Received: 22 April 2020 | First decision: 11 May 2020 | Accepted: 7 October 2020

DOI: 10.1111/apt.16130

AP&T Alimentary Pharmacology & Therapeutics WILEY

Targeted versus universal tuberculosis chemoprophylaxis in 1968 patients with inflammatory bowel disease receiving anti-TNF therapy in a tuberculosis endemic region

Lingna Ye[1] | Thomas P. Chapman[2] | Zhenzhen Wen[3] | Lang Lin[4] | Yun Qiu[5] | Zhanju Liu[6] | Zhihua Ran[7] | Jiaming Qian[8] | Kaichun Wu[9] | Xiang Gao[4] | Pinjin Hu[4] | Minhu Chen[5] | Simon P. L. Travis[2] | Qian Cao[3] | The Chinese IBD Elite Union

[1]Department of Gastroenterology, Xiasha Branch of Sir Run Run Shaw Hospital, College of Medicine Zhejiang University, Hangzhou, China

[2]Translational Gastroenterology Unit, NIHR Oxford Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust, John Radcliffe Hospital, Oxford, UK

[3]Department of Gastroenterology, Sir Run Run Shaw Hospital, College of Medicine Zhejiang University, Hangzhou, China

[4]Department of Gastroenterology, The Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

[5]Department of Gastroenterology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

[6]Department of Gastroenterology, The Shanghai Tenth People's Hospital, Tongji University, Shanghai, China

[7]Division of Gastroenterology and Hepatology, Key Laboratory of Gastroenterology and Hepatology, Ministry of Health, Shanghai Inflammatory Bowel Disease Research Center, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China

[8]Department of Gastroenterology, Peking Union Medical College Hospital, Chinese Academy Medical Sciences and Peking Union Medical College, Beijing, China

[9]State Key Laboratory of Cancer Biology, National Clinical Research Center for Digestive Diseases and Xijing Hospital of Digestive Diseases, Fourth Military Medical University, Xi'an, China

Summary

Background: Anti-tumour necrosis factor (anti-TNF) therapy increases the risk of tuberculosis (TB). Given limitations of screening techniques, it remains uncertain if patients receiving anti-TNF in TB endemic regions should be screened for latent infection with chemoprophylaxis restricted to those with proven infection, or if all patients should receive chemoprophylaxis.

Aims: To compare the incidence of active TB with infliximab (IFX) following targeted and universal TB chemoprophylaxis, and to determine the rates of adverse events (AE) related to TB chemoprophylaxis

Methods: A multi-centre retrospective cohort study was performed at 18 hospitals in China of 1968 adult patients with IBD receiving IFX from 2009 to 2017. TB screening prior to IFX was performed with chest X-ray and/or computed tomography [CT] and immune reactivity testing (interferon-γ release assay and/or tuberculin skin test). Patients were followed-up for a minimum of 3 months after IFX discontinuation, or until last hospital visit if IFX therapy was ongoing. Targeted strategy was defined as TB chemoprophylaxis only for patients with a positive latent TB screen, with universal strategy defined as TB chemoprophylaxis for all patients.

Results: Mean follow-up was 1.07 ± 0.87 years with a total follow-up of 2102 patient-years. There were 1433 patients in the targeted and 483 patients in the universal TB chemoprophylaxis groups, with no significant difference in the incidence rates of active TB between groups (673.3 per 100 000 population per year vs 891.5 per 100 000 population per year, $P = 0.60$). In the targeted group, 55/1433 patients received TB chemoprophylaxis compared with 483/483 in the universal group, with significantly fewer AEs related to TB chemoprophylaxis in the targeted compared to the universal group (0.35% (5/1433) vs 6.8% (33/483), $P < 0.05$).

Lingna Ye and Thomas P Chapman contributed equally to this work.

The Handling Editor for this article was Professor Jonathan Rhodes, and it was accepted for publication after full peer-review.

Correspondence
Qian Cao, Inflammatory Bowel Disease Center of Sir Run Run Shaw Hospital, College of Medicine Zhejiang University, No. 3 East Qingchun Road, Hangzhou 310016, Zhejiang Province, China.
Email: caoq@zju.edu.cn

Simon PL Travis, Translational Gastroenterology Unit, NIHR Oxford Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust, John Radcliffe Hospital, Oxford, OX3 9DU, UK.
Email: simon.travis@ndm.ox.ac.uk

Funding information
This work was supported by Zhejiang Medical and Health Science and Technology Project (grant number 2019ky422).

Conclusions: In this study of patients receiving IFX in a TB endemic area, universal chemoprophylaxis was not associated with a reduced risk of active TB when compared to a targeted chemoprophylaxis strategy, and AEs were more common. This supports the use of targeted TB chemoprophylaxis when anti-TNF therapy is initiated in TB endemic regions.

1 | INTRODUCTION

Tumour necrosis factor (TNF) inhibitors have become a mainstay of treatment for inflammatory bowel disease (IBD) following their emergence over 20 years ago, and are increasingly used in countries such as China where tuberculosis (TB) is endemic.[1] Anti-TNF therapies including infliximab (IFX) act by neutralising the pro-inflammatory cytokine TNF-α, which is of key pathophysiological importance in both ulcerative colitis (UC) and Crohn's Disease (CD), leading to mucosal healing and clinical remission.[2] However, TNF-α is also of critical importance in host control of *Mycobacterium tuberculosis*, mediating phagocyte activation and granuloma organisation.[3] Approximately one third of the global population are infected with tuberculosis, although 90% have latent tuberculosis infection, defined as an immune response against TB without clinical manifestations.[4] It is now well established that anti-TNF therapy increases the risk of TB at least 3-fold, primarily through reactivation of latent TB infection.[5] Indeed, a study in South Korea reported that the relative risk of TB was 30-fold higher in patients with rheumatoid arthritis receiving anti-TNF.[6] This is of greatest concern in regions where TB is endemic, such as China which has the second highest number of active TB cases worldwide.[4] Active TB infection may be associated with considerable morbidity and mortality.[7] Consequently, careful consideration of strategies to reduce the risk of active TB infection in patients with IBD receiving anti-TNF therapy is essential.

