Risk of tuberculosis in patients with rheumatoid arthritis in Hong Kong – the role of TNF blockers in an area of high tuberculosis burden

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Abstract

Objectives

To elucidate the incidence rate and relative risk of tuberculosis (TB) in patients with rheumatoid arthritis (RA) compared to the general population in Hong Kong between 2004 and 2008, and to assess whether this risk is associated with exposure to tumour necrosis factor (TNF) blockers after adjusting for other known risk factors.

Methods

We reviewed all the medical records of RA patients to determine the standardised incidence ratio (SIR) of TB in RA patients. Independent explanatory variables associated with active TB in RA were ascertained using the Cox regression model.

Results

A total of 2441 RA patients followed at the 5 centres were recruited. The mean age at the start of follow up was 56±14 years. The median follow-up duration was 6,616 and 185 patient-years for the TNF naive and TNF treated groups, respectively. Compared to age- and sex-matched population controls, the SIR of active TB in RA was significantly increased (SIR for TNF naïve RA: 2.35, 95% CI 1.17–4.67, p=0.013, SIR for TNF treated RA: 34.92, 95% CI 8.89–137.20, p<0.001). Independent explanatory variables associated with an increase risk of active TB included older age at study entry (RR 1.05, p=0.013) a past history of pulmonary TB (RR 5.48, p=0.001), extra-pulmonary TB (RR 16.45, p<0.001), Felty's syndrome (RR 43.84, p=0.005), prednisolone >10mg daily (RR 4.44, p=0.009) and the use of TNF blockers (RR 12.48, p<0.001).

Conclusion

Exposure to TNF blockers remained to be an independent risk factor for TB in RA after adjusting for other known risk factors.

Key words

Rheumatoid arthritis, TNF blockers, risk factors, tuberculosis.

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Introduction

Tumour necrosis factor (TNF) blockers have been used in patients with refractory rheumatoid arthritis (RA) and ankylosing spondylitis in Europe and North America since 1998 (1). TNF plays a dominant role in the protection against mycobacterial infection (2), and there is growing concern that frequent use of TNF blockers may increase vulnerability to tuberculosis (TB) (3-7). TB is re-emerging as an infectious disease in developed countries with a low TB burden, partly as a result of the use of immunosuppressive drugs including TNF blockers (8). The prevalence of latent TB infection is estimated to be 33% in Hong Kong (9). The crude incidence rate of active TB in the general population from 2004 to 2008 ranged from 91.8 to 82.1 cases per 100,000 persons annually (10), which is markedly higher than the rates in other developed countries (11). TNF blockers have been available in Hong Kong since 2004, and their application in spondyloarthritis and RA is increasing. Consensus statements on the indications and monitoring of anti-TNF therapy for rheumatic diseases in Hong Kong has been published in July 2005 (12).

The risks of TB in patients with RA have been conflicting. Vulnerability to infection and increased risk of TB in patients with RA, independent of TNF-blocker therapy, has been reported in Spain, Sweden, Japan, Korea and Canada (3, 4, 7, 13-15), with a relative risk (RR) of TB infection ranging from 2 to 11-fold higher in RA patients, while the rate of TB in RA patients from the US has not increased (7). The factors contributing to this increased TB risk are unclear.

Most studies on RA and TB, especially in patients with RA exposed to TNF blockers, have been conducted in developed countries with low or intermediate TB burdens. In contrast, our study was conducted in a country with a high TB burden (according to the 2008 World Health Organization (WHO) Report WHO/HTM/TB/2008.393). Moreover, we examined the association between the use of TNF blockers and TB in patients with RA by comparison with the Hong Kong population and after adjustment for other known risk factor for TB including socio-demographic, clinical and treatment factors.

We aimed to elucidate the incidence rate and relative risk of TB in patients with RA compared to the general population in Hong Kong between 2004 and 2008, and to assess whether this risk is associated with exposure to TNF blockers after adjusting for other known risk factors.

Materials and methods

Data source

The Government Chest Clinics under the TB and Chest Service are free for all Hong Kong citizens with chest symptoms, and provide over 80% of the care for patients with active TB all over Hong Kong. Moreover, there is a statutory requirement for notification of all TB cases to the Department of Health. To ensure quality and timeliness of notification data, continuing effort has been invested by the Government to promote accurate reporting from both public and private sectors. Data from the TB laboratories and the death registry are also regularly captured and cross-matched with the TB notification registry. The city-wide data from the TB and Chest Service was used as a control to compare the relative risk of active TB from 5 cohorts of patients with RA.

