ORIGINAL ARTICLE

A retrospective record review of tuberculous infections in rheumatoid arthritis patients on biologics in Malaysia

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ABSTRACT

Introduction: The aim of this study was to analyse the clinical characteristics of patients with rheumatoid arthritis receiving biologics therapy and investigate the association between types of biologics and tuberculosis (TB) infections in 13 tertiary hospitals in Malaysia.

Materials and Methods: This was a retrospective study that included all RA patients receiving biologics therapy in 13 tertiary hospitals in Malaysia from January 2008 to December 2018.

Results: We had 735 RA patients who received biologics therapy. Twenty-one of the 735 patients were diagnosed with TB infection after treatment with biologics. The calculated prevalence of TB infection in RA patients treated with biologics was 2.9% (29 per 1000 patients). Four groups of biologics were used in our patient cohort: monoclonal TNF inhibitors, etanercept, tocilizumab, and rituximab, with monoclonal TNF inhibitors being the most commonly used biologic. The median duration of biologics therapy before the diagnosis of TB was 8 months. 75% of patients had at least one co-morbidity and all patients had at least one ongoing cDMARD therapy at the time of TB diagnosis. More than half of the patients were on steroid therapy with an average prednisolone dose of 5 mg daily.

Conclusion: Although the study population and data were limited, this study illustrates the spectrum of TB infections in RA patients receiving biologics and potential risk factors associated with biologics therapy in Malaysia.

KEYWORDS:
Risk of tuberculosis; biologic therapy; tumour necrosis factor-alpha inhibitor; rheumatoid arthritis

INTRODUCTION

The World Health Organisation (WHO) estimates that 19 to 43% of the world's population is infected with *M. tuberculosis*; 18 million new cases and 12 million deaths from tuberculosis (TB) infection occur each year.[1] In Malaysia, the reported rate for TB infection is less than 100 cases per 100,000 population and the mortality rate was 5.5 cases per 100,000 population in 2015.[2]

Rheumatoid arthritis (RA) is a common, multisystemic autoimmune disease that can lead to deformities and functional limitations without appropriate treatment. The innate immune system in RA is important for maintaining the immune response and protecting against infection. It is also responsible for initiating the inflammatory response and activating the adaptive immune response.[3]

It is well known that RA patients have a four-fold higher rate of infections[4] and up to 13% infection-related mortality compared with the general population, especially TB infections.[5] Several factors predispose RA patients to infections, including the disease and its complications, cumulative doses of disease-modifying antirheumatic drugs (DMARDs),[2,4] prolonged use of steroids, and the advent of biologics therapy, which may further alter the immune system.

In one study,[6] RA patients treated with biologics had a 2.5-fold higher risk of TB infection compared with the biologic-naïve group. Tumour necrosis factor-alpha inhibitors (TNFα-i), particularly etanercept (ETN), had the lowest risk of TB infection compared with biologics in the same group.

To date, there are only a few studies reporting TB infections in RA patients treated with biologics therapy in Asian countries.[7,8] Most of the available studies aimed to analyse the adverse events associated with biologics therapy in RA

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patients, especially infections.[9,10] In Malaysia, the risk of TB infection in RA patients receiving DMARDs or biologics therapy has not been reported. Although it is known that the risk is higher compared to the general population, it is important for us to know the data in relation to Malaysian population.

In this study, we analysed the baseline characteristics and demographic data of RA patients who received biologics therapy and investigate the association between types of biologics and tuberculosis infections in 13 tertiary hospitals in Malaysia.

MATERIALS AND METHODS

This was a retrospective study that included all RA patients who received biologics therapy from January 2008 to December 2018 at 13 tertiary hospitals in Malaysia. The aim of this study was to analyse the clinical characteristics of patients with RA receiving biologics therapy and investigate the association between types of biologics and tuberculosis infections in 13 tertiary hospitals in Malaysia. Ethics approval for the study was given by the National Medical Research Register (NMRR) under research number ID 58004. As this was a retrospective study, a consent waiver was granted by the research ethics committee.

All RA patients from rheumatology follow-up in 13 tertiary hospitals in Malaysia who received biologic therapy were included for this study. The inclusion criteria were patients: (i) diagnosed with RA based on the American College of Rheumatology (ACR) 2010 criteria;11 (ii) aged 18 years and older; and (iii) who received biologics therapy between January 2008 and December 2018. The exclusion criteria were RA patients: (i) with a concurrent diagnosis of psoriatic arthritis, spondyloarthritis or Bechet's disease; and (ii) who had received biologics therapy before January 2008 or after December 2018.

