalence of active pulmonary TB was 367 per 100,000, the prevalence of smear-positive pulmonary TB was 122 per 100,000, and the prevalence of bacteriological-positive pulmonary TB was 160 per 100,000 [22].

Results from a study of 101 Chinese patients with active RA who received a recombinant human TNF-Fc fusion protein (etanercept) indicated no cases of TB after 24 weeks of follow-up [23]. In another study, two cases of pneumonia and one case of lymphatic TB were recorded for 87 RA patients who received five infusions of infliximab [24]. There was one reported case of lymphatic TB in the RA cohort of 67 patients treated with infliximab from a Chinese registry [25]. A study of 242 Chinese patients who received adalimumab in a 24-week double-blind trial indicated three cases of TB over the follow-up period [26]. All of these results suggest there are fewer serious infections with etanercept than with the anti-TNF antibodies, infliximab, and adalimumab [17].

The prevalence of TB in Hong Kong has been reported to be 98 per 100,000 in the population [19]. A study carried out in Hong Kong assessed the risk for TB in patients with RA versus that in the general population over the period from 2004 to 2007. This record review included information from 2,441 RA patients from five different centers. The median follow-up was 6,616 patient-years for patients not receiving a TNF inhibitor and 185 patient-years for those who received anti-TNF agents. When results for these patients were compared with those from age- and sex-matched controls from the general population, the standardized incidence ratio (SIR) for active TB in TNF-inhibitor-naive RA patients was 2.35 times that for the controls ($p=0.013$) and the SIR for TNF-treated RA patients was 34.92 that for controls ($p<0.001$) [27].

Results for AS in patients from China are limited relative to RA, but are generally similar. Results from a small clinical trial indicated no cases of TB in 63 patients treated with infliximab and 70 who received etanercept [28]. Similarly, no TB cases were reported in the AS cohorts of 74 patients treated with infliximab and 95 patients treated with etanercept in a Chinese registry study [25].

Taiwan

Results from 35 Taiwanese RA patients who were treated for 12 weeks with adalimumab plus methotrexate indicated three serious infections (one case of TB, one case of pneumonia, and one case of sinusitis) [29]. Results from a study that evaluated the QuantiFERON-TB Gold (QFT-G) assay and tuberculin skin test (TST) for latent TB infection (LTBI) in 43 RA patients being treated with adalimumab indicated that before starting this treatment, eight patients (18.6 %) had positive and 35 patients (81.4 %) had negative TST results. Results from this study also indicated that 37 % of 27 patients who completed 12 months of adalimumab therapy had TST conversion. One of these patients developed active TB. Of all 43 patients who received adalimumab therapy, 9.3 % developed active TB after starting this treatment [30]. The incidence of TB in this small patient sample is much higher than that reported for the entire population of Taiwan (0.075 %). Results from this study support previous reports which state that the application of TST for detecting LTBI is limited in RA patients receiving TNF inhibitor treatment. Combining the QFT-G assay with the TST may assist in detection of patients with LTBI who are receiving immunosuppressive treatments, such as adalimumab therapy [30].

Results from 242 RA patients who received anti-TNF therapy indicated that 31.0 % had a positive TST and 45 (18.6 %) had positive QFT-G results at baseline. Four patients (three with baseline QFT-G-positive results) developed TB within the first 3 months of anti-TNF therapy, and five patients with negative baseline TST and QFT-G results developed active TB after 20 to 24 months of anti-TNF therapy. Results from this study suggest that emergence of active TB follows a biphasic pattern and the presence of persistently high levels of released interferon-γ or QFT-G conversion indicate the development of active TB in patients undergoing long-term anti-TNF therapy [31].

Philippines

Results from a small-scale study of 64 patients in this country indicated that two (one with RA and one with AS) developed pneumonia during the course of treatment with infliximab [32].

Korea

A large-scale assessment of the incidence rate and relative risk of TB in patients with RA and in those treated with TNF inhibitors has been carried out in Korea [33]. This study included 1,285 patients with RA not exposed to TNF blockers and 90 and 103 patients with RA treated with infliximab or etanercept, respectively, between 2001 and 2005. The mean incidence rate of TB was 67.2 per 100,000 patient-years from 2001 to 2004. In the TNF-blocker-naïve RA cohort, nine cases of TB developed during 3497 patient-years of follow-up (257 per 100,000). In the infliximab-treated RA group, two cases of TB developed during 78.17 patient-years of follow-up (2,558 per 100,000 patient-years), and there were no cases of TB during 73.67 patient-years of follow-up in the etanercept-treated group [33].

