

# Biologics and Tuberculosis Risk: The Rise and Fall of an Old Disease and Its New Resurgence

Tuberculosis (TB) is an ancient disease, recognized in Egyptian mummies and defined by Hippocrates as “phthisis” (*φθισις*, Greek for “consumption”)<sup>1</sup>. Over the centuries, the epidemiology of TB was characterized by a long period of a relatively stable incidence rate of infection, but the crowding of European cities and the Industrial Revolution favored the spread of *Mycobacterium tuberculosis*, and TB became an epidemic, a devastating disease with a high mortality rate<sup>2</sup>. The frequency of TB probably reached its peak in the 18th and 19th centuries with an estimated prevalence in Europe of 900 deaths per 100,000 persons<sup>3</sup>. This impressive *flagellum* had a strong influence on social life, and famous artists such as poets John Keats, Percy Bysshe Shelley, and Giacomo Leopardi, authors Robert Louis Stevenson, Emily Brontë, Katherine Mansfield, and Edgar Allan Poe, musicians Niccolò Paganini and Frederic Chopin, and sculptor and painter Amedeo Modigliani were all affected. Contemporaneously, TB became a preferred subject in the arts, as witnessed by Edvard Munch’s portrait of his sister Sophie dying of TB and the touching histories of protagonists of lyric opera such as Mimì in Puccini’s *La Bohème* and Violetta in Verdi’s *La Traviata*.

Over the following decades, public health measures, improvements in microbiology procedures with the isolation of *M. tuberculosis* by Robert Koch, and the availability of effective therapies led to a reduction in the incidence of this disease. In the United States, there was a 6% yearly progressive decline in the incidence of TB until 1980, followed by a recrudescence of recorded TB cases, with an increase of 20% between 1985 and 1992 owing to the spread of human immunodeficiency virus (HIV)<sup>4</sup>. Once again, public health measures and effective anti-HIV therapies achieved a progressive reduction of the incidence of TB. The incidence of active TB in developed countries is now estimated to be 4–6 cases/100,000/year<sup>5</sup>. The fluctuating epidemiology of TB observed over the past 3 centuries has been attributable to external environmental or host risk factors rather than to an increased virulence of *M. tuberculosis* itself.

Among subjects infected by *M. tuberculosis*, only 5–10% develop active disease during their lifetime. Because the host immune response is able to inhibit replication of *M. tuberculosis* and the spread of infection, most patients carry a latent TB infection (LTBI), remaining asymptomatic and noninfectious<sup>6</sup>. However, if the immune system is impaired,

patients with LTBI are at increased risk of developing active TB<sup>6</sup>.

Over time, drugs commonly employed in clinical practice, such as corticosteroids and other traditional immunosuppressive therapies, have been recognized as increasing the risk of TB reactivation in LTBI<sup>7</sup>. At the end of the 20th century, the newly available targeted biologic agents counteracting the effects of tumor necrosis factor- $\alpha$  (anti-TNF- $\alpha$ ) raised a new threat for a further peak in the incidence of cases of active TB. Infliximab (IFX), a chimeric monoclonal antibody anti-TNF- $\alpha$ , was licensed for the treatment of fistulizing Crohn disease in 1998 and in 1999 for use in rheumatoid arthritis (RA), while etanercept, a soluble receptor for TNF- $\alpha$ , was approved for RA in 1998. A few years later, a review of the US Food and Drug Administration (FDA) Adverse Event Reporting System data revealed 70 cases of active TB in 147,000 patients receiving IFX worldwide<sup>8</sup>. Of these, 47 occurred in patients with RA, 18 in those with Crohn disease, and 5 in people with other types of arthritis, with a median interval of 12 weeks from starting the biologic therapy. The incidence rate of TB was 4 times higher in IFX-treated patients with RA than the estimated incidence in people with RA not receiving biologic therapy (24.2 cases/100,000/yr vs 6.2 cases/100,000/yr, respectively). Nine cases of active TB in 102,000 etanercept-exposed patients were also recorded<sup>8</sup>. Consequently, in October 2001, Centocor Inc. revised the IFX labeling, adding a boxed warning containing the recommendation to evaluate patients for LTBI before starting the drug. In the same FDA database, 25 cases of reactivated TB were subsequently observed in 113,238 etanercept-exposed patients with RA, with a median interval from the beginning of therapy of 11.5 months. According to these data, there was also a slight increased risk of 10 cases/100,000/year for etanercept<sup>9</sup>. Soon afterward, in early 2002, another monoclonal antibody anti-TNF, adalimumab, obtained approval for the treatment of RA, and this compound, too, was labeled with the recommendation for LTBI screening. Over the following years IFX, adalimumab, and etanercept have been approved for the treatment of autoimmune diseases covered by different medical specialties, including ankylosing spondylitis, psoriatic arthritis, psoriasis, and inflammatory bowel diseases (IFX and adalimumab only). Because TNF plays a pivotal role in controlling TB-granuloma formation and the growth of *M. tuberculosis*, the increased risk of TB reactivation associated with