Subjects

All RA patients who fulfilled the American College of Rheumatology (ACR) 1987 revised criteria (16), and who were being followed at any of the 5 centres, were invited to participate. Hong Kong has a dual system with public and private provision for both ambulatory and hospital inpatient care. Public care is available to all residents and is heavily subsidised, and therefore over 95% of patients with chronic illnesses were under public care. The public health care system of Hong Kong is divided into 7 clusters (regions). These 5 public hospitals are the largest referral centres amongst 4 out of the 7 clusters, serving a well-defined population of almost 4 million people, out of a total population of around seven million in Hong Kong. The patients were divided into 2 categories:

1. RA patients not exposed to TNF blockers (TNF blockers naïve cohort).

We evaluated 5 cohorts of RA patients meeting the criteria of the American College of Rheumatology. None of the patients had been exposed to TNF blockers.

2. RA patients exposed to TNF blockers (TNF blockers treated cohort). RA patients refractory to conventional disease modifying anti-rheumatic drugs (DMARDs) are candidates for TNF blockers.

Methods

As a reference, we used the sex and age-specific incidence rates of TB in the general population from 2004 to 2008. To determine the relative risk of TB in RA patients with or without TNF blockers versus the general population, we reviewed all the medical records of RA patients. The ethics committee of the Chinese University of Hong Kong and the Hospital Authority approved this study, and all patients provided written informed consent.

Clinical records of TNF naïve RA patients were reviewed at baseline, defined as 1) first clinic visit if the visit was after January 1st, 2004, or 2) first visit in the year 2004 for patients attending the clinic before 2004. Baseline data recorded including socio-demographic (race, sex, age, marital status, education level, home environment-privately owned or others, employment status and public means-tested financial assistance status); clinical markers of disease severity (disease duration; presence of extra-articular features, rheumatoid factor (RF) and x-ray erosion; haemoglobin, serum albumin, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels), use of DMARDs, and risk factors such as smoking, current use of alcohol, low body mass index (BMI), a history of TB and the presence of diabetes mellitus (DM), cancer, silicosis, pulmonary fibrosis, chronic renal failure/dialysis, gastrectomy or jejunoileal bypass, and the chest radiograph findings. All patients were prospectively followed until the end of 2008, and they were interviewed during routine follow up for the detail assessment of the socio-economic status at baseline and to verify any personal history of active TB.

For the TNF treated patients, we gathered demographic information together with clinical characteristics of RA and factors related to TB infection listed before. In addition, tuberculin skin tests (TST) and TB prophylaxis prior to TNF blocker therapy were retrieved. Chest radiographic findings were also reviewed before initiation of TNF blockers.

For each patient diagnosed with TB, data regarding the date and mode of diagnosis, TB localisation, the use of DMARD, steroid in the 6 months prior, and TNF blocker duration and outcome of the infection were retrieved from medical records. For those lost to follow up, data from the TB notification registry and death registry were retrieved to verify whether the patient could have TB during that period of time.

Definition of TB cases.

An active case of TB was defined as disease proven by isolation of *Mycobacterium tuberculosis*, or in the absence of bacteriological confirmation, disease diagnosed on clinical, radiological and/or histological grounds together with an appropriate response to anti-TB treatment.

Statistical analyses.

For the comparison of the incidence rates of TB among patients with RA, the total patient-years of follow-up in the TNF blocker exposed and naïve RA cohort were used to estimate TB incidence rates in RA, which were compared with the Hong Kong general population TB incidence rate through indirect sex and age-adjustment. Individuals in the TNF blocker exposed cohort who appeared in TNF blockers naïve cohorts were censored from the latter cohorts on the date of entry into the TNF blocker exposed cohort. The sex and age-specific TB incidence rates of the general population for each year were applied to the TNF blocker exposed and naïve RA cohorts for the period 2004-2008 to obtain the estimated TB incidence for each group. The observed incidence of either group was divided by the corresponding estimated TB incidence to give the standardised incidence ratio (SIR) for that group. The 95% confidence intervals and *p*-value were obtained by comparing either group with a corresponding hypothetical population reference group bearing the same age and sex structure that would be expected to give the same number of observed TB cases over the same observation period.

In order to ascertain the independent explanatory variables associated with active TB in RA, potential explanatory variables in RA patients with and without active TB were compared with Student's *t*-test or analysis of variance for continuous variables and the chi-square test or Fisher exact test for the categorical variables as appropriate. Variables with a *p*-value of <0.05 in the univariate analysis were examined by Cox regression analyses. Probability values of $p<0.05$ were considered significant. The analyses were performed using The Statistics Package for Social Sciences (SPSS for Windows, version 13.0, 2006, SPSS Inc, Chicago, IL).

