Tuberculosis Risk in Patients Treated with Non-Anti-Tumor Necrosis Factor-α (TNF-α) Targeted Biologics and Recently Licensed TNF-α Inhibitors: Data from Clinical Trials and National Registries

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ABSTRACT. This review aimed to evaluate the risk of active tuberculosis (TB) occurrence in patients with rheumatic disorders receiving non-anti-tumor necrosis factor (TNF) targeted biologics anakinra (ANK), tocilizumab (TCZ), rituximab (RTX), abatacept (ABA), and recently approved anti-TNF golimumab (GOL), and certolizumab pegol (CTP). In recent findings, no cases of active TB were recorded in patients with rheumatoid arthritis (RA) and other rheumatic conditions treated with anti-CD20+ RTX and anti-CD28 ABA. No patient receiving anti-interleukin 1 (IL-1) ANK developed active TB, and an increased risk was excluded in a Canadian database. In contrast, 8 active TB cases were observed in 21 trials of patients with RA receiving anti-IL-6 TCZ, while no increased TB risk resulted from Japanese postmarketing surveillance. Among GOL-treated and CTP-treated patients, 8 and 10 active TB cases occurred, respectively, while no data are available from registries. However, all but 1 TB case recorded in patients treated with TCZ, GOL, and CTP occurred in TB-endemic countries. No TB risk resulted for ANK, RTX, and ABA, suggesting pretreatment screening procedures for latent TB infection detection are unnecessary. Because all TB cases occurred in countries at high risk for TB, where TB exposure could have occurred during treatment, no definitive conclusions can be drawn for TCZ, GOL, and CTP. (J Rheumatol Suppl. 2014 May; 91:56–64; doi:10.3899/jrheum.140103)

Key Indexing Terms:
GOLIMUMAB CERTOLIZUMAB PEGOL ANTI-TUMOR NECROSIS FACTOR
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Anti-tumor necrosis factor-α (TNF-α) agents have ensured important efficacy advantages in the treatment of inflammatory rheumatic diseases such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), and juvenile idiopathic arthritis (JIA). Moreover, wide off-label use of these drugs is made in other rheumatic disorders such as vasculitis, Behçet disease, and adult-onset Still disease. However, it has long been recognized that currently used TNF-α infliximab, etanercept, and adalimumab increase the risk of tuberculosis (TB) reactivation, and latent TB infection (LTBI) detection and TB prevention represent a current worldwide challenge for rheumatologists[1]. Indeed, anti-TNF-α agents facilitate the progression from LTBI to active TB by interfering with different steps of immune response against *Mycobacterium tuberculosis* such as chemokine secretion, downregulation of adhesion molecules, interferon-γ (IFN-γ) production and its effects on macrophage activation, and CD4+ and CD8+ T cell function[2]. Multiple biologics targeted to cytokines other than TNF-α, or to T and B cells of immune response, have been licensed over time, including anti-interleukin 1 (IL-1) anakinra (ANK), IL-6 inhibitor tocilizumab (TCZ), anti-CD20 rituximab (RTX), and anti-CD28 abatacept (ABA). Moreover, 2 new anti-TNF-α agents, golimumab (GOL) and certolizumab pegol (CTP), have recently been approved, the former for the treatment of RA, AS, and PsA, and the latter for RA only.

The aim of the present report was to assess TB risk in patients with rheumatic diseases exposed to currently available non-anti-TNF biologics and to the new anti-TNF drugs, through a review of safety results in clinical trials and, when available, data from national biologic registries. The literature search was extended to May 31, 2013.

Anakinra

ANK is a recombinant non-glycosylated homolog of the human IL-1 receptor antagonist (IL-1Ra) that competitively inhibits binding of IL-1 with its receptor[3]. The drug has

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been licensed for the treatment of RA at the dose of 100 mg/day by subcutaneous injection. In recent years ANK has also been used in the treatment of JIA, autoinflammatory diseases[4], and gout[5]. IL-1 does not seem to be implicated in the control of TB infection[6]; this may explain the low or absent risk of TB in patients treated with ANK observed in clinical trials and real-life practice: Indeed, only 1 case of TB reactivation in a Greek female after 23 months of ANK therapy has been reported[7]. Of note, this patient was treated for active pulmonary TB 6 years before, and there is no information regarding correct adherence to TB therapy, and of TB recovery evaluation. Otherwise, no cases of TB were observed in 7964 patients with RA[8,9,10,11,12,13,14,15,16,17,18,19], 35 patients with adult-onset Still disease[20,21,22], and 216 with JIA[23,24,25,26,27,28]. In addition, data from a Canadian registry confirm no increased risk of TB in ANK-treated patients[29]. According to these data, ANK does not increase the risk of TB reactivation or new active TB cases.

