Prophylactic Antitubercular Therapy Is Associated With Accelerated Disease Progression in Patients With Crohn's Disease Receiving Anti-TNF Therapy: A Retrospective Multicenter Study

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INTRODUCTION: **Prophylactic antitubercular therapy (ATT) is widely prescribed in patients with Crohn's disease (CD) receiving antitumor necrosis factor (anti-TNF) treatment. However, antitubercular agents have been demonstrated to possess profibrotic effects. We aimed to evaluate whether ATT accelerated disease progression in patients with CD receiving anti-TNF treatment.**

METHODS: **A retrospective, multicenter study was performed in CD patients presented with inflammatory behavior (B1) and treated with anti-TNF agents. Disease progression was defined as the development of a stricturing (B2) or penetrating (B3) phenotype. ATT users were propensity score-matched with non-ATT users. Survival and multivariable Cox analyses were used to identify factors associated with disease progression.**

RESULTS: **We enrolled 441 patients, including 295 ATT users and 146 non-ATT users, with a median follow-up of 3.15 years (interquartile range: 1.6–4.7). The cumulative rates of disease progression in the ATT group were constantly higher than those in the non-ATT group after 1-, 3-, 5-, and 10-year follow-ups, respectively ($P = 0.031$). Multivariable Cox analysis identified ATT as an independent risk factor for disease progression using both the whole (hazard ratio = 2.22; 95% confidence interval: 1.11–4.48; $P = 0.025$) and propensity score-matched cohorts (hazard ratio = 2.35; 95% confidence interval: 1.07–5.14; $P = 0.033$). In subgroup analysis, patients receiving ATT ≥4.5 months had a significantly higher rate of disease progression compared with patients receiving ATT <4.5 months ($P = 0.005$) and non-ATT treatment ($P = 0.036$).**

DISCUSSION: **Prophylactic ATT with duration over 4.5 months was associated with disease progression in patients with CD receiving anti-TNF treatment.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A808

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INTRODUCTION

Crohn's disease (CD) is a complex and long-lasting disorder of the gastrointestinal tract, with gradual progression to stricturing or penetrating complications. Biologics such as antitumor necrosis factor-α (anti-TNFα) agents have revolutionized the treatment of CD with proven efficacy in achieving clinical remission (1) and mucosal healing (2,3). However, the risk of opportunistic infections, such as activation of latent tuberculosis infection (LTBI), remains a concern (4–6). To prevent LTBI activation, tuberculosis exposure history, interferon-gamma release assays, tuberculin skin test, and chest imaging are suggested to perform before initiating anti-TNF therapy. Prophylactic antitubercular therapy (ATT), such as isoniazid (INH) and rifampicin (RFP) monotherapy or combination therapy, is recommended for CD patients with LTBI, which has been proven as an effective strategy to decrease TB activation for patients with CD receiving anti-TNF therapy (7).

Nevertheless, prophylactic ATT can cause potential side effects. Much attention has been drawn to the hepatotoxicity of

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ATT agents; the "indolent" effects of these agents on the disease course of CD thus may be neglected. A recent study has raised a concern over patients with CD who had a history of empirical ATT before CD diagnosis because they were more apt to develop intestinal stricture (8). Indeed, several studies have demonstrated that ATT agents, including INH and RFP, have the potential to facilitate fibrosis (9,10). Noteworthily, once intestinal fibrosis and its associated complications such as stricture or penetration occur, there are no specific antifibrotic drugs that can reverse the disease progression yet. Eventually, up to 70% of patients with CD undergo surgery in their lifetime (11,12). With the strikingly increasing use of biologics in patients with CD, it is of significant importance to clarify the impact of ATT on disease progression in patients with CD and identify a well balance between benefits and risks of ATT for patients with CD.

Our previous study revealed that universal ATT was not correlated with a reduction of TB activation when compared with targeted ATT, whereas adverse events such as hepatotoxicity, skin rash, and gastrointestinal symptoms were significantly higher in the universal strategy (13). However, it remains unknown whether prophylactic ATT can accelerate disease progression in patients with CD receiving anti-TNF treatment. The aim of our study was to compare the incidences of disease progression from the Montreal Classification B1 (nonstricturing and nonpenetrating) to B2/B3 (stricturing/penetrating) between ATT users and non-ATT users in patients with CD receiving anti-TNF treatment. In addition, the correlation between ATT duration and disease progression was evaluated.