Kim and colleagues carried out an assessment of the incidence and relative risk of new TB infections in Korean patients with AS and patients with AS undergoing treatment with TNF blockers [34]. This review included the medical records of 919 patients with AS not treated with TNF blockers and those of 354 patients with AS who received adalimumab (n=66), infliximab (n=78), or etanercept (n=210) between 2002 and 2009. The mean incidence rate of TB was 69.8 per 100,000 patient-years in the general population, 308 per 100,000 patient-years in the TNF blocker-naive AS cohort, and 561 per 100,000 patient-years in the TNF blocker-exposed AS cohort. The incidence rate for TB in the infliximab-treated AS cohort (540 per 100,000 patient-years) was higher than that in the adalimumab-treated AS cohort (490 per 100,000 patient-years). No cases of TB occurred in the etanercept-treated AS cohort [34].

Thailand

A retrospective study carried out in Thailand reviewed all infections from 100 consecutive patients who were treated with either etanercept or infliximab (46 % for RA and 41 % for AS) [35]. Results from this analysis indicated two events of suspected active TB and suspected hepatitis-B virus reactivation in patients who received etanercept. Two out of 23 patients (8.7 %) who were initially treated with infliximab had herpes zoster skin infection. The overall incidences of infection post-anti-TNF treatment were 0.122 and 0.201 cases per patient-year in patients who started treatment with etanercept and infliximab, respectively (p<0.0001) [35].

India

Results from one study carried out in India indicated that 10.6 % of patients with RA treated with infliximab had reactivation of TB versus 5 % of those receiving etanercept [36].

Africa and Middle East Region

Morocco

A retrospective review of medical records of 494 RA patients living in Morocco revealed the incidence rate for TB was 3,640 per 100,000 persons. No patients in this study were treated with anti-TNF agents [37]. A single-center, cross-sectional, descriptive study of AS in Moroccan tertiary referral rheumatology centers reports that all patients (n=117) used non-steroidal anti-inflammatory drugs, only 2.6 % reported using anti-TNF therapy, and TB incidence was not reported [38]. The 3 year (2008 to 2010) average incidence rates of TB per 100,000 population, as reported by the World Health Organization, is as follows: 88 for Algeria, 64 for Iraq, 29 for Bahrain, 43 for Qatar, 29 for Turkey, 24 for Tunisia, 14 for Oman, 6 for Jordan, and 3 for the United Arab Emirates [39].

Comparison of results from Asia, Africa, and the Middle East with those from North America and Europe

Results from studies carried out in Asia, Africa, and the Middle East are generally similar to those from large-scale analyses carried out in Europe and the USA. A study of patients in the Research Axed on Tolerance of Biotherapies (RATIO) registry in France assessed all cases of opportunistic infection (OI) in patients receiving anti-TNF treatment for any indication. A case-control design was used with three controls per case that were matched for inflammatory disease and sex. A total of 45 cases of non-TB OIs were recorded in 43 patients. There were 29 infections with infliximab, ten with adalimumab, and four with etanercept. Opportunistic infections were bacterial (four listeriosis, four nocardiosis, four atypical mycobacteriosis, three non-typhoid salmonellosis), viral (eight severe herpes zoster, three varicella, three extensive herpes simplex, four disseminated cytomegalovirus infections), fungal (five pneumocystosis, three invasive aspergillosis, two cryptococcosis), or parasitic (two leishmaniasis). The risks for OIs with infliximab (p<0.0001) or adalimumab (p=0.002) were significantly higher than that for etanercept [40]. The RATIO registry was also used to carry out a case-controlled analysis to investigate the risk of newly diagnosed TB associated with the use of anti-TNF agents. A total of 69 cases of TB were identified. The sex- and age-adjusted incidence rate of TB was 116.7 per 100,000 patient-years. The SIR was 12.2 and was higher for therapy with infliximab (18.6) and adalimumab (29.3) than for therapy with etanercept (1.8). Exposure to infliximab or adalimumab versus etanercept was an independent risk factor for TB [odds ratio (OR)= 13.3, 95 % confidence interval (CI) 2.6 to 69.0 and OR= 17.1, 95 % CI 3.6 to 80.6, respectively].

The British Society for Rheumatology Biologics Register was used to assess the risk for infection in patients being treated with TNF inhibitors [41]. A total of 1,808 patients in this registry had at least one serious infection (1,512 for anti-TNFs and 296 for nonbiologic treatments). Incidence rates were 42 per 1,000 patient-years (p<0.05, 95 % CI 40, 44) for anti-TNFs and 32 per 1,000 patient-years for nonbiologic treatments (p<0.05, 95 % CI 28, 36); they were 38 per 1,000 patient-years for etanercept (p<0.05, 95 % CI 35, 42), 46 per 1,000 patient-years for infliximab (p<0.05, 95 % CI 42, 50), and 43 per 1,000 patient-years for adalimumab (p< 0.05, 95 % CI 39, 47). Assessment of TB from this registry indicated 40 cases, all in patients receiving TNF inhibitors. The rate of TB was higher for the monoclonal antibodies

adalimumab (144 events per 100,000 patient-years) and infliximab (136 per 100,000 patient-years) than for etanercept (39 per 100,000 patient-years). After modification, the incidence rate ratio (IRR) compared with etanercept-treated patients was 3.1 (95 % CI 1.0, 9.5) for infliximab and 4.2 (95 % CI 1.4, 12.4) for adalimumab [42].