Current guidelines state that patients with IBD should be screened for latent TB infection prior to starting anti-TNF therapy, and if detected, TB chemoprophylaxis should be prescribed to reduce the risk of reactivation.[8-10] Most commonly, either a tuberculin skin test (TST) or the more sensitive Interferon Gamma Release Assay (IGRA) is paired with a chest x-ray, but there is significant local variation in choice of screening modality.[11] Importantly, the performance of these screening tests may be hindered by concurrent immunosuppressive therapies including the oral steroid prednisolone, which reduce the sensitivity of both TST and IGRA.[12] Furthermore, TST lacks specificity for the pathogenic MTB strains due to cross-reactivity with environmental *Mycobacteria and* BCG vaccination; indeed, a number of countries with high TB burden including China have a universal BCG vaccination policy.[12-15] Patients may, therefore, still develop TB despite a negative screening result, either due to a false-negative test result, or following a new infection,[16] with a recent meta-analysis of 128 studies across low, intermediate and high TB burden countries reporting that 73% of patients who developed active TB following anti-TNF therapy had a negative screening result.[17] In addition, United Kingdom (UK) recommendations from 2005 that South Asians born outside the UK with Crohn's disease requiring anti-TNF should receive 6 months empirical TB therapy have remained influential in many countries including China.[18] For these reasons, together with the challenges of differentiating active TB from IBD, there is widespread use of empirical TB therapy in patients with IBD in countries with a high incidence of TB, with data from the IBD Emerging Nations' Consortium recently reporting prescription rates highest in Bangladesh (32% of all patients with Crohn's disease), India (25%) and Thailand (18%).[19]

Consequently, it remains uncertain whether in TB endemic regions, all patients with IBD receiving anti-TNF therapy should receive TB chemoprophylaxis, or whether it should be restricted to those with proven latent TB infection. In current clinical practice in China, there are two TB chemoprophylaxis strategies, targeted and universal. In the targeted TB chemoprophylaxis strategy, patients found to have latent TB infection following screening receive TB chemoprophylaxis, starting either shortly before or at initiation of anti-TNF. In the universal chemoprophylaxis strategy, all patients receive TB chemoprophylaxis, regardless of TB screening result which in this context is primarily performed to differentiate IBD from active TB. For both strategies, the duration of TB chemoprophylaxis varies according to the drug regimen chosen in keeping with World Health Organization (WHO) guidelines, with 3 months of therapy when isoniazid is used in combination with rifampicin, and 6 months of therapy when isoniazid is used alone.[11] Importantly, no studies have yet compared the efficacy of targeted versus universal TB chemoprophylaxis in the prevention of active TB in patients receiving anti-TNF

therapy, with particular concern surrounding the potential increased risk of adverse events (AE) from universal chemoprophylaxis.

The primary aims of this study were to compare the incidence of active TB following IFX therapy, the only anti-TNF licensed for IBD in China during the study period, in the targeted and universal TB chemoprophylaxis groups and to determine the rates of adverse events related to TB chemoprophylaxis. The secondary aims were to determine the overall incidence of active TB in patients with IBD receiving IFX therapy in China, and assess the efficacy of TB chemoprophylaxis in patients with latent TB infection receiving IFX therapy.

2 | METHODS

2.1 | Patient selection

A multi-centre retrospective cohort study was performed at 18 academic hospitals in China, distributed throughout seven administrative regions of diverse socio-economic background, serving approximately 30 000 patients with IBD. Patients with IBD receiving IFX therapy were retrospectively enrolled from January 1, 2009 to June 31, 2017. Eligible patients were at least 18 years old with a diagnosis of IBD according to the Chinese consensus on diagnosis and treatment of IBD, and had received IFX therapy.[20] For TB chemoprophylaxis, the regimens were as follows: combination isoniazid and rifampicin at a dose of 300 mg/450 mg once daily for 3 months or isoniazid at a dose of 300 mg once daily for 6 months. The choice of targeted or universal chemoprophylaxis regimen was made by the primary treating physician, and varied both within and between institutions. All patients received screening for TB regardless of chemoprophylaxis strategy. Patients were excluded if (a) they had active TB or had discontinued TB medication less than 2 months before initiation of IFX, or (b) they had not completed TB screening before initiation of IFX or (c) there was incomplete demographic or clinical information. A group of patients, henceforth, referred to as the escape group, were diagnosed with latent TB infection following TB screening prior to commencement of IFX therapy but did not receive TB chemoprophylaxis. The study was approved by the Clinical Research Ethics Committee of Sir Run Run Shaw Hospital Affiliated to Zhejiang University School of Medicine, register number 20170116-4 with Institutional Review Board (IRB) approval for all hospitals involved in the study.

2.2 | Data collection

All data were collected from medical records and, if necessary, by follow-up telephone consultation. Collected data included demographics, clinical characteristics of IBD, previous and current treatment for IBD, duration of IFX therapy and reason for discontinuation, previous history and treatment of TB, TB screening results before IFX treatment (chest X-ray or computed tomography (CT), TST, IGRA), TB chemoprophylaxis regimen, AE while on TB chemoprophylaxis and the incidence of active TB and time interval to active TB after IFX therapy. Patients were followed-up for a minimum of 3 months after IFX discontinuation, or until last hospital visit if IFX therapy was ongoing.

2.3 | Diagnosis of latent tuberculosis

Latent TB infection was diagnosed if (a) either IGRA or TST was positive, with a normal chest X-ray or CT without symptoms of active TB or (b) there was evidence of previous TB infection on chest X-ray/CT without a history of TB treatment and without symptoms of active TB, in accordance with expert consensus.[21] A positive TST result was defined as an induration diameter ≥10 mm after 48-72 hours, regional lymphangitis or vesicle formation. A positive IGRA result was defined as T-spot.TB test ≥6 spots.[21] No patients were screened with the IGRA QuantiFERON-TB Gold.