METHODS

Study design and population

We conducted a multicenter retrospective cohort study at 3 tertiary referral hospitals in China, consisting of The First Affiliated Hospital of Sun Yat-sen University; Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University; and The Sixth Affiliated Hospital of Sun Yat-sen University. All eligible patients had been followed up at inflammatory bowel disease (IBD) centers since January 2008. This study was approved by an Institutional Review Board of The First Affiliated Hospital of Sun Yat-sen University (number: 2021-527). Informed consent was waived because of the retrospective nature of this study.

The inclusion criteria included CD patients with (i) a definite diagnosis of CD based on a combination of medical history, serological findings, endoscopic appearances, histological examinations, and imagings according to the European Crohn's and Colitis Organization guidelines (14), (ii) inflammatory phenotype (B1) according to the Montreal Classification when receiving anti-TNF therapy including infliximab or adalimumab, and (iii) more than 3 months of follow-up.

The exclusion criteria consisted of CD patients with (i) stricture (B2) or penetration (B3), (ii) primary nonresponse to anti-TNF therapy, (iii) secondary nonresponse to anti-TNF therapy preceding disease progression, (iv) previous exposure to any types of antitubercular agents, (v) a preexisting history of abdominal surgeries, or (vi) lack of baseline and/or follow-up imaging/colonoscopy to precisely evaluate disease behaviors. The diagnosis of stricture was defined by the inability of colonoscopy to pass through the narrowed lumina or by the presence of 2 of the following 3 imaging indexes, including bowel wall thickening, luminal narrowing, along with prestenotic dilation on magnetic resonance enterography or computed tomography enterography (15). Penetration comprised any of the following forms, including enterocutaneous, enteroenteric, enterovesical, enterovaginal, and enterouterine fistulas (16). Primary nonresponse and secondary nonresponse to anti-TNFs were defined according to the change of the Clinical Disease Activity Index (17).

Antitubercular therapy

The recommended ATT regimens vary among different countries, according to the TB epidemiological distributions (18). The adopted regimens in China include at least 3 months of daily INH monotherapy or 3 months of daily INH plus RFP (19). Because false-negative results can occur during the LTBI screening and China has a popular policy of BCG vaccination (20), in our countries' clinical practice, there are 2 prophylactic ATT strategies including universal and targeted chemoprophylaxes. For universal chemoprophylaxis, patients will be recommended to receive prophylactic ATT, regardless of the results of LTBI. For targeted chemoprophylaxis, only patients who have LTBI will be recommended prophylactic ATT. Therefore, in this study, patients were divided into an ATT group and non-ATT group based on whether they received any of the aforementioned regimens, rather than the results of LTBI tests.

Clinical parameters and medical therapy

Clinical characteristics included sex, age at symptom onset, age at CD diagnosis (A1: ≤16 years; A2: between 17 and 40 years; and A3: >40 years), and disease location (L1: terminal ileum; L2: colon; L3: ileocolon; and L4: isolated upper gastrointestinal involvement) (21), perianal disease, smoking history (categorized as current smoker, ex-smoker, and non-smoker), and medical therapy before and after anti-TNF therapy were documented. Serum levels of C-reactive protein were recorded when initiating anti-TNF treatment. Other parameters such as duration of follow-up (defined as from the last follow-up to CD diagnosis), diagnostic delay (defined as from the establishment of diagnosis to the occurrence of symptoms) (22), and duration of ATT treatment were calculated.

Outcome

The primary outcome was that CD patients who were diagnosed with an inflammatory phenotype at initiation of anti-TNF therapy progressed to a stricturing or penetrating phenotype during the follow-up.

Statistical analysis

All statistical analyses were performed using SPSS version 24.0 (SPSS, Chicago, IL) and R version 3.2.3 (R Foundation for Statistical Computing) statistical software. Continuous variables were shown as median and interquartile range (IQR) or mean and SD and compared using the Student *t* test or Mann-Whitney *U* test. Categorical variables were compared using the χ^2 test or Fisher exact test.