Rituximab

RTX is a genetically engineered chimeric mouse-human monoclonal antibody that selectively depletes the CD20+ peripheral B cell subpopulation. CD20+ B cell depletion occurs through multiple mechanisms, including antibody-dependent cellular toxicity, complement-mediated lysis, and induction of apoptosis[30]. Because the immune response toward TB infection and reactivation is under the control of T lymphocytes[31], as expected, no cases of active TB were recorded in 9 randomized controlled trials of RTX recruiting 3623 patients with RA[32,33,34,35,36,37,38,39,40]. In addition, no TB cases were observed in patients receiving RTX for the treatment of Sjögren syndrome[41,42], mixed cryoglobulinemia[43,44], antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis[45,46], and systemic lupus erythematosus (SLE)[47,48]. Confirming the data from clinical trials, no cases of TB reactivation or new active TB were recorded in the French AutoImmunity and Rituximab registry, including 1681 patients with RA and SLE treated with RTX[49,50]. In keeping with these findings, none of 370 patients receiving RTX for the treatment of different autoimmune disorders included in the GRAID registry from Germany developed active TB over a longterm followup period[51]. Similar results were observed in 58 patients with ANCA-associated vasculitis in a recent report from the same registry[52].

Hence, according to the Rituximab Consensus Expert Committee[53], data from the literature indicate a negligible TB risk in patients with rheumatic diseases receiving RTX, and suggest that screening procedures for LTBI detection before starting therapy are unnecessary.

Tocilizumab

TCZ is a recombinant, humanized, monoclonal, anti-IL-6 receptor antibody competing for both the membrane-bound and soluble forms of human IL-6 receptor with inhibition of the binding of IL-6 to its receptors and its proinflammatory activity[54]. The drug is currently approved, combined or in monotherapy, for the treatment of RA. Our literature search disclosed 21 clinical trials of 10,281 patients with RA[55–59,60-69,70-75], with clinical observation over 24 weeks in 8384 patients (81.5%) in 14 trials, during 1 year in 1754 patients (17%) in 3 trials, and during 5 years in 143 patients (1.5%) in 1 study. Of note, LTBI screening procedures and TB reactivation prophylaxis were included in the protocol as an inclusion criterion in only 2 studies[59,63]. Moreover, 4 clinical trials of TCZ in 205 patients with JIA[76,77,78,79], 2 open clinical series of 31 patients with SLE[80,81], 1 of 21 patients with spondyloarthritis[82], and 3 open-label studies of 13 patients with large-vessel vasculitis and 3 patients with polymyalgia rheumatica[83,84,85] were found.

Overall, no TB cases were recorded in any reported series, even if the short-term duration of clinical observation in most trials may have not exactly highlighted the topic, especially for worldwide multicenter studies involving countries at higher risk of TB infection. Confirming this issue, 8 patients with active TB were reported over time[86], respectively, from Thailand, Spain, South Africa, Peru, Singapore, Brazil, and Mexico (Table 1).

Owing to its recent use in clinical practice, there are no data on TCZ and TB risk from national registries. In published postmarketing surveillance from Japan[87], 4 out of 3881 patients developed active TB at intervals ranging from 24 days to 4 months after starting TCZ therapy, with an incidence of 22/100,000/year, which was not higher than that reported by the World Health Organization in Japan, where TB incidence in the general population ranges from 15 to more than 30/100,000/year[88].

Data from clinical trials suggest a very low risk of TB reactivation in patients receiving TCZ. However, although the reported frequency of active TB is low, LTBI screening procedures are suggested before starting TCZ.