Patient demographics including age, sex, concomitant diseases (diabetes mellitus [DM], cardiovascular disease [CVD], chronic kidney disease [CKD], and chronic lung disease), screening prior to biologics therapy, treatment received for RA including conventional synthetic DMARDs (csDMARDs) and steroids, and treatment received for TB including TB infection and latent tuberculosis infection (LTBI) were obtained from the Malaysian National Inflammatory Arthritis Registry (MyNIAR), the Malaysian Rheumatology Biologic Registry (MARBLE), and the patient's medical records and recorded in the data collection forms. Data were expressed as mean ± standard deviation (SD) unless otherwise stated.

RESULTS

Patient Characteristics

During the study period from January 2008 to December 2018, 735 RA patients received biologics therapy. A total of 21 of the 735 patients were diagnosed with TB infection after treatment with biologics. Therefore, the calculated prevalence of TB infection in RA patients treated with biologics was 2.9% (29 per 1000 patients).

We were able to analyse only 21 patients diagnosed with TB infection because only limited data was available for the remaining patients. Of these 21 patients, 71.4% were women and the majority were of Malay ethnicity (52.45%). The median disease duration was 162 months. The sociodemographic characteristics of the subjects are shown in Table I.

Biologic Therapy

Four groups of biologics were used in our patient cohort: monoclonal TNFα-i, etanercept (ETN), interleukin-6; tocilizumab (TCZ), and anti-CD20; rituximab (RTX). Monoclonal TNFα-i was the most commonly used biologic (seven patients), namely, adalimumab (45.5%), infliximab (27.3%), golimumab (18.2%), or certolizumab (9.0%). The median duration of biologic therapy before diagnosis of TB was 8 months, with anti-CD20 having a minimum duration of 4.5 months. 16 (76.2%) had pulmonary TB, while the remaining 23.8% had extra-pulmonary TB, which included TB lymphadenitis, military TB, and disseminated TB (Table II).

Associated Risk Factors

Of the 21 patients, only 3 (14.3%) were smokers or had a history of smoking. Most of them had no history of TB (71.4%) and had never been treated for latent TB (71.4%). 75% of patients had at least one pre-existing disease, with hypertension (33.3%) being the most frequently reported comorbidity, followed by dyslipidaemia (19.0%) and ischemic heart disease (14.3%). As regards occupational status, 23.8% of patients were housewives, 14.3% worked in the hospital, and some had their own business (14.3%) or were retired (14.3%) (Table III).

All the patients had at least one ongoing cDMARDs therapy at the time of diagnosis TB. The most commonly used cDMARDs were leflunomide (71.4%), followed by methotrexate (61.9%) and sulfasalazine (38.1%). More than half had ongoing steroid therapy with an average steroid dose of 5 mg daily (Table III).

DISCUSSION

A paper published by Keane et al triggered the emergence of studies and registries on the risk of TB infections after biologics therapy.[8] Most of the available registries provided valuable data and estimates of the relative risk of TB associated with the use of different biologics. The result of our study showed that the calculated prevalence of TB infections in the Malaysian RA cohort treated with biologics was higher than in the Malaysian general population, and the incidence was almost comparable to reports from the Brazilian registry,[12] the Swedish population,[13] and the Korean population.[14] A French prospective study had reported a lower adjusted annual incidence rate of TB in patients receiving ETN, infliximab (IFX), and adalimumab (ADA).[15]

The median latency of TB infection after exposure to biologics in our patient cohort was 8 months, with the earliest being 4.25 months in patients exposed to anti-CD20, followed by 8.0 months for interleukin-6 (IL-6), 9.0 months for ETN, and 12.0 months for monoclonal TNFα-i. A retrospective

Table I: Sociodemographic data of the subjects

	Median	Min, Max
Demographic		
Age (years)	53	33, 82
Gender		
Male	6 (28.6)	
Female	15 (71.4)	
Race		
Malay	11 (52.4)	
Chinese	5 (23.8)	
Indian	5 (23.8)	
Duration of RA (months)	162	87, 336
Duration of biologic (months)	8.0	2.5, 72

RA: rheumatoid arthritis
Data presented as either counts (percentages) or median

Table II: Type of biologics, duration of therapy and tuberculosis infection

	ETN	Monoclonal TNF -i	Anti-CD20	IL-6	Total patients
Total number of patients (in percent)	6 (28.6)	7 (33.3)	2 (9.5)	6 (28.6)	21
Duration of biologics exposure before TB infection (months, median)	9.0	12.0	4.25	8.0	8.0
Steroid therapy at time of TB diagnosis (number of patients, dose)	2 (5mg)	3 (5mg) 1 (10mg) 1 (20mg)	1 (5mg) 1 (10 mg)	1 (5mg) 2 (2.5mg)	
History of TB infection	2 (9.5)	3 (14.3)	0	1 (4.8)	6
History of LTBI	1 (4.8)	2 (9.5)	0	3 (14.2)	6
Type of TB infection	4 PTB 2 EPTB	5 PTB 2 EPTB (Goli, Certo)	All PTB	5 PTB 1 EPTB	16 PTB 5 EPTB