2.4 | Outcome measures

Active TB was diagnosed in three clinical settings. (a) Positive MTB test (culture and/or polymerase chain reaction) and symptoms of active TB infection, such as cough for greater than 14 days, weight loss, fever and/or night sweats. (b) Symptoms of active TB infection, and abnormal chest imaging, with improvement following TB treatment. (c) Symptoms of active TB infection and positive histopathology, such as caseating granuloma.[22] Reactivation of TB in patients with latent TB infection and newly diagnosed active TB in patients not known to have latent TB infection were considered to be active TB infections during IFX therapy or in the 3 months following the last infusion. Recording of all AE was based on data reported by the treating physician. Routine blood tests including full blood count, renal and liver function were checked prior to initiation of IFX, at week 2, week 4 and then 4 weekly while on IFX, or at other time points dictated by clinical need. Hepatotoxicity was defined as either transaminitis (an increase in alanine aminotransferase and/or aspartate aminotransferase above the laboratory upper limit of normal) or hyperbilirubinaemia (an increase in total bilirubin level above 34.2 μmol/L, or a combination of both). The presence of any comorbidities including pre-existing liver, renal or respiratory disease and diabetes that might influence risk of AE were also recorded.

2.5 | Statistical analysis

The normal distribution of continuous variables was evaluated by the Kolmogorov-Smirnov test. Normally distributed data are presented as the mean ± standard deviation (SD), and non-normally distributed data are presented as the median with interquartile range (IQR). Categorical variables are presented as the frequency (n) with percentage (%). Percentages are rounded up to the nearest integer

where simplification assists understanding of results. To determine the incidence of active TB in patients with IBD receiving IFX, the incidence density was calculated using the following equation: incidence density = number of new cases/number of patients × years of follow-up, as previously described with modification.[23] The incidence of active TB between the targeted and universal groups was evaluated by the conditional maximum likelihood estimate of rate ratio. Other outcomes between groups were evaluated by the Chi-squared (χ^2) test and Fisher's exact test for categorical variables and Mann-Whitney *U* test for continuous variables. The median interval to development of active TB between those with a negative TB screen and those with a positive TB screen was also evaluated by Mann-Whitney *U* test. Logistic regression was used to calculate the odds ratio (OR) of developing active TB in patients with latent TB infection in comparison to those without latent TB infection receiving IFX therapy. All data were analysed using SPSS 22.0 (IBM, Armonk, NY, USA). A two-tailed p-value of less than 0.05 was defined as significant.

3 | RESULTS

3.1 | Study population

The base cohort retrospectively recruited all 2100 patients with IBD aged greater than 18 years who had received IFX therapy at 18 Chinese hospitals from 2009 to 2017. Due to incomplete demographic or clinical information, 132 patients were subsequently excluded. In summary, 1968 patients were, therefore, included to calculate the overall incidence of active TB. Mean follow-up was 1.07 ± 0.87 years with a total follow-up of 2102 patient years.

3.2 | Groups according to latent TB infection status

Based on the results of TB screening before the commencement of IFX therapy, the 1968 patients were divided into two groups, latent TB infection positive (n = 166) and latent TB infection negative (n = 1802). Over two thirds of patients had both TST and IGRA together with either chest X-ray or CT. There were no differences in the combinations of screening modalities used between patients found to be latent TB infection positive and negative (Table 1). The clinical characteristics of the total study population and these two groups are shown in Table 2. There were no significant differences between the groups in age, gender, subtype of IBD, duration of IBD, smoking status, duration of IFX, frequency of IFX or concurrent therapy with oral steroids or immunomodulator (IM).

3.3 | Groups according to TB chemoprophylaxis strategy

Fifty-two patients were diagnosed with latent TB infection following TB screening prior to commencement of IFX therapy but did not receive TB chemoprophylaxis, and were therefore excluded from the assessment of TB chemoprophylaxis strategy but are considered later as an escape group. The clinical characteristics of this escape group are shown in Table S1. Therefore, 1916 patients with IBD receiving IFX were divided into two groups: targeted strategy (targeted chemoprophylaxis only for patients with latent TB infection) and universal strategy (universal chemoprophylaxis for all patients). The clinical characteristics of these two groups are shown in Table 3. There were no significant differences between the groups in age, gender, subtype of IBD, duration of IBD, smoking status, duration of IFX, frequency of IFX, concurrent therapy with oral steroids or immunomodulator, or comorbidities.

3.4 | Risk of active TB infection

3.4.1 | The incidence of active TB in all patients with IBD receiving IFX therapy

Active TB developed in 21 (1.07%) of the 1968 patients with IBD receiving IFX therapy; 19 CD patients (1.07%) and 2 UC patients (1.06%). The incidence rate of TB was 999.1 per 100 000 population per year for all patients with IBD. No significant difference was found in TB incidence between patients with CD or UC ($P = 0.97$), with incidence rate 978.8 per 100 000 population per year for CD and 1244.0 per 100 000 population per year for UC. TB incidence was higher in those

TABLE 1 TB Screening modalities used in total study population, latent TB infection positive and latent TB infection negative groups

TB screening modalities	Total (N = 1968)	Latent TB infection positive (n = 166)	Latent TB infection negative (n = 1802)	*P* value
Chest X-ray + TST	134 (7%)	11 (7%)	123 (7%)	0.92
Chest X-ray + IGRA	240 (12%)	18 (11%)	222 (12%)	0.58
Chest X-ray + TST + IGRA	701 (36%)	61 (37%)	640 (36%)	0.75
Chest CT + TST	28 (1%)	2 (1%)	26 (1%)	0.80
Chest CT + IGRA	177 (9%)	15 (9%)	162 (9%)	0.98
Chest CT + TST + IGRA	688 (35%)	59 (36%)	629 (35%)	0.87

Abbreviations: CT, computed tomography; IGRA, interferon gamma release assay; n, frequency; TST, tuberculin skin test.