Results from the Consortium of Rheumatology Researchers of North America registry in the USA also indicated increased risk for infection in patients receiving TNF inhibitors [43]. Analysis of 7,971 patients with RA indicated that the adjusted rate of infections per 100 patient-years was increased among those who received methotrexate (30.9), TNF inhibitors (40.1), the combination of methotrexate plus a TNF inhibitor (37.1) versus patients who received nonbiologic agents other than methotrexate (24.5). Treatment with a TNF inhibitor was also associated with an increased risk for OI (IRR=1.67) [43].

The *Registro Español de Acontecimientos Adversos de Terapias Biológicas en Enfermedades Reumáticas* registry in Spain was used to assess infection rates in 4,006 RA and 1,524 AS patients taking infliximab, etanercept, or adalimumab. The risks of infections for patients with RA taking infliximab, adalimumab, or etanercept were 5.87, 18.9, and 1.01 times those for controls, respectively. The risks of infections for patients with AS taking infliximab, adalimumab, or etanercept were 7.07, 12.71, and 1.74 times those for controls, respectively [44].

Discussion and conclusions

RA is a worldwide inflammatory joint disease with variable degrees of joint damage and extra-articular manifestations (EAMs) in different regions. Generally, RA is less severe and has fewer EAMs in Eastern Mediterranean countries in comparison with Northern Europe [45]. Several radiological studies of RA patients in Saudi Arabia showed the proportion with erosions is lower than data reported from Western European and North American populations [46]. In contrast, an evaluation of EAMs of Saudi Arabian RA patients showed that the frequency of EAMs was similar to the British population but higher than in North American populations [45]. These differences in disease progression and outcome are influenced by a multitude of factors including different expression of combinations of genes. The higher expression of HLA-DRB1 gene (DRB1*0401) in French RA patients was associated with high RA severity compared to Syrian patients who had lower expression DRB1 and less severe RA [47]. An exhaustive discussion of the genetics and other factors contributing to the different regional severity of RA is beyond the scope of this review.

While there are regional differences in RA disease severity, results from safety studies carried out in Asia, Africa, and the Middle East are generally similar to those from large-scale analyses carried out in Europe and the USA. Prescribing information for all TNF inhibitors contains the same boxed warning with respect to infections. It is noted that there is increased risk of serious infections leading to hospitalization or death, including TB, bacterial sepsis, invasive fungal infections (such as histoplasmosis), and infections due to other opportunistic pathogens and that the TNF inhibitor should be discontinued if a patient develops a serious infection or sepsis during treatment. It is also recommended that a test for latent TB be performed, and if positive, treatment for TB should be started prior to initiation of TNF inhibitor treatment. The TST is most frequently used to detect LTBI. However, due to known limitations of the TST, interferon-γ release assays (IGRAs), including QFT-G and T-SPOT.TB, have been developed. Unlike IGRAs, the TST may result in non-specific reactivity in patients exposed to non-tubercular mycobacteria (NTM) or in patients vaccinated with Bacille Calmette–Guérin (BCG). Thus, the use of IGRAs is particularly important in areas with a high-risk of TB, where BCG vaccination or NTM exposure is prevalent. Although there are no guidelines regarding how often TB screening should be repeated, periodic testing is recommended in areas with a high prevalence of TB, particularly prior to TNF inhibitor treatment. Additionally, repeated testing is especially important in immunosuppressed patients who may have been exposed to TB, but have had prior negative screening tests [48]. All patients should also be monitored for active TB during treatment [17]. Chest radiography is the method most often utilized to evaluate the possibility of active TB [48].

Results from the present review (summarized in Table 1) underscore the need of patient registries for assessment of the safety of medications used for the treatment of RA and AS. Evaluation of the results of such registries and clinical trials in Asia, Africa, the Middle East, as well as in North America and Europe indicates that RA and AS patients taking TNF inhibitors have an increased risk for serious infections versus similar patients not receiving these agents and that there are no substantial differences in risk for patients from different regions. These studies have also indicated that patients taking etanercept have lower risk for infections versus those receiving adalimumab or infliximab [17]. Several explanations have been put forward to explain this difference [48, 49]. It has been proposed that the monoclonal antibodies infliximab and adalimumab bind to membrane TNF with greater affinity and, more importantly, greater stability compared to TNF soluble receptors [49, 50]. More stable binding to membrane TNF induces a number of biological events in cells that express membrane TNF, such as apoptosis and loss of function via reverse signaling [49]. Membrane TNF expression plays a crucial role in granuloma development [49], and this difference in the

mechanism of action explains the higher risk of TB and other OI with monoclonal antibodies. Regardless of the underlying mechanism, registries worldwide have suggested a difference in the risk for infection with etanercept versus anti-TNF monoclonal antibodies [17]. While there are limitations regarding safety information from patient registries, the consistency of results from around the world support this conclusion [17].

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