Results

A total of 2,441 RA patients followed at the 5 centres were recruited. The female to male ratio was 4.3 (1978 female, 81%) to 1 (463 male, 19%). Majority (96.5%) of the patients were Chinese. The mean age at the diagnosis of RA and at the start of follow up was 50±15 and 56±14 years respectively, with a median disease duration of 3.0 (0.1–8.8) years. Rheumatoid factor was positive in 72%. The TNF naïve cohort consisted of 2424 patients, including 64 patients who were subsequently started on TNF blockers. Altogether, 81 patients were treated with at least one TNF antagonists.

For the TNF treated cohort, 49 (60.5%) patients were started on TNF blockers before the local guideline were published. Data on both the TST and chest radiography were recorded for 58 (71.6%) patients. A positive TST was reported in 16/58 patients (19.8%), and chest radiography findings suggestive of past TB were found in 4 (4.9%) patients. According to the recommendations in place, 17 (21%) patients considered to have possible latent TB infection were treated with isoniazid (INH). Out of the 81 patients, 71

Table I. Standardised incidence ratios (SIR) of TB for different RA cohorts compared to community controls between 2004–2008.

RA cohorts	No of patients at risk	Observed TB cases	Expected risk*	Population denominator**	SIR	95% CI	*p*-value
RA combined	2441	20	6.954	6972	2.876	1.55–5.35	<0.001
TNF blockers naïve RA	2424	16	6.839	5706	2.354	1.17–4.67	0.013
TNF blockers treated RA	81	4	0.115	2829	34.922	8.89–137.20	<0.001

*Expected number of TB cases at the sex and age-adjusted rate of the Hong Kong population. **Size of hypothetical control population of same sex and age mix as the RA cohorts and with similar sex and age-adjusted TB rates as the Hong Kong population that would be expected to give the same number of observed TB cases within the same period.

(87.7%) and 10 (12.3%) had received one and two TNF blockers respectively. Most patients had received infliximab (n=65, 81.2%), followed by etanercept (n=23, 28.4%) and adalimumab (n=3, 3.7%).

Between 2004-2008, the total treatment exposure rate for the TNF naïve and TNF treated cohorts was 6,616 and 185 patient-years respectively. Active TB developed in 20/2441 (0.8%) RA patients. Compared to age- and sex-matched population controls, the SIR of active TB was significantly increased (Table I). Active TB developed in 16/2424 (0.7%) TNF naive patients and 4/81 (4.9%) TNF treated patients after a median follow up duration of 1.3 (1.0–3.4) and 0.2 (0.2–1.7) years respectively (p=0.03). For the TNF treated group, all 4 cases of TB were reported among patients taking infliximab (2 pulmonary TB (pTB) and 2 lymph adenitis). Before July 2005, 3 patients developed active TB 2-3 months after taking infliximab, and none of them was treated with INH (TST was not done in 2 patients and negative in 1 patient). The fourth patient with a positive TST was given INH prophylaxis for 9 months and then subsequently developed pTB 18 months later. The use of common immunosuppressants including methotrexate, leflunomide, hydroxychloroquine and prednisolone remained the same in all the 20 patients at baseline and 6 months prior to the diagnosis of TB.

Table II. Baseline socio-demographic characteristics and co-morbidities of RA patients with and without TB

	TB (n=20)	No TB (n=2421)	*p*-value
Age at RA diagnosis, Mean ± SD	53 ± 17	50 ± 15	0.3
Age at study entry, Mean ± SD	63 ± 11	56 ± 14	0.02
Education years, Median (IQR)	6 (1–9)	7 (3–11)	0.3
	Odds ratio	95% CI	*p*-value
Chinese (n=2355)	–	–	1.0
Male (n=463)	0.9	0.3–2.8	0.8
Married (n=1603)	–	–	0.4
Current smoker (n=143)	–	–	0.5
Current alcohol use (n=179)	–	–	0.4
Home environment			
Privately owned flat (n=1671)	0.9	0.4–2.4	1.0
Employment			0.9
Retired / Unemployed / sick leave, n (%)	8 (1.0)	764 (99.0)	
Housewife/ Student, n (%)	8 (0.9)	929 (99.1)	
Employed, n (%)	5 (0.7)	727 (99.3)	
Receiving public means-tested financial assistance status (n=211)	2.8	0.9–9.1	0.09
Other co-morbidities			
Low BMI (≤18.5) (n=127)	–	–	1.0
Cancer (n=62)	2.0	0.3–15.4	0.4
Silicosis (n=5)	–	–	1.0
Gastrectomy (n=24)	–	–	1.0
Jejunoileal bypass (n=4)	–	–	1.0
Chronic renal failure/dialysis (n=11)	12.6	1.5–103.7	0.09
Diabetes mellitus (n=194)	0.6	0.1–4.5	1.0
History of TB (n=154)	12.8	5.2–31.4	<0.001
History of pulmonary TB (n=132)	9.8	3.9–25.0	<0.001
History of extra-pulmonary TB (n=25)	19.2	5.2–70.3	0.001
Old TB on chest x-ray (n=52)	–		0.4