TABLE 2 Characteristics of total study population, latent TB infection-positive and latent TB infection-negative groups

Clinical characteristics	Total (N = 1968)	Latent TB infection positive (n = 166)	Latent TB infection negative (n = 1802)	*P* value
Age, years (median, IQR)	27 (21-35)	27 (24-38)	26 (21-36)	0.31
Gender				
Male (n, %)	1389 (71%)	128 (77%)	1261 (70%)	0.054
Female (n, %)	579 (29%)	38 (23%)	541 (30%)	
IBD subtype				
CD (n, %)	1779 (90%)	149 (90%)	1630 (91%)	0.77
UC (n, %)	189 (10%)	17 (10%)	172 (10%)	
Disease duration, months (median, IQR)	36.0 (10.0-72.0)	37.5 (10.5-72.5)	36.0 (10.0-72.0)	0.68
Smoking status				
Never (n, %)	1792 (91%)	150 (90%)	1642 (91%)	0.10
Ex (n, %)	87 (4%)	4 (3%)	83 (5%)	
Current (n, %)	89 (5%)	12 (7%)	77 (4%)	
Concurrent treatment at screen				
Steroids (n, %)	60 (3%)	6 (4%)	54 (3%)	0.66
Immunomodulator (n, %)	708 (36%)	56 (34%)	653 (36%)	0.53
IFX duration, months (median, IQR)	9.6 (7.1-15.1)	9.7 (7.4-15.3)	9.4 (6.9-14.0)	0.17
IFX infusions, total (median, IQR)	7 (6-10)	7 (6-10)	7 (6-9)	0.14
Concurrent treatment during IFX				
Oral steroids (n, %)	4 (0.2%)	1 (0.6%)	3 (0.2%)	0.77
Immunomodulator (n, %)	1109 (56%)	95 (57%)	1014 (56%)	0.81

Abbreviations: CD, Crohn's disease; IFX, infliximab; IBD, inflammatory bowel disease; IQR, interquartile range; n, frequency; UC, ulcerative colitis.

receiving concurrent immunosuppression with oral steroids or immunomodulator, although this did not reach statistical significance (789.5 per 100 000 population per year for monotherapy vs 1317.0 for combination therapy, p = 0.34).

3.4.2 | The incidence of active TB according to screening result for latent TB infection

The identification of 52 patients who were diagnosed with latent TB infection prior to commencement of IFX therapy, but did not receive TB chemoprophylaxis, allowed quantification of the risk of developing active TB in this high-risk setting. These patients did not receive TB chemoprophylaxis for four reasons: (a) uncertainty among treating physicians over the requirement for treatment of latent TB infection prior to IFX therapy, 39% (20/52 patients); (b) patient refusal, 29% (15/52); (c) positive screening result missed, 19% (10/52) and (d) concern from treating physician over risk of AE, 14% (7/52). Six of the 52 patients (12%) developed active TB. As expected, TB chemoprophylaxis for latent TB infection during IFX therapy significantly reduced this risk (2.6% (3/114) of those who received TB chemoprophylaxis vs 12% (6/52) of those who did not receive TB chemoprophylaxis, $\chi^2 = 3.92$, $P = 0.048$). The overall incidence of active TB with IFX therapy was significantly higher in patients with latent TB infection compared to those without latent TB infection (5.4% (9/166) vs 0.7% (12/1802), OR = 8.55 [95% CI: 3.55–20.61], $P < 0.001$) (Figure 1). However, there was no significant difference in TB incidence between patients without latent TB infection who did or did not receive TB chemoprophylaxis (0.71% (3/424) vs 0.65% (9/1378), $\chi 2 = 0.05$, p = 0.83). Twelve patients with a negative TB screen developed active TB following IFX therapy (0.7% 12/1802 of all patients with a negative screen) (Table 4). The median interval to development of active TB was significantly longer in those with a negative TB screen when compared to those with a positive TB screen (248 days (IQR 136-492) vs 124 days (IQR 30-218), $z = -2.203$, $P = 0.028$) (Table S2).

4 | THE INCIDENCE OF ACTIVE TB ACCORDING TO TB CHEMOPROPHYLAXIS STRATEGY

There was no significant difference in the incidence of active TB between the targeted and universal TB chemoprophylaxis groups (673.3 per 100 000 population per year vs 891.5 per 100 000 population per year, $P = 0.60$), or in the frequency (0.70% (10/1433) vs 1.04% (5/483), $\chi^2 = 0.18$, $P = 0.67$) (Figure 2). Importantly, all patients who developed active TB were subsequently cured with no deaths, regardless of initial screening result or use of TB chemoprophylaxis.

TABLE 3 Characteristics of TB chemoprophylaxis groups

Clinical characteristics	Targeted strategy (n = 1433)	Universal strategy (n = 483)	*P* value
Age, years (median, IQR)	27 (22-36)	26 (19-33)	0.20
Gender			
Male (n, %)	1010 (71%)	338 (70%)	0.83
Female (n, %)	423 (30%)	145 (30%)	
IBD subtype			
CD (n, %)	1305 (91%)	427 (88%)	0.09
UC (n, %)	128 (9%)	56 (12%)	
Disease duration, months (median, IQR)	36.2 (10.3-72.0)	37.3 (10.0-72.3)	0.70
Smoking status			
Never	1302 (91%)	437 (91%)	0.79
Ex	67 (5%)	21 (4%)	
Current	64 (4%)	25 (5%)	
IFX duration, months (median, IQR)	9.7 (7.2-15.2)	9.8 (7.8-15.5)	0.18
IFX infusions, total (median, IQR)	7 (6-9)	7 (6-10)	0.16
Concurrent treatment during IFX	3 (0.2%)	1(0.2%)	0.99
Oral steroids (n, %)			
Immunomodulator (n, %)	820 (57%)	266 (55%)	0.41
Comorbidities	15 (1%)	5 (1%)	0.98

Abbreviations: CD, Crohn's disease; IFX, infliximab; IBD, inflammatory bowel disease; IQR, interquartile range; n, frequency; UC, ulcerative colitis

4.1 | Adverse events from TB chemoprophylaxis

As expected, there were significantly fewer AE related to TB chemoprophylaxis in the targeted group compared to the universal group (0.35% (5/1433) vs 6.8% (33/483), $\chi^2 = 78.11$, $P < 0.05$) (Table 5). AE were reported more frequently in patients who received combination isoniazid and rifampicin (20% (18/90) vs isoniazid alone (3.1% (14/448), $\chi^2 = 39.72$, $P < 0.01$). However overall, AE were relatively uncommon and notably none led to the complete discontinuation of TB chemoprophylaxis. Data on drug resistance patterns to isoniazid and rifampicin in patients who developed active TB were not available.