ETN: etanercept, TNFα-i: tumour necrosis factor alpha-inhibitor, IL-6: interleukin-6, TB: tuberculosis, LTBI: latent tuberculosis infection, PTB: pulmonary tuberculosis, EPTB: extra pulmonary tuberculosis, Goli: golimumab, Certo: certolizumab pegol
Data presented as either counts (percentages) or median

Table III: Risk factors associated with tuberculosis infections in biologics therapy

Occupations	
Housewife	5 (23.8)
Hospital setting	3 (14.3)
Retired	3 (14.3)
Business	3 (14.3)
Office	2 (9.5)
Factory	2 (9.5)
Teacher	2 (9.5)
Driver	1 (4.8)
Smoking status	
Yes	3 (14.3)
No	18 (85.7)
History of TB infections before biologics therapy	
Yes	6 (28.6)
No	15 (71.4)
History of LTBI before biologics therapy	
Yes	6 (28.6)
No	15 (71.4)
Other co-morbidities	
Nil	5 (23.8)
1	4 (19.0)
2	7 (33.3)
3 and more	5 (23.8)
Number of DMARDs therapy at TB diagnosis	
1	6 (28.6)
2	8 (38.1)
3 and more	7 (33.3)
Steroid usage at TB diagnosis	
Yes	12 (57.1)
No	9 (42.9)

TB: tuberculosis, LTBI: latent tuberculosis infection, DMARDs: disease-modifying antirheumatic drugs
Data presented as counts (percentages)

Canadian study in 2006 found that the median time to diagnosis TB from IFX and ETN exposure was 4.25 and 19.75 months, respectively.[16] However, in the UK population, the median time from first TNFα-i exposure to diagnosis of TB was 13.4 months for ETN, 5.5 months for IFX, and 18.5 months for ADA.[17] Although the data were not comparable to our patient cohort, it suggests that we need to monitor the possibility of TB infection in patients receiving biologics as early as 4.25 months.

The association between TNFα-i therapy and reactivation of latent TB is well known. As mentioned in many studies[15,17,18] monoclonal TNFα-i was known to have a higher risk of TB infection compared with ETN. In the Korean population, two cases of TB were reported in 90 patients receiving IFX, and no case was reported in 103 patients receiving ETN.[19] In the UK registry, the incidence of TB was 1.5 per 1,000 patient-years for IFX and 0.5 per 1,000 patient-years for ETN.[20] A study of data from the British Society for Rheumatology Biologics Registry (BSRBR) confirmed a three- and four-fold risks of TB for IFX and ADA, respectively, compared with ETN.[17] Similarly, in our cohort, most patients who contracted TB were from the TNFα-i monoclonal group (33.3%). The TNFα-i agent inhibits the TNFα receptor, an important cytokine involved in the defence against infection, particularly mycobacterial infection, through a number of mechanisms include inhibition of reactivation of dormant bacilli.[21]

In the present study only two patients who had TB infection after RTX, none of whom had a prior history of TB. An open-label extension study by Keystone et al showed that the rate of severe infections was low in patients treated with RTX.[22] A 2-year, multicentre, randomised, double-blind, placebo-controlled trial of RTX therapy showed that RA patients had significant improvement in their disease activity after an inadequate response to TNFα-i. This study also found no evidence of TB reactivation with rituximab.[23] In patient treated with RTX, peripheral blood remains clear of B cells for 6 to 2 months after a single therapy. However, the reduction in B cells is not necessarily dramatic, and the long-lived plasma cells, the main source of protective antibodies, are not eliminated. Because RTX acts primarily on the humoral immune response, the risk of acquiring TB or reactivating latent TB is very low.[24] This is important in clinical practice because RTX may be one of the options for the treatment of RA patients at risk of developing TB, especially in patients with prior TB infection.

Data from the randomised controlled trials have shown that the newer TNFα-i monoclonal antibodies, such as golimumab (Goli) and certolizumab pegol (Certo), do not have an increased TB risk compared with placebo.[18] The risk of severe infections also appears to be significantly lower with these agents than with other TNFα-i.[18] In our patient pool, we had two patients receiving Goli and one patient with Certo who had TB infection after treatment.