Except when indicated otherwise, values are the unadjusted odds ratio (OR) and 95% CI. OR cannot be estimated if no patients who were exposed to the risk factor of interest developed TB.
BMI: body mass index.

Characteristics of active TB in RA

Amongst the 20 patients, 11 (55%) had pTB, 9 (45%) had extra-pulmonary TB, including lymph node (n=3), military TB (n=1), joint (n=3), spine (n=1), pleural effusion (n=1). TB was confirmed by culture in 16 patients, 4 were diagnosed based on typical radiologic findings on CXR. All except one patient completed a course of anti-TB treatment with good response. One patient refused further treatment after 3 months of anti-TB treatment due to skin rashes.

Risk factors for TB in RA

Univariate analysis showed that potential explanatory variables associated with TB in RA included older age at study entry (p=0.02), a past history of any TB (p<0.001), pTB (p<0.001), or extrapulmonary TB (p=0.001), longer disease duration (p=0.02), Felty's syndrome (p=0.02), use of prednisolone (p=0.04), highest dose of prednisolone

>10mg daily (p=0.02), methotrexate (p=0.03) and the use of TNF blockers (p=0.004). The socio-demographic, other clinical characteristics and the use of other immunosuppressants were not associated with an increased risk of active TB.

Independent explanatory variables associated with an increase risk of active TB included older age at study entry (p=0.013) a past history of pTB (p=0.001), extra-pulmonary TB (p<0.001), Felty's syndrome (p=0.005), prednisolone >10mg daily (p=0.009) and the use of TNF blockers (p<0.001) (Table IV).

Discussion

Our study provides new data on TB incidence in RA patients from an area of high TB burden, and confirms that an increased risk of TB was present with and without biologic agents. The incident rate of TB in USA was similar to the general population between 1998–1999 (7). In contrast, the age- and sex-standardised incident rate of TB in RA in this study was 2 times that of the general population, similar to previous studies performed in Japan (13), Sweden (3) and Spain (17) (Table V). The reported TB risk was even higher in the studies from Korea (14) and Canada (15). Apart from the older age in the Canadian cohort, the factor contributing to this increased risk was unclear in these two studies since they did not capture other factors associated with the risk of TB diseases *e.g.* socioeconomic status, smoking behaviour, etc.

Government reimbursement for TNF blockers in Hong Kong has only been available since late 2007, therefore only around 3% of the RA patients received TNF blockers in this cohort due to financial constraint. Despite the small number of patients exposed to TNF blockers, we noticed a 12.5-fold increased risk of active TB in TNF exposed RA patients after adjusting for all the potential risk factors. Previous studies on the risk of TB in RA patients exposed to TNF blockers have been conducted in countries with low TB burden prior to the era of screening for latent TB infection (3, 4, 7), or in country with intermediate TB burden with incomplete treatment for latent TB infection (14). In this study, we have also included TNF blockers treated patients before the local guideline for screening of latent TB infection were published in order to reflect the risk of TB in TNF blockers treated patients in an area of high TB burden. This magnitude of increased risk of TB (12.5-fold) is similar to other TNF blocker (mainly infliximab) treated cohorts (4, 7, 14). The 4 fold increased risk of TB in Sweden (3) is apparently lower probably related to the inclusion of a large number of patients given etanercept. Recent report suggested that risk of TB was higher for therapy with infliximab and adalimumab than for therapy with etaner-

Table III. Baseline clinical characteristics and the use of immunosuppressants of RA patients with and without TB.