5 | DISCUSSION

This is the largest study to date reporting the incidence of active TB in patients receiving anti-TNF therapy in a high TB burden region, and the first study in China in patients with IBD. In this retrospective hospital-based cohort study, the incidence of active TB was 999.1 per 100 000 population per year. This equates to a 16-fold increased risk when compared to the incidence of TB in the general population in China, most recently reported as 61 per 100 000 population per year.[4] This strikingly high incidence underlines the importance of implementing a robust strategy to reduce the risk of active TB in patients receiving anti-TNF therapy where TB is endemic. However, the proportion of patients found to have latent TB infection on screening prior to initiation of IFX was relatively low (8.4% 166/1968), given an estimated population prevalence of over 25% in China.[24] This reflects a number of factors beyond the known limitations of screening assays, including understandable reluctance from physicians to prescribe IFX in patients with proven latent TB infection, the younger age of patients and the higher socioeconomic status of patients typically able to afford IFX therapy. A similarly low proportion of patients in high TB burden regions were found to have latent TB infection on screening prior to initiation of anti-TNF therapy in a meta-analysis (10.3%).[17]

As expected, the risk of active TB in patients with IBD and latent TB infection receiving IFX was significantly higher than in patients without latent TB infection (OR 8.55). The use of chemoprophylaxis significantly reduced, but did not abolish this risk, with 2.6% of patients still developing active TB. Chemoprophylaxis failure may represent drug resistance or poor compliance, with a previous meta-analysis demonstrating that both TB chemoprophylaxis regimens used in this study (3 months isoniazid and rifampicin, or 6 months isoniazid) have comparable efficacy.[25] This study also highlights the challenges of ensuring patients who initiate anti-TNF therapy that receive TB chemoprophylaxis following a positive screening result for latent TB infection. This did not occur in 52 patients, and underlines the need for institution of fail-safe strategies for the follow-up of TB screening results, education and support of physicians who may be unfamiliar with the management of latent TB infection, and careful counselling of patients about the importance of TB chemoprophylaxis. Furthermore, and consistent with previous research, this study found that active TB may still develop in patients with a negative TB screen, occurring in 12 patients (0.7% 12/1802 of all patients with a negative screen).[16,26,27] While a higher rate of active TB following IFX with a negative TB screen (8.8% 7/79 patients) was described in a study from India, this may represent higher local prevalence of TB, or bias in a much smaller dataset.[27] Although concurrent immunosuppression is known to reduce screening sensitivity, only 2/12 patients in our study were on oral steroids and/or immunomodulator at the time of the screen.[12] Furthermore, the majority (9/12) were screened using the more sensitive IGRA, while one third had both a negative IGRA and TST.

Notably, the majority of patients who developed TB following IFX had pulmonary disease (18/21) while only three patients had extrapulmonary disease. This is in contrast to previous studies which have reported much higher rates of extrapulmonary TB (57-91%) following IFX.[7,16] This may reflect earlier and more aggressive investigation for active TB during IFX therapy in China, where awareness

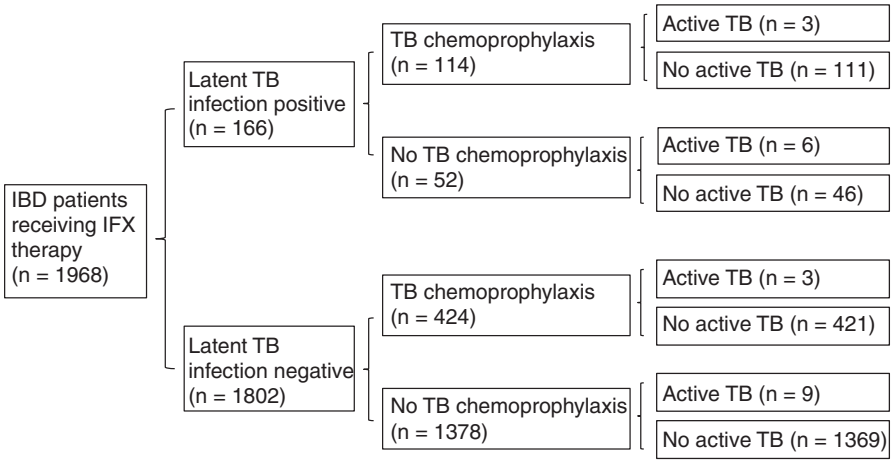


FIGURE 1 Analysis of the incidence of active TB in the latent TB infection and no latent TB infection groups with IFX therapy

IBD, inflammatory bowel disease; IFX, infliximab; TB, tuberculosis

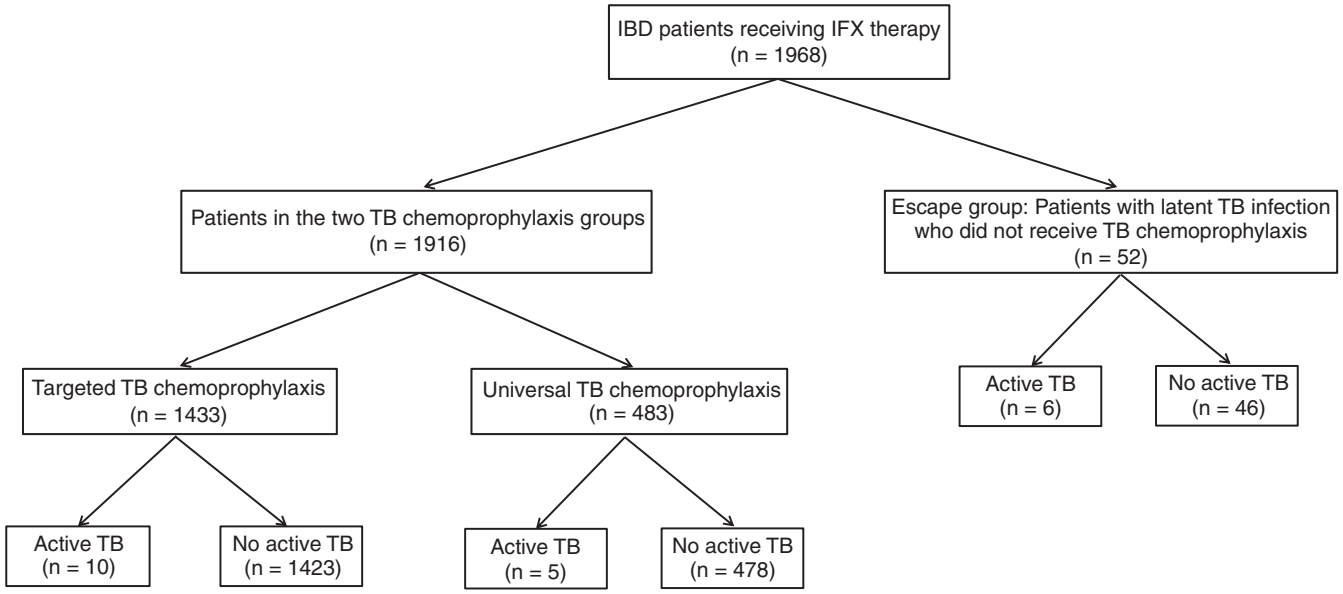
TABLE 4 Characteristics of patients with a negative TB screen who developed active TB following IFX therapy