The methodology of propensity score (PS)-matching was used to balance confounding factors such as age, disease location, and smoking history. Prophylactic ATT users were matched with non-ATT users at a 2:1 ratio with the logit of the PS less than 0.2 SD using a greedy distance-based matching algorithm. The absolute standardized difference was used to assess the balance of the 2 groups after matching, with a value less than 0.2 indicating a good balance (23).

Table 1. Demographic and baseline characteristics of study population

	Whole cohort (N = 441)	ATT group[a] (N = 295)	Non-ATT group (N = 146)	*P*
Age at symptom onset, yr, mean ± SD	22.0 ± 7.8	21.8 ± 8.0	22.5 ± 7.3	0.364
Age at diagnosis, yr, mean ± SD	23.5 ± 8.2	23.3 ± 8.5	23.9 ± 7.6	0.435
Sex, male, n (%)	315 (71.4)	213 (72.2)	102 (69.9)	0.609
Smoking history, n (%)				**0.001**
Current smoker	13 (3.0)	13 (4.4)	n.a.[b]	
Ex-smoker	11 (2.5)	4 (1.4)	7 (4.8)	
Nonsmoker	417 (94.6)	278 (94.2)	139 (95.2)	
Duration of follow-up,[c] yr, median (IQR[b])	3.2 (1.6–4.7)	3.0 (1.6–4.6)	3.3 (1.7–4.8)	0.655
Diagnostic delay,[d] yr, median (IQR)	0.7 (0.3–1.9)	0.5 (0.3–1.6)	0.8 (0.3–2.0)	0.552
Delay in initiation of anti-TNF treatment, median[a] (IQR), yr	0.1 (0.1–0.5)	0.2 (0.1–0.5)	0.1 (0.1–0.5)	0.248
Age at diagnosis, yr, n (%)				0.096
≤16, A1	83 (18.8)	64 (21.6)	19 (13)	
17–40, A2	334 (75.7)	216 (73.1)	118 (81.4)	
>40, A3	23 (5.2)	15 (5)	8 (5.4)	
Location of disease presentation, n (%)				**<0.001**
Ileum, L1	53 (12)	30 (11.2)	23 (15.8)	
Colon, L2	29 (6.6)	19 (6.4)	10 (6.8)	
Ileocolon, L3	354 (80.3)	241 (81.7)	113 (77.4)	
Isolated upper GI, L4	5 (1.1)	5 (1.7)	n.a.[b]	0.176
Perianal disease, n (%)	267 (60.5)	176 (59.6)	91 (62.3)	0.559
CRP, mg/L, median (IQR)	13.2 (6.8–32.1)	11.9 (7.6–32.1)	14.8 (4.8–30.6)	0.376
ATT therapy regimens, n (%)				
INH monotherapy		286 (96.9)	/	
INH combined with RFP		8 (2.7)	/	
RFP monotherapy		1 (3.4)	/	
Treatment duration of anti-TNF, mo, median (IQR)	18.2 (7.0–36.2)	14.5 (7.0–29.4)	20.6 (12.1–40.6)	**0.006**
Medical therapy before anti-TNF initiation, n (%)				**<0.001**
None		91 (30.8)	79 (54.1)	
Mesalazine		39 (13.2)	20 (13.6)	
Steroid		42 (14.2)	19 (13)	
Immunomodulators		123 (41.6)	28 (19.1)	
Therapy regimens after anti-TNF initiation, n (%)				**0.001**
Monotherapy		133 (45.1)	40 (27.4)	
Combination therapy with immunomodulators		162 (54.9)	106 (72.6)	

Bold values denote statistical significance at the $P < 0.05$ level.
ATT, antitubercular therapy; CD, Crohn's disease; CRP, C-reactive protein; GI, gastrointestinal; INH, isoniazid; IQR, interquartile range; RFP, rifampicin; TNF, tumor necrosis factor.
[a]Delay in initiation of anti-TNF treatment: from CD diagnosis to anti-TNF initiation.
[b]Results were not available because there were no events in patients with current smoker and isolated upper GI involvement.
[c]Duration of the follow-up: from CD diagnosis to the last time of follow-up.
[d]Diagnostic delay: from symptom onset to CD diagnosis.