	TB (n=20)	No TB (n=2421)	p-value
Disease duration, median (IQR)	5.9 (2.1–18.6)	2.9 (0.1–8.8)	0.02
Hemoglobin (g/dl), mean ± SD	11.9 ± 1.7	12.3 ± 1.6	0.3
Albumin (g/dl), mean ± SD	40.4 ± 3.4	40.6 ± 4.2	0.2
ESR (mm/hr), median (IQR)	44 (22–63)	34 (17–62)	0.3
CRP (mg/dl), median (IQR)	16.5 (4.2–31.6)	7.0 (4.0–22.0)	0.1
	Odds ratio	95% CI	p-value
RF +ve (n=1,758)	0.6	0.2–1.5	0.3
Erosion on x-ray (n=1,594)	0.6	0.2–2.1	0.5
Extra-articular features			
Rheumatoid nodule (n=63)	2.0	0.3–15.1	0.4
Vasculitis (n=13)	–	–	1.0
Sicca (n=155)	0.8	0.1–5.8	1.0
Scleritis (n=7)	–	–	1.0
Serositis (n=5)	–	–	1.0
Pulmonary fibrosis (n=59)	–	–	1.0
Neurologic (n=215)	0.5	0.1–4.0	1.0
Felty's syndrome (n=2)	126.3	7.6–2093.7	0.02
Any joint surgery (n=342)	2.1	0.7–5.7	0.2
Immunosuppressants			
Prednisolone (n=487)	2.7	1.1–6.6	0.04
Prednisolone dose >10 mg/day (n=117)	5.0	1.6–15.1	0.02
Methotrexate (n=863)	2.7	1.1–6.7	0.03
Leflunomide (n=303)	0.8	0.2–3.4	1.0
Sulphasalazine (n=945)	0.4	0.1–1.2	0.1
Hydroxychloroquine (n=518)	1.9	0.8–5.0	0.2
Intramuscular gold (n=52)	2.4	0.3–18.4	0.4
Auranofin (n=15)	–	–	1.0
Penicillamine (n =19)	–	–	1.0
Azathioprine (n=45)	2.8	0.4–21.5	0.3
Cyclosporine A (n=17)	–	–	1.0
Cyclophosphamide (n=3)	–	–	1.0
TNF blockers (n=81)	7.6	2.5–23.3	0.004

Except when indicated otherwise, values are the unadjusted odds ratio (OR) and 95% CI. OR cannot be estimated if no patients who were exposed to the risk factor of interest developed TB. ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; RF: rheumatoid factor.

Table IV. Independent explanatory variables associated with an increased risk of active TB in RA

	p-value	RR	95% CI	
Exposure to TNF blocker	<0.001	12.48	3.46	44.69
History of pulmonary TB	0.001	5.48	2.06	14.57
History of extra-pulmonary TB	<0.001	16.45	4.54	59.55
Older age at study entry	0.013	1.05	1.01	1.09
Highest prednisolone dose >10mg daily	0.009	4.44	1.45	13.59
Felty's syndrome	0.005	43.84	3.04	631.78

Table V. Incidence rate and relative risk of TB in different RA cohorts with and without TNF blockers

Country	General population	TNF naïve RA		TNF treated RA		
	Incidence rate per 100,000 population	Incidence rate per 100,000 population	Relative risk compared to healthy control (95% CI)	Incidence rate per 100,000 population	Relative risk compared to healthy control (95% CI)	Relative risk compared to TNF naïve RA (95% CI)
US (7)	6.2	6.2		52.5*		9 (NA)
Sweden (3)	5	–	2.0 (1.2–3.4)	105	–	4 (1.3–12)
Spain (2000) (4) (2001)	21	95	4.13 (2.59–6.83)	1,893* 1,113*	90.1 (58.8–146.0) 53.0 (34.5–89.0)	19.9 (16.2–24.8) 11.7 (9.5–14.6)
Canada (15)	4.2	45.8	10.9 (7.9–15.0)	–	–	–
Japan (13)	25.8	42.4	3.21 (1.21–8.55)			
Korea (14)	67.2	257	8.9 (4.6–17.2)	2,558*	30.1 (7.4–122.3)	10 (NA)
Hong Kong	85	211	2.4 (1.2–4.7)	2,162	34.9 (8.9–137.2)	12.5 (3.5–44.7)

*for infliximab treated patients only.

cept (18). A recent study has reported the possibility of switching to another TNF blocker in patients with loss of efficacy and adverse events (19), whether patients with TB reactivation after infliximab or adalimumab would be safe to switch to etanercept may worth exploring.