Age, years/Gender	TST	IGRA	Chest X-ray	Chest CT	Steroids/ IM	Universal TB chemoprophylaxis	Site of TB	Interval to TB infection, months
46/M	(-)	(-)	(-)	(-)	No	ND	Lung	8.6
25/F	ND	(-)	(-)	ND	No	ND	Lung	10.1
42/M	(-)	(-)	(-)	ND	IM	INH	Lung	48.3
29/F	(-)	ND	(-)	ND	No	INH	Lung	4.7
29/M	ND	(-)	(-)	(-)	No	ND	Lung, CNS	3.8
19/M	(-)	(-)	(-)	ND	No	ND	Lung	4.4
23/M	ND	(-)	(-)	(-)	No	ND	Lung	4.9
37/M	ND	(-)	(-)	ND	Both	ND	Lung	10.2
25/M	ND	(-)	(-)	ND	No	INH + RFP	Lung	7.7
24/M	(-)	ND	(-)	ND	No	ND	Lung	36.4
20/M	(-)	(-)	ND	(-)	No	ND	Lung, peritoneum	18.2
25/M	(-)	ND	(-)	ND	No	ND	Lung	2.3

is high among treating physicians, thereby reducing delays in diagnosis and extrapulmonary spread. It might also be explained by differences in the diagnosis of extrapulmonary disease, most notably interpretation of lymph node involvement.

The interval to active TB infection was significantly longer in patients with a negative initial screen, with two cases occurring at least 3 years after commencement of IFX therapy, although most (9/12) occurred in the first year. Importantly, the delayed development of active TB in some cases may represent new TB infection, rather than re-activation of latent TB infection. Our finding that universal TB chemoprophylaxis at initiation of IFX therapy did not reduce subsequent incidence of active TB further supports the importance of new TB infection in this setting. Indeed, a very recent meta-analysis has demonstrated that the risk of active TB following anti-TNF therapy is critically dependent upon local TB burden, yet the proportion of patients who tested positive for latent TB infection was similar between low and high TB burden countries.[17] Thus, physicians must be aware of the need for careful monitoring for symptoms and signs of active TB in all patients receiving anti-TNF therapy, regardless of the TB screening result or the use of TB chemoprophylaxis.

This leads to the critical question of how best to reduce the risk of active TB in patients receiving anti-TNF therapy where TB is endemic. Importantly, this study found no difference in efficacy between targeted and universal chemoprophylaxis strategies. Adverse events related to TB chemoprophylaxis were, however, significantly less frequent in the targeted group. AE were reported in 5.6% of patients receiving universal chemoprophylaxis, with the most significant, hepatotoxicity, occurring in 2.1%. Hepatotoxicity is a major adverse effect of isoniazid and increases markedly with age. The relatively high incidence of hepatotoxicity in our cohort, which had a median age below 35 is notable, with an incidence of just 0.2% in this younger age group reported by a systematic review.[28] In our study, hepatotoxicity was reported by the treating physician, and therefore the higher incidence may represent variation in definition, or it may represent the effect of concurrent therapy for IBD, such as thiopurines or methotrexate. Remarkably,



IBD, inflammatory bowel disease; IFX, infliximab; TB, tuberculosis

FIGURE 2 Analysis of active TB infection in the two TB chemoprophylaxis strategy groups with IFX therapy

TABLE 5 Frequency of AE with TB chemoprophylaxis in the targeted and universal strategy groups

Variable	Targeted strategy (n = 1433)	Universal strategy (n = 483)	*P* value
Patients with latent TB-positive screen	55	59	
Chemoprophylaxis (n)	55	483	
INH 6 months (n, %)	43 (78%)	405 (84%)	0.29
INH + RFP 3 months (n, %)	12 (22%)	78 (16%)	
Patients with AE (n, %)	5 (0.4%)	27 (5.6%)	<0.05
Frequency of AE (n, %)	5 (0.4%)	33 (6.8%)	<0.05
Type of AE (n, %)			
Hepatotoxicity	1 (0.1%)	10 (2.1%)	<0.05
Skin rash	1 (0.1%)	5 (1.0%)	<0.05
Gastrointestinal symptoms	3 (0.2%)	14 (2.9%)	<0.05
Dizziness	0	2 (0.4%)	
Arthralgia	0`	2 (0.4%)	
Patients with ≥ 2 types of AE (n, %)	0	6 (1.2%)	
AE leading to discontinuation (n)	0	0	

Abbreviations: AE, adverse events; INH, isoniazid; LTBI n, frequency; RFP, rifampicin.

no AE led to complete discontinuation of TB chemoprophylaxis, which may in part be explained by the younger age of our cohort, with increasing age and co-morbidities established risk factors for intolerance of chemoprophylaxis.[29] The use of universal chemoprophylaxis may also theoretically increase the risk of drug resistance, and is associated with the need for additional blood tests and follow-up to monitor for AE. Given that universal chemoprophylaxis does not significantly reduce the incidence of active TB, this study suggests that targeted chemoprophylaxis may be the optimal strategy in regions where TB is endemic. However, we emphasise that a robust system of TB screening must be in place, and recognise the challenges and associated costs of this. Only a single study has previously addressed the question of TB chemoprophylaxis during anti-TNF therapy following a negative TB screen. Pooled data from trials of certolizumab in rheumatoid arthritis, psoriasis, psoriatic arthritis and axial spondyloarthritis suggested that isoniazid chemoprophylaxis in patients with a negative TST did not significantly reduce the incidence of TB, but the numbers

were small, with just one patient developing active TB following chemoprophylaxis.[30]