Because TB disease is highly endemic in Malaysia, screening for TB is mandatory in all patients before starting the treatment with biologics. Methods used for TB screening in Malaysia include the tuberculin skin test (TST), chest radiograph, direct smear of sputum for acid-fast bacilli, and the most recent method available is the interferon-gamma release assay (IGRA). TST is the standard method for identifying LTBI, but it has low specificity and does not distinguish between infection with nonspecific mycobacteria or a reaction due to BCG vaccination. In contrast, IGRA is more specific and sensitive for LTBI but has not been validated in patients taking TNFα-i.[25] False-negative results in TST or IGRA may occasionally be observed especially in immunosuppressed patients treated with biologics, corticosteroids, or DMARDs.[26] Park et al. reported that serial TST combined with IGRA may be useful for the identification of false-negative results for LTBI and new TB infections in patients undergoing long-term anti-TNF therapy.[27]

Reactivation of LTBI has become a major concern since the introduction of IFX for RA.[8] In our cohort of patients who were found to have LTBI, isoniazid (INH) prophylaxis was administered for at least 6 to 9 months, with a treatment duration of at least 1 to 2 months before starting treatment with biologics. Several guidelines have recommended this treatment regimen on the basis of studies reporting up to a 10-fold increased risk of reactivation of latent TB in patients undergoing TNFα-i therapy and a decrease with appropriate prophylaxis in the same group of individuals.[21] Starting TNFα-i therapy after 1 month of TB prophylaxis in patients with RA who tested positive for LTBI significantly reduced the risk of TB reactivation. However, if the activity of the underlying disease and the general condition of the patient permit, it is preferable to wait another 1 month, because the side effects of therapy with isoniazid occur mainly in the first 2 months. Although the risk of LTBI reactivation is not the same with all biologics, screening for LTBI is strongly recommended in all current guidelines when initiating therapy with a TNFα-i.[28]

Older age, male sex, use of corticosteroids, and the presence of comorbidities such as DM, chronic obstructive pulmonary disease (COPD), and CKD were all significant risk factors for the development of TB in the cohort of RA.[29] We also attempted to assess the potential risk factors that might contribute to the development of TB infections in our patient cohort but were unable to analyse the correlation because of very limited data. We had expected that patients with a history of smoking or active smoking, a history of previous TB infections or LTBI, and occupational status might contribute to TB infection, but this was not the case. However, patients with ongoing steroid use and DMARDs and at least one comorbidity had a higher percentage of TB infections than the other patients. Comorbidities in our patients included hypertension, dyslipidaemia, ischemic heart disease, and diabetes mellitus.

We also investigated the types of TB infection in our patient cohort and up to 76% of them had pulmonary TB infection. The rest (five patients in total) had extrapulmonary TB (EPTB) infection, which included TB lymphadenitis and disseminated TB. Two of them received ETN, two received monoclonal TNFα-i, and one IL-6. TB lymphadenitis is known to be the most common EPTB reported in Malaysia,[30] but it is somewhat different in other countries.[31] Severe immunosuppression increases the risk of developing EPTB, as opposed to PTB alone.[30,31] To our knowledge, there has been no study addressing the association between biologics therapy and EPTB per se. Diagnosis of EPTB is also clinically challenging because of its atypical clinical features, but the risk of developing extrapulmonary tuberculosis was definitely

higher in RA patients. It is also difficult to distinguish symptoms such as fever and elevated inflammatory markers from other infections or a RA disease flare. In addition, TST results may be false-negative in cases of EPTB.[26]

There are some limitations to this study. This study did not have enough data from RA patients without biologics therapy, which would make it difficult to assess the association between risk factors in patients on and off biologics. Assessing risk factors in patients before and during biologics therapy would help improve treatment success without interruption and reduce the risk of infection for patients. Although the number of cases that developed TB in our study cohort was limited and the assessment of risk factors was not robust, we drew some conclusions about which biologics could be used in patients who previously had TB infections. This study also lacked data on disease activity before and after TB infections in patients treated with biologics. We were unable to assess treatment outcome in patients with TB infections. We anticipate that it will be difficult for patients with TB infections to control their disease activity because treatment options are limited during this time. It would be helpful to have the full data on this so that we can evaluate the impact of TB not only on the patient's infection status but also on disease control. We also were not able to compare whether RA disease alone is a risk factor for TB without biologics therapy.

A prospective cohort study of TB infections in patients with RA receiving biologics in the Malaysian population and the effects of different classes of biologics could provide useful information to help clinicians in the prevention of TB in this patient group.

CONCLUSION

Although the study population and data were limited, the findings of this study illustrate the spectrum of TB infections in RA patients receiving biologics and potential risk factors associated with biologics therapy. The incidence rates and types of biologics associated with TB appear comparable to other Asian and Western data. Identification of high-risk patients and appropriate screening before biologics therapy is an important tool to reduce the risk of progression to active TB. Patients with negative screening tests may need to be closely followed and monitored for possible TB reactivation. Effective prophylaxis helps to significantly reduce the risk of infection or TB reactivation in patients treated with biologics.

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