Abatacept

ABA is a soluble fully human fusion protein consisting of the extracellular domain of human cytotoxic T lymphocyte-associated antigen 4-IgG1 fusion linked to the modified Fc (hinge CH2 and CH3 domains) portion of human immunoglobulin G1 (IgG1). ABA blocks activation of T cells by binding to costimulatory proteins present on antigen-presenting cells (APC; CD80/86 on APC and CD28 on T cells)[89]. The drug has been approved for the treatment of RA, and it is administered intravenously every 4 weeks at a dose of 10 mg/kg. Although CD8/CD28 T cell-reduced expression may interfere with the immune response against TB infection[90], no cases of active TB were registered in 16 trials of ABA administered either intravenously or subcutaneously in 7530 patients with RA[89,91–99,100,101,102,103,104,105], with a followup extended up to 5 years[106].

Table 1. Reported cases of tuberculosis (TB) in patients receiving other than anti-tumor necrosis factor (TNF) biologics and recently licensed TNF inhibitors.

Biologic (Target)	Clinical Trials, Disease/Patient, No.	No. Cases	Cases from TB Endemic Countries, No.	National Registries and PM Surveillance, No. Cases/Patients	Incidence Rate Case/100,000/yr
ANK (IL-1)	RA/7964	0	0	Pharmetrics (Canada) 19/NA	NA*
	AOSD/35	0	0		
	JIA/216	0	0		
RTX (CD20+)	RA/3623	0	0	AIR (France) 0/1681	0
	ANCA+VASC/422	0	0		
	SS/107	0	0		
	SLE/700	0	0		
	MC/381	0	0		
TCZ (IL-6)	RA/10281	8	8[#]	Japan 4/3881	22[§]
	JIA/205	0	0		
	SLE/35	0	0		
	SpA/21	0	0		
	GCA/16	0	0		
ABA (CD28)	RA/7530	0	0	ORA (France) 0/682	0
	JIA/190	0	0		
	SLE/175	0	0		
	PsA/170	0	0		
GOL (TNF-α)	RA/2626	7	6**	NA	NA
	AS/356	1	1		
	PsA/405	0	0**		
CTP (TNF-α)	RA/3167	10	10[§§]	NA	NA

*Incidence rate available; relative risk 1.2 (95% CI 0.9–1.6) reported, with no increased risk compared to controls; [§]World Health Organization estimated TB incidence rate in Japan is 15–30/100,000/yr; [#]TB cases: Thailand 2 cases, vs Spain, South Africa, Peru, Singapore, Brazil, Mexico, with 1 case per country; [**]TB cases: Philippines 2 cases, vs Ukraine, Taiwan, Argentina, Mexico, South Korea, with 1 case for each country; [§§]TB cases: Russia 5 cases, vs Poland, Latvia, Estonia, Bulgaria, Ukraine, with 1 case for each country. RA: rheumatoid arthritis; AOSD: adult-onset Still disease; JIA: juvenile idiopathic arthritis; ANCA+VASC: antineutrophil cytoplasmic antibody+Vasc/422; IL: interleukin; SS: Sjögren syndrome; SLE: systemic lupus erythematosus; GCA: giant cell arteritis; PsA: psoriatic arthritis; MC: mixed cryoglobulinemia; AS: ankylosing spondylitis; SpA: spondyloarthritis; ANK: anakinra; RTX: rituximab; TCZ: tocilizumab; ABA: abatacept; GOL: golimumab; CTP: certolizumab pegol; NA: not available; PM: postmarketing.

Similarly, no TB cases were recorded in 1 trial of 175 patients with SLE[107], 190 with JIA[108], and 170 with PsA[109]. Data from real-life practice confirm the absence of ABA-related TB reactivation risk. Indeed, no TB cases were recorded in 682 patients included in the ORA French registry[110], and to the best of our knowledge no single case description of TB occurrence in patients treated with ABA is reported.

This large body of evidence suggests that ABA does not increase the risk of TB reactivation, and although required by regulatory authorities, the screening procedures for LTBI detection seem unnecessary.