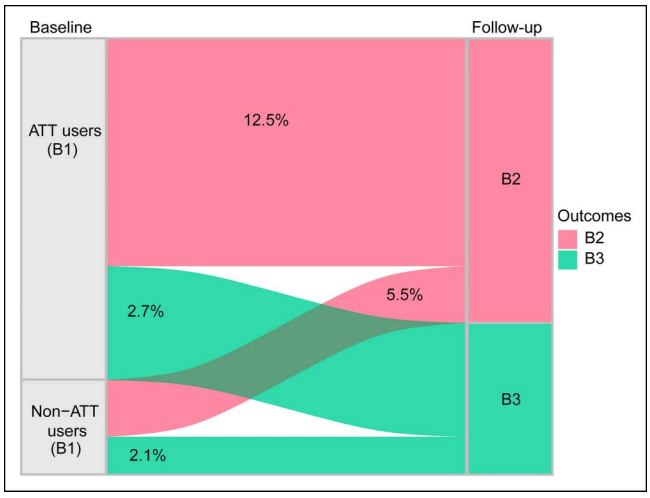

Figure 1. Progression of disease behavior from the Montreal Classification B1 (nonstricturing and nonpenetrating) to B2/B3 (stricturing/penetrating) in the whole cohort. ATT, antitubercular therapy.

Univariate analysis was used to identify factors that were associated with disease progression, and parameters with $P < 0.10$ were considered in a multivariate Cox proportional regression analysis. Multiple imputation was adopted to deal with missing data by constructing 10 complete data sets (24). Survival analysis was performed to analyze the relationship between ATT therapy and primary outcome using the Kaplan-Meier method using the whole cohort and PS-matched cohort, respectively. In the case that a statistically significant association was noted between ATT therapy and primary outcome, a duration-response relationship was further performed to confirm the causality. The optimal predictive cutoff value of ATT duration was determined by the construction of receiver operating characteristic with the Youden index (25). A 2-sided P value of < 0.05 was considered as statistically significant.

RESULTS

Baseline clinical characteristics of subjects

A total of 441 patients with CD presented with a B1 phenotype and treated with anti-TNFs were retrospectively enrolled from the 3 IBD centers, including 295 ATT users (66.9%) and 146 non-ATT users (33.1%). Table 1 summarizes the clinical characteristics of the whole cohort. There were 315 males patients (71.4%), with a mean age at symptom onset of 22.1 years. The median duration of follow-up was 3.2 years (IQR: 1.6–4.7). According to the Montreal Classification, the ATT group had a numerically higher percentage of younger patients (≤16 years) compared with the non-ATT group, albeit not statistically significant (21.6% vs 13%, $P = 0.096$). The predominate disease location in the whole cohort was L3 (80.3%), and the distribution of disease location was significantly different between the 2 groups ($P < 0.001$). Regarding smoking history, a pronounced significance was detected between the 2 groups ($P = 0.001$). The treatment duration of anti-TNFs in the ATT group (14.5, IQR: 7.0–29.4) was significantly lower than that in the non-ATT group (20.6, IQR: 12.1–40.6) ($P = 0.006$). No significant differences existed between the 2 groups regarding other parameters including C-reactive protein, percentage of L4 involvement, sex, perianal disease, duration of follow-up, and diagnostic delay.

Antitubercular regimens and progression of disease behavior

Among 295 patients with ATT, 286 patients (96.9%) received INH monotherapy (300 mg/d), 8 patients received combination therapy of INH (300 mg/d) with RFP (450 mg/d), and 1 patient received RFP monotherapy (450 mg/d) because of INH-induced hepatotoxicity. The median duration of ATT was 3 months (IQR: 3–6).

During the follow-up, 56 patients developed stricturing (45, 10.2%) or penetrating (11, 2.5%) disease complications. Supplementary Table 1 (see Supplementary Digital Content 1, http://links.lww.com/CTG/A808) provides the clinical characteristics of these patients. In the ATT group, 37 (12.5%) and 8 (5.5%) patients progressed to stenosis and penetration, respectively, whereas 8 (2.7%) and 3 (2.1%) patients developed stricturing and penetrating phenotypes in the non-ATT group, respectively. The rate of disease progression to stricture and penetration phenotypes in the ATT group was significantly higher than that in the non-ATT group ($P = 0.022$) (Figure 1).