The present study has some important limitations. Firstly, there was no healthy age-matched control group, and thus the relative risk of active TB during IFX therapy can only be estimated using population data from the WHO. Secondly, IFX was the only anti-TNF therapy assessed, although studies suggest the risk of developing active TB is similar with adalimumab.[31] Thirdly, one must be cautious in extrapolating the data to other diseases where anti-TNF therapy is used, as it appears that the treatment indication may modulate the risk of developing active TB. For example, the risk of active TB in rheumatoid arthritis is significantly increased independently of anti-TNF therapy.[31] Finally, we acknowledge the potential risk of bias in the physician selection of targeted or universal TB chemoprophylaxis in this retrospective study, but highlight that differing practice across China has predominantly been shaped by variance in the adoption of historical guidelines, and not by perceived risk of TB.[18]

In conclusion, this is the largest study to date assessing TB chemoprophylaxis strategies in patients receiving anti-TNF therapy where TB is endemic. Universal chemoprophylaxis was not associated with a reduced risk of active TB when compared to a targeted chemoprophylaxis strategy, and AE were more common. This supports the use of targeted TB chemoprophylaxis when anti-TNF therapy is initiated in TB endemic regions. With increasing use of anti-TNF therapy in countries such as China and India, which carry the greatest burden of TB in the world, this study provides a valuable resource to guide preventive strategies. It may also aid decision making when treating high-risk groups, such as migrants from endemic regions, in countries where the overall incidence of TB is lower.

ACKNOWLEDGEMENTS

We would like to thank the following for their great help and support with this work: all participating units and participating doctors; Ren Mao from The First Affiliated Hospital of Sun Yat-sen University; Liangru Zhu from Union Hospital, Tongji Medical College, Huazhong University of Science and Technology; Yihong Fan from The First Affiliated Hospital of Zhejiang University of Traditional Chinese Medicine; Naizhong Hu from The First Affiliated Hospital of Anhui Medical University; Yuqin Li from The First Affiliated Hospital of Jilin University; Yufang Wang from Huaxi Hospital Affiliated to Sichuan University; Yan Jia from Beijing Military Region General Hospital; Wen Tang from The Second Affiliated Hospital of Suzhou University; Chengdang Wang from The First Affiliated Hospital of Fujian Medical University; Hong Yang from Peking Union Medical College Hospital; Zhanju Liu from The Tenth People's Hospital Affiliated to Tongji University; Hongjie Zhang from Jiangsu Provincial People's Hospital; Yinglei Miao from The First Affiliated Hospital of Kunming Medical University; Chunxiao Chen from The First Affiliated Hospital of Zhejiang University School of Medicine; Lianjie Lin from Shenyang Shengjing Hospital; Wensong Ge from Xinhua Hospital, Shanghai Jiao Tong University School of Medicine and Kaichun Wu from Xijing Hospital Affiliated to the Fourth Military Medical University. This work was supported by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Declaration of personal interests: LY, TPC, ZW, LL, YQ, ZL, ZR, JQ, KW, XG, MC and QC declare that they have no competing interests. SPLT declares the following: *Grants/Research Support*: AbbVie, Buhlmann, Celgene, IOIBD, Janssen, Lilly, Takeda, UCB, Vifor and Norman Collisson Foundation. *Consulting Fees*: AbbVie, Allergan, Amgen, Arena, Asahi, Astellas, Biocare, Biogen, Boehringer Ingelheim, Bristol-Myers Squibb, Buhlmann, Celgene, Chemocentryx, Cosmo, Enterome, Ferring, Giuliani SpA, GSK, Genentech, Immunocore, Immunometabolism, Indigo, Janssen, Lexicon, Lilly, Merck, MSD, Netbiotix, Neovacs, Novartis, NovoNordisk, NPS Pharmaceuticals, Pfizer, Proximagen, Receptos, Roche, Sensyne, Shire, Sigmoid Pharma, SynDermix, Takeda, Theravance, Tillotts, Topivert, UCB, VHsquared, Vifor and Zeria. *Speaker fees*: AbbVie, Amgen, Biogen, Ferring, Janssen, Shire and Takeda. No stocks or share options.

Ethics approval: The study was approved by Clinical Research Ethics Committee of Sir Run Run Shaw Hospital Affiliated to Zhejiang University School of Medicine, with Institutional Review Board (IRB) approval for all hospitals involved in the study.

Patient and public involvement: This was a retrospective observational study, and there was no involvement from patients or public in the research design or process.

AUTHORSHIP

Guarantor of the article: Professor Qian Cao.

Author contributions: LY and TPC contributed equally to this work and are co-first authors. LY, TPC and QC participated in conception, design and coordination of the study; LY, ZW, LL,YQ, ZL, ZR, JQ, KW, XG, PH and MC participated in acquisition of data; LY, TPC, ZW and QC participated in analysis and interpretation of data; LY and ZW participated in statistical analysis; LY participated in obtaining funding; LY, TPC and SPLT participated in drafting the manuscript; LY, TPC, ZW, SPLT and QC participated in revision of manuscript for important intellectual content.

All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this published article.

ORCID

Thomas P. Chapman https://orcid.org/0000-0002-5298-4780

REFERENCES

1. Rogler G, Bernstein CN, Sood A, et al. Role of biological therapy for inflammatory bowel disease in developing countries. *Gut*. 2012;61:706–12.