Recent data provide information on the effectiveness of adherence to guidelines for screening and treatment of latent TB infection (20). Using data from the Spanish national registry of rheumatic diseases patients being treated with biologic response modifiers, the incidence of active TB per 100,000 person-years decreased from 472 (95% CI, 384–642) to 172 (95%CI, 103–285) after the TB testing recommendations implementation (20). We would expect that a substantial decrease in risk of TB reactivation in our group of patients who have been adhering to the local guideline. Indeed, only 1 out of 32 patients developed active TB after the local screening guideline was published.

Most TB cases representing reactivation of a previous TB infection are evident after 2–3 months of infliximab, or 12 months of etanercept treatment (21). In this study, 3 patients developed active TB 2–3 months after taking infliximab (none of them was treated with INH) similar to previous reports. There were 2 cases of active TB that occurred when the recommendations for the treatment of latent TB infection has been followed, similar to another case report (22). This is not very surprising, since present evidence indicates that 9 months of treatment with INH does not fully protect against the development of active TB, although the decrease in the rate is around 70% (23). Cases occurring after longer intervals (both TB and nontuberculous mycobacterial disease) are most likely new infections (21). The patient who developed pTB 18 months after completing INH prophylaxis for 9 months most likely represents new infection. New infection of TB in an endemic area could never be avoided with pre-treatment screening. Individuals treated with anti-TNF agents with or without risk factors of TB must continue to be monitored (24).

The increased risk of active TB after exposure to prednisolone has been reported in a recent study in RA patients (15), and in another local study on patients with systemic lupus erythematosus (25). In this study, patients exposed to prednisolone >10 mg daily were have a 4-fold increased risk of TB after adjusting for other risk factors. Our findings are supportive of published guidelines that recommend TB screening before initiation of immunosuppressive therapy especially patients on long-term prednisolone (26). The use of the lowest possible GC dose, at night, and for the shortest possible time should therefore greatly reduce the risk of infections (24).

A past history of pTB and extra-pulmonary TB was an independent risk factor associated with a 5- and 16-fold increased risk of active TB in our cohort of RA patients respectively. Similarly, 4/9 (44.4%) RA patients who developed active TB in the Korean study had a past history of TB, compared with 10% in the background RA population (14). Recently, the genetic component in susceptibility to TB has been examined. Three whole-genome-based approaches have yielded moderate linkage to various chromosomal regions, which have been different in each population studied (27-29).

There is an increased frequency of bacterial infections in Felty's syndrome (30), including TB (31). Neutropenia is believed to be the main cause of this increased rate of infection (32). Impaired phagocytosis and intracellular killing, impaired chemotaxis and superoxide production may also contribute to the risk of recurrent infections (30).

A great strength of our study is that all the diagnosis of RA and TB were validated by reviewing case notes. The possibility of under-reporting of active TB was minimised by cross-checking with the Hong Kong TB registry. Moreover, risk factors for TB including socio-economic status, comorbidities and other clinical information on disease severity were included in the analysis. Other potential risk factors for TB including a history of recent contact with an individual with TB, information on human immunodeficiency virus infection status, and the prevalence of latent TB infection in the TNF naïve group were lacking in this study. Another potential limitation would be the possibility of

under-diagnosis of active TB due to treatment at the private sector. Nonetheless, the chance would not be high since the Government chest clinic is free for all HK citizens with chest symptoms, and provided over 80% of the care for patients with active TB all over Hong Kong. Moreover, to ensure quality and timeliness of notification data, continuing effort has been invested by the Government to promote accurate reporting from both public and private sectors. Data from the TB laboratories and the death registry are also regularly captured and cross-matched with the TB notification registry. Reminders will be sent to relevant institutions or practitioners for notification of un-notified cases. Moreover, all patients who are actively being followed were interviewed at different centres to verify any personal history of active TB. For those lost to follow up, data from the TB notification registry and death registry were retrieved to verify whether the patient could have TB during that period of time. Last but not least, given the relatively small number of TB cases in the TNF blocker group, we are not able to address whether there is any differential risk of TB between the 3 TNF blockers.

Conclusions

The age-and sex-standardised incidence rates of TB in TNF naïve RA patients are 2 times that of the general population. The use of TNF blockers was associated with a 12-fold increased risk of TB in RA patients in an area of high TB burden after adjusting for other risk factors. Our data support TB screening before initiation of immunosuppressive therapy especially patients on long-term prednisolone. Patients treated with anti-TNF agents with or without risk factors of TB in an endemic area must continue to be monitored for the possibility of developing new infections.

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