Comparison of disease progression between ATT and non-ATT groups using the whole cohort

As demonstrated by the Kaplan-Meier survival curve (Figure 2a), the cumulative rates of disease progression in the ATT group after 1, 3, 5,

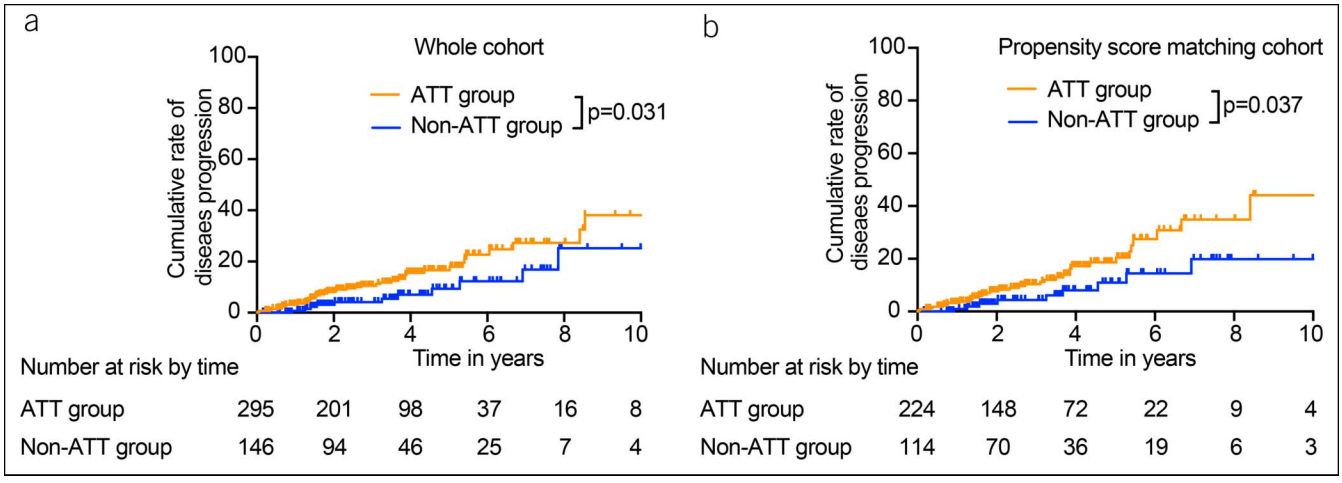

Figure 2. Cumulative rates of disease progression in the ATT group vs non-ATT group in the whole cohort (**a**) and the PS-matching cohort (**b**). ATT, antitubercular therapy; PS, propensity score.

Table 2. Risk factors for disease progression in the whole and PS-matching cohorts

	Whole cohort			PS-matching cohort		
	P (univariate)	*P* (multivariate)	HR (95% CI) in multivariate analysis	*P* (univariate)	*P* (multivariate)	HR (95% CI) in multivariate analysis
Age at symptom onset, yr	0.564			0.596		
Sex						
Female	Reference					
Male	0.743			0.861		
Smoking history						
Nonsmoker	Reference					
Current smoker	0.173			0.159		
Ex-smoker	0.971			0.967		
Diagnostic delay[a]	0.315			0.089		
Delay in initiation of anti-TNF treatment[b]	0.612			0.581		
Age at diagnosis, yr						
≤16, A1	0.912			0.931		
17–40, A2	0.467			0.351		
>40, A3	Reference					
Location of disease presentation						
Ileum, L1	Reference					
Colon, L2	0.416			0.887		
Ileocolon, L3	0.666			0.686		
Isolated upper GI, L4						
No	Reference					
Yes	0.648			0.807		
Perianal disease						
No	Reference					
Yes	0.805			0.932		
ATT usage						
Without ATT usage	Reference					
With ATT usage	0.034	**0.025**	2.22 (1.11–4.48)	0.044	**0.033**	2.35 (1.07–5.14)
Treatment duration of anti-TNFs	<0.001	**0.001**	0.97 (0.95–0.99)	0.003	**0.022**	0.94 (0.91–0.99)
Medical therapy before anti-TNF initiation						
None	Reference					
Mesalazine	0.893			0.451		
Steroid	0.487			0.234		
Immunomodulators	0.027	**0.001**	0.27 (0.13–0.58)	0.018	**0.001**	0.23 (0.05–0.47)
Therapy regimens after anti-TNF initiation						
Monotherapy	Reference			Reference		
Combination therapy with immunomodulators	0.837			0.787		