anti-TNF- $\alpha$  agents is directly related to their action on TNF blocking<sup>10</sup>. However, the different mechanisms of TNF inhibition exerted by IFX and adalimumab compared to etanercept may explain the higher risk of TB reactivation associated with the 2 monoclonal anti-TNF agents, and the shorter interval between starting monoclonal anti-TNF- $\alpha$  treatment and TB reactivation<sup>10</sup>.

To reduce the risk of TB reactivation, several sets of recommendations/guidelines have been formulated by different countries, describing what should be done before starting therapy with adalimumab, IFX, and etanercept<sup>11,12,13,14,15,16,17,18,19,20,21,22,23,24</sup>, with an evident reduction of cases of TB reactivation when correctly applied<sup>14</sup>. Apart from some differences dictated by the specific TB risk in different countries, all recommendations state that LTBI screening procedures, based on the performance of the tuberculin skin test (TST) or an interferon- $\gamma$  release assay (IGRA) together with chest radiography, are mandatory. In the case of a diagnosis of LTBI [positive score to an immune diagnostic test (TST or IGRA) and a chest radiograph negative for active TB lesions], active TB prevention with a 9-month course of isoniazid is recommended, while biologic therapy is suggested to be postponed for at least 1 month thereafter.

Nevertheless, reports from national clinical registries and postmarketing surveillance show that a 2 to 6-fold increased risk of TB reactivation still persists in patients treated with an anti-TNF- $\alpha$  biologic, often because of low adherence to recommended screening procedures<sup>25,26,27,28</sup>.

Several biologics, with a mechanism of action targeting cytokines rather than TNF- $\alpha$ , or T and B cells of the immune response system, have been licensed for the treatment of autoimmune disorders in rheumatology and dermatology specialties, including an anti-interleukin 1 (IL-1, anakinra), an IL-6 inhibitor (tocilizumab), an anti-CD20 (rituximab), an anti-CD28 (abatacept), and an anti-IL-12/23 (ustekinumab). Moreover, a new anti-TNF- $\alpha$  agent, golimumab, has recently been approved for the treatment of RA, ankylosing spondylitis, and psoriatic arthritis; and certolizumab pegol for RA. A low or absent risk of TB reactivation has been recorded for anakinra, tocilizumab, rituximab, abatacept, and ustekinumab<sup>29,30,31,32,33</sup>, while no definitive conclusion on TB reactivation risk associated with golimumab and certolizumab pegol can be drawn because of their recent approval.

However, although clinicians have achieved a consolidated awareness of the risk of TB, and on the mandatory performance of LTBI screening procedures when prescribing biologic agents, several questions remain. These include the less-than-unanimously recommended performance of TST or IGRA, or both, and of chest radiography for the detection of LTBI; the type of drugs and duration of treatment suggested for active TB prophylaxis, and finally the interval between starting TB prophylaxis and biologic

agent initiation. Further, it is unclear when to restart biologic therapy in patients treated for active TB, and no indications are available concerning the treatment of patients under TB therapy who have flares of RA, psoriatic arthritis, ankylosing spondylitis, or psoriasis.

In addition, data from national registries indicate remarkable discrepancies between the TB risk associated with different anti-TNF- $\alpha$  agents, thus raising important criticisms about data collection and relative risk adjustment. Indeed, incomplete or missing data regarding host-related risk factors, including country of birth and/or residence, ethnicity, comorbidities, drug abuse, concomitant treatments, defective LTBI screening procedures, and TB prophylaxis may lead to important biases. Finally, concerns such as legal and pharmacoeconomic aspects related to prescribing biologics and risk of TB have not been sufficiently considered in all reports.

