The introduction of TNF inhibitors more than a decade ago marked the beginning of an exciting era in the management of RA. Despite the development of biologics with alternative modes of action, TNF inhibitors remain today the most widely prescribed class of biologics for RA. However, tuberculosis (TB) is a major safety concern with TNF inhibitors. The risk of active TB is increased up to 56-fold compared with the general population, more so with the monoclonal antibody agents, and greatest in the first year of TNF inhibitor therapy, with a relative excess of extra-pulmonary TB [1, 2]. The background prevalence of latent TB infection (LTBI), previous TB infection, oral corticosteroid use, older age, high-risk occupation (e.g., health workers, prison staff) and low socio-economic status, all contribute to the ongoing TB risk.

Mandatory screening for LTBI before commencing TNF inhibitor therapy has resulted in a marked reduction but not complete eradication of the TB risk. One important reason for the ongoing TB risk is the uncertainty surrounding the sensitivity and specificity of the tuberculin skin test (TST) and newer IFN-γ release assays (IGRA) as screening tests for LTBI, particularly in high TB-burden settings [3]. In part this is because the pathobiology and nature of LTBI is poorly understood. At the pathological level, the concept of presumed LTBI is based largely on historical autopsy findings indicating that dormant Mycobacterium tuberculosis bacilli in tissues of macroscopically normal-appearance and healed granulomas in lymph nodes and the lung could be cultured when inoculated into guinea pigs [4]. More recent work based on in situ PCR and RT-PCR has suggested the presence of viable bacilli throughout apparently normal lung tissue [5].

The TST and IGRA are in reality only a measure of the magnitude of an effector memory T cell response to M. tuberculosis from either recent or remote exposure [3]. Previous Bacillus Calmette–Guerin (BCG) vaccination can produce a false positive TST but does not affect the IGRA. At a clinical level, neither of these tests distinguishes LTBI (either transient or long standing) from subclinical or apparently active TB. The premise that a positive TST/IGRA result may be indicative of LTBI arises from observations that patients with a positive test are at greater risk of developing active TB in the short term (~2 years) compared with those who test negative [6]. However, the positive predictive value of these tests for the development of active TB is only of the order of 1–2%.

Postrmplementation of LTBI screening and treatment recommendations is a further contributing factor to ongoing risk of active TB in patients. European registry data and a Korean study have shown that screening or treatment for LTBI is incorrectly carried out in 12–39.5% of cases [1, 2]. In a Greek study of patients on TNF inhibitors, of nine patients who fulfilled criteria for LTBI treatment but who took chemoprophylaxis either incorrectly or not at all, three developed active TB [7].

To complicate matters further, even when there is apparent adherence and completion of chemoprophylaxis, there is incomplete protection against active TB. Early large randomized controlled trials showed that treating TST-positive persons with isoniazid decreases the subsequent risk of developing active TB by only ~60% [8]. Not surprisingly, there have been cases of patients treated with TNF inhibitors who have developed active TB after completing chemoprophylaxis [2, 7]. New infection occurring after prophylactic therapy rather than reactivation of LTBI may explain the lack of complete protection and is likely to be particularly important in high-burden settings.

In the developing world, mainly in Africa and parts of Asia, the incidence of TB reaches endemic proportions. For example, the annual incidence of TB in South Africa in 2010 was 808 per 100 000 [9]. There are currently no registry data on the impact of TNF inhibitors on TB risk in RA patients resident in TB-endemic areas. There are two possible options to reduce the risk of TB in this setting. Offering chemoprophylaxis to all patients commencing TNF inhibitors, regardless of TST/IGRA result, is one option. The potential downside of this approach is isoniazid-related hepatotoxicity, particularly in elderly patients and where there is co-prescription of other potentially hepatotoxic agents such as MTX. The risk of introducing drug resistance through the use of single-drug therapy seems to be small, but only if active TB has been excluded before starting chemoprophylaxis.

The safer alternative is to avoid TNF inhibitors as first-line biologics in DMARD-resistant RA now that biologics with other modes of action are available. Countries like Morocco, Algeria and South Africa have recommended this approach [9]. The choice of the non-TNF inhibitor is dependent on resources, convenience of administration...
and potential adverse effects of the agent. Rituximab, a monoclonal anti-CD20 antibody, is widely accessible and easy to administer. To date there has been no TB signal with this agent [10]. Rituximab is contraindicated in patients with hepatitis B infection, which is a problem in parts of the developing world. However, the incidence of active infection is declining worldwide with the introduction of effective immunization programmes. The risk of progressive multifocal encephalopathy, one reason for rituximab not being approved as a first-line biologic therapy in the USA, is small compared with the TB risk associated with TNF inhibitors. Other non-TNF inhibitors to consider are tocilizumab and abatacept. No signal of increased TB risk has been reported with abatacept [10]. A few TB cases have been reported with tocilizumab, but it is unclear whether the risk is any higher than with traditional DMARDs [10].

In summary, the priority for the developing world for effective disease control in RA is early diagnosis and treatment with traditional DMARDs. In the minority of cases of DMARD-resistant disease, we would argue that non-TNF inhibitors be considered as first-line biologics because of the high risk of TB with TNF inhibitors. There is a clear need for biologics registries in developing countries to better understand the relative safety of the various drugs.

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Mohammed Tikly¹, Bridget Hodkinson¹,² and Keertan Dheda²

¹Division of Rheumatology, Chris Hani Baragwanath Academic Hospital, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg and ²Department of Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa.

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Correspondence to: Mohammed Tikly, Division of Rheumatology, Chris Hani Baragwanath Academic Hospital, PO Box Bertsham 2013, Johannesburg, South Africa.

E-mail: mohammed.tikly@wits.ac.za

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