Bold values denote statistical significance at the $P < 0.05$ level.
ATT, antitubercular therapy; CD, Crohn's disease; CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; INH, isoniazid; PS, propensity score; RFP, rifampicin; TNF, tumor necrosis factor.
[a]Diagnostic delay: from symptom onset to CD diagnosis.
[b]Delay in initiation of anti-TNF treatment: from CD diagnosis to anti-TNF initiation.

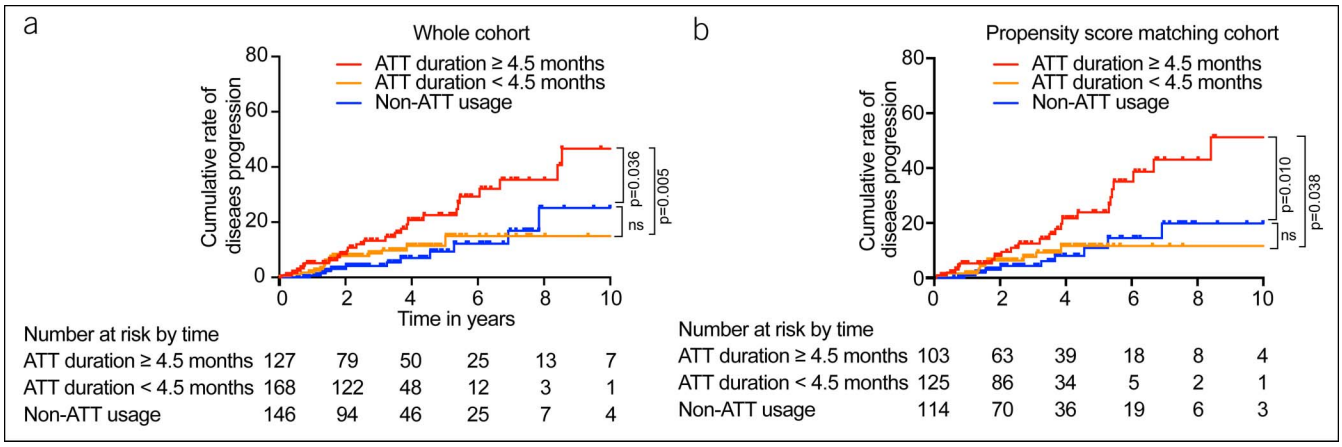

Figure 3. Comparison of cumulative rates of disease progression according to the duration of ATT (ATT ≥4.5 months, ATT <4.5 months, and non-ATT usage) in the whole cohort (**a**) and the PS-matching cohort (**b**). ATT, antitubercular therapy; PS, propensity score.

and 10 years were 3.2%, 10.6%, 18.0%, and 38.1%, respectively, which were significantly higher than those in the non-ATT group with 0.7%, 4.1%, 9.3%, and 25.2% of disease progression at the corresponding time points, respectively ($P = 0.031$).

Comparison of disease progression between ATT and non-ATT groups using the PS-matching cohort

Since age, disease location, and smoking have been previously found to be correlated with disease progression (26–28). PS matching was performed to diminish their impact at a ratio of 2:1. Among the PS-matched cohort, 342 patients were analyzed, including 228 ATT users and 114 non-ATT users. Supplementary Table 2 (see Supplementary Digital Content 1, http://links.lww.com/CTG/A808) presents the clinical characteristics of the PS-matched cohort. The overall 1-, 3-, 5-, and 10-year cumulative rates of disease progression in the ATT group were 3.2%, 11.2%, 20.5%, and 44.2%, respectively, which were significantly higher than those in the non-ATT group with 0.9%, 4.4%, 10.9%, and 19.8% of disease progression, respectively ($P = 0.037$) (Figure 2b).