The articles included in this supplement to *The Journal of Rheumatology* discuss these highlighted topics with special attention to unresolved issues, in the hopes of clarifying at least some of them.

**FABRIZIO CANTINI**, MD, PhD,

Consultant in Rheumatology,  
Director, Rheumatology Division,  
Hospital of Prato, Prato, Italy;

**DELIA GOLETTI**, MD, PhD,

Translational Research Unit,  
Department of Epidemiology and Preclinical Research,  
L. Spallanzani National Institute for Infectious Diseases  
(INMI), IRCCS, Rome, Italy.

Address correspondence to Prof. Cantini, Rheumatology Division,  
Hospital of Prato, Piazza Ospedale, 1 59100 Prato, Italy.  
E-mail: fbrzcantini@gmail.com

## REFERENCES

1. Herzog H. History of tuberculosis. *Respiration* 1998;65:5-15.
2. Bates JH, Stead WW. The history of tuberculosis as a global epidemic. *Med Clin North Am* 1993;77:1205-17.
3. Daniel TM. The history of tuberculosis. *Respir Med* 2006;100:1862-70.
4. Centers for Disease Control and Prevention (CDC). Tuberculosis morbidity — United States, 1992. *MMWR Morb Mortal Wkly Rep* 1993;42:696-7;703-4.
5. World Health Organization Global Tuberculosis Report WHO Library Cataloguing-in-Publication Data. ISBN 9789241564502. Geneva: Information Resource Centre HTM/STB World Health Organization; 2012.
6. Zúñiga J, Torres-García D, Santos-Mendoza T, Rodríguez-Reyna TS, Granados J, Yunis EJ. Cellular and humoral mechanisms involved in the control of tuberculosis. *Clin Dev Immunol* 2012;2012:193923.
7. Brassard P, Lowe AM, Bernatsky S, Kezouh A, Suissa S. Rheumatoid arthritis, its treatments, and the risk of tuberculosis in Quebec, Canada. *Arthritis Rheum* 2009;61:300-4.
8. Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwiertman WD, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med* 2001;345:1098-104.