Golimumab

GOL is a human anti-TNF-α IgG1κ monoclonal antibody approved in 2009 for the treatment of RA, PsA, and AS at the dose of 50 mg, subcutaneously, monthly[111]. GOL safety data are available from 6 trials of 2626 patients with RA[112,113,114,115,116,117], with a clinical observation extended up to 3 years[118,119], 356 patients with AS followed for 2 years[120,121], and 405 patients with PsA observed for 2 years[122,123]. Seven cases of TB were recorded in the trials of RA[115,116,118,119], and 1 case in AS[121]. It should be noted that 7 out 8 TB cases occurred in TB-endemic countries, 1 case in Ukraine, 2 in Philippines[115], 1 in Taiwan[118], 1 each in Argentina, Mexico, and South Korea[116,121], and 1 case in an unspecified country[119]. The estimated TB incidence in 2011 in these countries ranges between 50 and 299 cases per 100,000 inhabitants[88], and at least in some of the previously mentioned cases, the possibility of primary TB infection cannot be ruled out. Moreover, some defective screening procedures were probably carried out in the cases recorded in Ukraine and in Philippines[115]. Indeed, a 64-year-old woman from Ukraine had back pain and radiologic abnormalities of the thoracic spine attributed to vertebral compression fracture before enrollment. She developed spinal TB 33 days after starting GOL, indicating a potentially unrecognized spinal TB at study entry. Similarly, the other 67-year-old woman from Philippines was enrolled despite interstitial lung disease demonstrated by chest radiography (attributed to RA). She developed pulmonary TB 1 month after receiving GOL.

No data are currently available from national registries and postmarketing surveillance, and there are no case reports of TB in patients treated with GOL in the literature.

A low number of TB cases have been recorded in patients

treated with GOL, mostly in TB-endemic areas, and as underlined in a recent analysis[124], 3 of these cases were presumed to be primary infections and 2 consistent with LTBI reactivation associated with unreliable screening procedures.

However, although the recorded active TB cases occurred in countries at high TB risk, similarly to the other anti-TNF-α agents, an accurate screening procedure for LTBI is recommended in candidates for GOL therapy.

Certolizumab pegol

CTP is an anti-TNF inhibitor composed by an engineered human anti-TNF-α antibody Fab9 fragment that is linked chemically to polyethylene glycol (PEG). The Fab9 fragment is made by microbial fermentation rather than in mammalian cell culture. The attachment of PEG increases the circulating half-life of Fab to about 14 days. The lack of an Fc portion may avoid potential Fc-mediated effects such as complement-dependent or antibody-dependent cell-mediated cytotoxicity[125]. CTP was approved by the US Food and Drug Administration in 2009 for adult patients with moderately to severely active RA. Six trials of CTP in 3167 patients with RA were published between 2002 and 2012[126,127,128,129,130,131]. As reported in Table 1, 10 patients developing active TB were observed in 2 trials[127,129], all occurring in countries at high risk of TB, with 5 cases observed in Russia, and 1 each in Poland, Latvia, Estonia, Bulgaria, and Ukraine. As underlined for GOL-associated TB cases, also in these patients the possibility of some cases of primary TB infection cannot be excluded. Moreover, in both studies, defective LTBI screening procedures were reported in 6 patients developing active TB[127,129], and 1 TB case occurred in a tuberculin skin test-negative worker in a TB clinic[127]. Notably, no active TB cases have been reported in CTP-exposed patients living in North America.

Because CTP was approved for the treatment of RA only recently, no data on TB cases in CTP-treated patients are available from national registries and postmarketing surveillance; and to the best of our knowledge, no case reports of CTP-associated TB have been published.

However, the consistent number of TB cases recorded in clinical trials, although occurring in high-risk countries, strongly suggest accurate screening for LTBI before starting CTP therapy.

Conclusion

Data from clinical trials seem to indicate increased risk of TB reactivation in patients treated with anti-TNF-α agents GOL and CTP with respect to non-anti-TNF targeted biologics (Table 1). This seems to confirm the class effect resulting from TNF inhibition, which leads to impaired TB granuloma formation[2]. However, the limited number of active TB cases, mostly occurring in countries at high risk of TB, and the lack of data from real-life practice do not allow definitive conclusions about TB risk associated with the recently licensed anti-TNF biologics GOL and CTP.

Regarding the non-anti-TNF-α targeted biologics, risk of TB associated with ANK and TCZ is negligible, whereas data from clinical trials and registries indicate the absence of TB risk in patients treated with RTX and ABA, thus suggesting LTBI detection procedures may be unnecessary.

Based on these findings, we suggest carefully taking into account host-related TB risks in patients with rheumatic disorders requiring biologic therapy, and to individualize the choice of therapy in view of the respective drug-related risk.

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