2. Billiet T, Rutgeerts P, Ferrante M, et al. Targeting TNF-alpha for the treatment of inflammatory bowel disease. *Expert Opin Biol Ther*. 2014;14:75–101.
3. Harris J, Keane J. How tumour necrosis factor blockers interfere with tuberculosis immunity. *Clin Exp Immunol*. 2010;161:1–9.
4. World Health Organization. Global tuberculosis report 2019. https://www.who.int/tb/publications/global_report/en/. Accessed 21 July, 2020.
5. Wang Q, Wen Z, Cao Q. Risk of tuberculosis during infliximab therapy for inflammatory bowel disease, rheumatoid arthritis, and spondyloarthropathy: a meta-analysis. *Exp Ther Med*. 2016;12:1693–1704.
6. Seong SS, Choi CB, Woo JH, et al. Incidence of tuberculosis in Korean patients with rheumatoid arthritis (RA): effects of RA itself and of tumor necrosis factor blockers. *J Rheumatol*. 2007;34:706–11.
7. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med*. 2001;345:1098–104.
8. Park DI, Hisamatsu T, Chen M, et al. Asian Organization for Crohn's and Colitis and Asia Pacific Association of Gastroenterology consensus on tuberculosis infection in patients with inflammatory bowel disease receiving anti-tumor necrosis factor treatment. Part 1: risk assessment. *Intest Res*. 2018;16:4–16.
9. Park DI, Hisamatsu T, Chen M, et al. Asian Organization for Crohn's and Colitis and Asia Pacific Association of Gastroenterology consensus on tuberculosis infection in patients with inflammatory bowel disease receiving anti-tumor necrosis factor treatment. Part 2: management. *J Gastroenterol Hepatol*. 2018;33:30–36.
10. Rahier JF, Magro F, Abreu C, et al. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis*. 2014;8:443–68.
11. World Health Organization. Latent Tuberculosis infection: Updated and consolidated guidelines for programmatic management. 2018. https://www.who.int/tb/publications/2018/latent-tuberculosis-infection/en/. Accessed 23 July, 2019.
12. Shahidi N, Fu YT, Qian H, et al. Performance of interferon-gamma release assays in patients with inflammatory bowel disease: a systematic review and meta-analysis. *Inflamm Bowel Dis*. 2012;18:2034–42.
13. Wong SH, Ip M, Tang W, et al. Performance of interferon-gamma release assay for tuberculosis screening in inflammatory bowel disease patients. *Inflamm Bowel Dis*. 2014;20:2067–72.
14. Belard E, Semb S, Ruhwald M, et al. Prednisolone treatment affects the performance of the QuantiFERON gold in-tube test and the tuberculin skin test in patients with autoimmune disorders screened for latent tuberculosis infection. *Inflamm Bowel Dis*. 2011;17:2340–9.
15. Mow WS, Abreu-Martin MT, Papadakis KA, et al. High incidence of anergy in inflammatory bowel disease patients limits the usefulness of PPD screening before infliximab therapy. *Clin Gastroenterol Hepatol*. 2004;2:309–13.
16. Abitbol Y, Laharie D, Cosnes J, et al. Negative screening does not rule out the risk of tuberculosis in patients with inflammatory bowel disease undergoing anti-TNF treatment: a descriptive study on the GETAID cohort. *J Crohns Colitis*. 2016;10:1179–85.
17. Kedia S, Mouli VP, Kamat N, et al. Risk of tuberculosis in patients with inflammatory bowel disease on infliximab or adalimumab is dependent on the local disease burden of tuberculosis: a systematic review and meta-analysis. *Am J Gastroenterol*. 2020;115:340–349.
18. Rampton DS. Preventing TB in patients with Crohn's disease needing infliximab or other anti-TNF therapy. *Gut*. 2005;54:1360–1362.
19. Banerjee R, Pal P, Hilmi I, et al. Sa1801; emerging IBD demographics in South Asia and Middle East: a Pilot Study from the IBD Emerging Nations' Consortium (IBDENC). *Gastroenterology*. 2019;156(6):S-406.
20. Chinese Cooperative Group For The Study On IBD, Chinese Society Of G, Ouyang Q, et al. Consensus on the management of inflammatory bowel disease in China in 2007. *J Dig Dis*. 2008;9:52–62.
21. Expert group on the prevention and management of tuberculosis in the application of tumor necrosis factor antagonists. Expert consensus on the prevention and management of tuberculosis in the use of tumor necrosis factor antagonists. *Chin J Rheumatol*. 2013;17:508–512.
22. To KW, Reino JJ, Yoo DH, et al. Tumour necrosis factor antagonist and tuberculosis in patients with rheumatoid arthritis: an Asian perspective. *Respirology*. 2013;18:765–73.
23. Liu J, Yan J, Wan Q, et al. The risk factors for tuberculosis in liver or kidney transplant recipients. *BMC Infect Dis*. 2014;14:387.
24. Houben RM, Dodd PJ. The global burden of latent tuberculosis infection: a re-estimation using mathematical modelling. *PLoS Med*. 2016;13:e1002152.
25. Ena J, Valls V. Short-course therapy with rifampin plus isoniazid, compared with standard therapy with isoniazid, for latent tuberculosis infection: a meta-analysis. *Clin Infect Dis*. 2005;40:670–6.
26. Byun JM, Lee CK, Rhee SY, et al. Risks for opportunistic tuberculosis infection in a cohort of 873 patients with inflammatory bowel disease receiving a tumor necrosis factor-alpha inhibitor. *Scand J Gastroenterol*. 2015;50:312–20.
27. Puri AS, Desai D, Sood A, et al. Infliximab-induced tuberculosis in patients with UC: experience from India-a country with high prevalence of tuberculosis. *J Gastroenterol Hepatol*. 2017;32:1191–1194.
28. Kunst H, Khan KS. Age-related risk of hepatotoxicity in the treatment of latent tuberculosis infection: a systematic review. *Int J Tuberc Lung Dis*. 2010;14:1374–81.
29. Smith BM, Schwartzman K, Bartlett G, et al. Adverse events associated with treatment of latent tuberculosis in the general population. *CMAJ*. 2011;183:E173–9.
30. Mariette X, Vencovsky J, Lortholary O, et al. The incidence of tuberculosis in patients treated with certolizumab pegol across indications: impact of baseline skin test results, more stringent screening criteria and geographic region. *RMD Open*. 2015;1:e000044.
31. Solovic I, Sester M, Gomez-Reino JJ, et al. The risk of tuberculosis related to tumour necrosis factor antagonist therapies: a TBNET consensus statement. *Eur Respir J*. 2010;36:1185–206.

SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

How to cite this article: Ye L, Chapman TP, Wen Z, et al. Targeted versus universal tuberculosis chemoprophylaxis in 1968 patients with inflammatory bowel disease receiving anti-TNF therapy in a tuberculosis endemic region. *Aliment Pharmacol Ther*. 2021;53:390–399. https://doi.org/10.1111/apt.16130