9. Mohan AK, Coté TR, Block JA, Manadan AM, Siegel JN, Braun MM. Tuberculosis following the use of etanercept, a tumor necrosis factor inhibitor. *Clin Infect Dis* 2004;39:295-9.
10. Harris J, Keane J. How tumour necrosis factor blockers interfere with tuberculosis immunity. *Clin Exp Immunol* 2010;161:1-9.
11. Centers for Disease Control and Prevention (CDC). Tuberculosis associated with blocking agents against tumor necrosis factor-alpha — California, 2002-2003. *MMWR Morb Mortal Wkly Rep* 2004;53:683-6.
12. Mariette X, Salmon D. French guidelines for diagnosis and treating latent and active tuberculosis in patients with RA treated with TNF blockers. *Ann Rheum Dis* 2003;62:791.
13. British Thoracic Society Standards of Care Committee. BTS recommendations for assessing risk and for managing Mycobacterium tuberculosis infection and disease in patients due to start anti-TNF-alpha treatment. *Thorax* 2005;60:800-5.
14. Carmona L, Gómez-Reino JJ, Rodríguez-Valverde V, Montero D, Pascual-Gómez E, Mola EM, et al. Effectiveness of recommendations to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists. *Arthritis Rheum* 2005;52:1766-72.
15. Fonseca JE, Lucas H, Canhão H, Duarte R, Santos MJ, Villar M, et al. Recommendations for the diagnosis and treatment of latent and active tuberculosis in patients with inflammatory joint diseases treated with tumour necrosis factor alpha inhibitors. *Acta Reumatol Port* 2006;31:237-45.
16. Valesini G, Montecucco C, Cutolo M. Recommendations for the use of biologic (TNF-alpha blocking) agents in the treatment of rheumatoid arthritis in Italy. *Clin Exp Rheumatol* 2006;24:413-23.
17. Salvarani C, Pipitone N, Marchesoni A, Cantini F, Cauli A, Lubrano E, et al. Recommendations for the use of biologic therapy in the treatment of psoriatic arthritis: update from the Italian Society for Rheumatology. *Clin Exp Rheumatol* 2011;29 Suppl 66:S28-41.
18. Beglinger C, Dudler J, Mottet C, Nicod L, Seibold F, Villiger PM, et al. Screening for tuberculosis infection before the initiation of an anti-TNF-alpha therapy. *Swiss Med Wkly* 2007;137:620-2.
19. Kavanagh PM, Gilmartin JJ, O'Donnell J, O'Flanagan D. Tumour necrosis factor-alpha and tuberculosis: guidance from the National TB Advisory Committee. *Ir Med J* 2008;101:6-7.
20. Diel R, Hauer B, Loddenkemper R, Manger B, Krüger K. Recommendations for tuberculosis screening before initiation of TNF-alpha-inhibitor treatment in rheumatic diseases. *Pneumologie* 2009;63:329-34.
21. Solovic I, Sester M, Gomez-Reino JJ, Rieder HL, Ehlers S, Milburn HJ, et al. The risk of tuberculosis related to tumour necrosis factor antagonist therapies: a TBNET consensus statement. *Eur Respir J* 2010;36:1185-206.
22. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res* 2012;64:625-39.
23. Nordgaard-Lassen I, Dahlerup JF, Belard E, Gerstoft J, Kjeldsen J, Kragballe K, et al. Guidelines for screening, prophylaxis and critical information prior to initiating anti-TNF-alpha treatment. *Dan Med J* 2012;59:C4480.
24. Bombardier C, Hazlewood GS, Akhavan P, Schieir O, Dooley A, Haraoui B, et al. Canadian Rheumatology Association recommendations for the pharmacological management of rheumatoid arthritis with traditional and biologic disease-modifying antirheumatic drugs: part II safety. *J Rheumatol* 2012;39:1583-602.
25. Gómez-Reino JJ, Carmona L, Angel Descalzo M. Risk of tuberculosis in patients treated with tumor necrosis factor antagonists due to incomplete prevention of reactivation of latent infection. *Arthritis Rheum* 2007;57:756-61.
26. Tubach F, Salmon D, Ravaud P, Allanore Y, Goupille P, Bréban M, et al. Risk of tuberculosis is higher with anti-tumor necrosis factor monoclonal antibody therapy than with soluble tumor necrosis factor receptor therapy: The three-year prospective French Research Axed on Tolerance of Biotherapies registry. *Arthritis Rheum* 2009;60:1884-94.
27. Dixon WG, Hyrich KL, Watson KD, Lunt M, Galloway J, Ustianowski A, et al. Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). *Ann Rheum Dis* 2010;69:522-8.
28. Koike T, Harigai M, Ishiguro N, Inokuma S, Takei S, Takeuchi T, et al. Safety and effectiveness of adalimumab in Japanese rheumatoid arthritis patients: postmarketing surveillance report of the first 3,000 patients. *Mod Rheumatol* 2012;22:498-508.
29. Brassard P, Kezouh A, Suissa S. Antirheumatic drugs and the risk of tuberculosis. *Clin Infect Dis* 2006;43:717-22.
30. Koike T, Harigai M, Inokuma S, Ishiguro N, Ryu J, Takeuchi T, et al. Postmarketing surveillance of tocilizumab for rheumatoid arthritis in Japan: interim analysis of 3881 patients. *Ann Rheum Dis* 2011;70:2148-51.
31. Gottenberg JE, Ravaud P, Bardin T, Cacoub P, Cantagrel A, Combe B, et al. AutoImmunity and Rituximab registry and French Society of Rheumatology. Risk factors for severe infections in patients with rheumatoid arthritis treated with rituximab in the autoimmunity and rituximab registry. *Arthritis Rheum* 2010;62:2625-32.
32. Mariette X, Gottenberg JE, Ravaud P, Combe B. Registries in rheumatoid arthritis and autoimmune diseases: data from the French registries. *Rheumatology* 2011;50:222-9.
33. Papp KA, Griffiths CE, Gordon K, Lebwohl M, Szapary PO, Wasfi Y, et al. Long-term safety of ustekinumab in patients with moderate-to-severe psoriasis: final results from 5 years of follow-up. *Br J Dermatol* 2013;168:844-54.

*J Rheumatol Suppl.* 2014 May; 91:1-3; doi:10.3899/jrheum.140095