Independent risk factors associated with disease progression

Using the whole cohort, univariate analysis demonstrated that ATT, immunomodulator monotherapy before anti-TNF treatment, and treatment duration of anti-TNFs were correlated with disease progression (all P values < 0.05). Multivariate analysis further identified ATT therapy as an independent risk factor of disease progression with a hazard ratio (HR) of 2.22 (95% confidence interval [CI]: 1.11–4.48; $P = 0.025$), whereas immunomodulator monotherapy before anti-TNF treatment and treatment duration of anti-TNFs were 2 protective factors against disease progression, with HRs of 0.27 (95% CI: 0.13–0.58; $P = 0.001$) and 0.97 (95% CI: 0.95–0.99; $P = 0.001$), respectively (Table 2).

Similar results were achieved using the PS-matched cohort. Multivariate analysis confirmed that ATT was an independent risk factor for disease progression (HR = 2.35; 95% CI: 1.07–5.14; $P = 0.033$), whereas immunomodulator monotherapy before anti-TNFs and treatment duration of anti-TNFs were still protective factors for disease progression (HR = 0.23, 95% CI: 0.05–0.47, $P = 0.001$; HR = 0.94, 95% CI: 0.91–0.99, $P = 0.022$, respectively). The remaining parameters, such as age, sex, disease location, and perianal disease, had no significant impacts on disease progression (Table 2).

Correlation between ATT duration and disease progression

Because ATT usage was an independent risk factor of disease progression, the impact of ATT duration on disease progression was subsequently evaluated. Based on the receiver operating characteristic and Youden index, the optimal cutoff level for ATT duration to predict disease progression was 4.5 months. Hence, the whole cohort was classified into 3 subgroups: duration of ATT ≥4.5 months (N = 127), duration of ATT <4.5 months (N = 168), and non-ATT treatment (N = 146). As shown in Figure 3a, the cumulative rate of disease progression in the ATT group ≥4.5 months was significantly higher than that in the ATT <4.5 months ($P = 0.036$) or non-ATT treatment group ($P = 0.005$). The analysis using the PS-matched cohort yielded a similar tendency. Patients with CD with ATT ≥4.5 months had a significantly higher rate of disease progression, compared with those with ATT <4.5 months ($P = 0.01$) or non-ATT treatment ($P = 0.038$) (Figure 3b).

DISCUSSION

This study was aimed to investigate the impact of ATT on progression of disease behavior in patients with CD with anti-TNF treatment. Both the whole and PS-matched cohorts identified ATT as an independent risk factor for the development of stricture and penetration complications. In addition, a duration-response relationship between ATT duration and disease progression was observed, in which patients with CD receiving ATT exceeding 4.5 months had a significantly higher risk of disease progression than those who received ATT less than 4.5 months or non-ATT treatment. The probabilities of disease progression in our study were in line with previous studies (27,29), which showed that 30%–38.7% of patients with initial inflammatory phenotypes could progress to more complicated disease phenotypes after 10 years.

In TB-endemic regions such as China, whether ATT chemoprophylaxis should be administered to all patients with CD receiving anti-TNF therapy or restricted to those with proven LTBI remains controversial in clinical practice. Our previous study showed that universal chemoprophylaxis did not reduce the risk of TB activation, compared with targeted chemoprophylaxis. Furthermore, a higher rate of adverse events, such as hepatotoxicity and gastrointestinal symptoms, was observed in the group with universal chemoprophylaxis than that with targeted chemoprophylaxis (13). After this study, the present study found that ATT was an independent risk factor for disease progression, revealing

another harmful effect of the strategy of universal chemoprophylaxis. In addition, the finding was consistent with a previous study from India showing that a diagnostic ATT to distinguish CD from intestinal TB was associated with a higher risk of disease progression (8). It is assumed that ATT predisposing disease progression may be ascribed to the activation and proliferation of intestinal stromal cells (e.g., fibroblasts, myofibroblasts, and smooth muscle cells) or immune cells, followed by the overproduction of extracellular matrix and profibrogenic cytokines (e.g., transforming growth factor-β, interleukin-17A, and interleukin-6) (9,10). However, the exact mechanism of antitubercular agent-induced intestinal fibrosis needs to be elucidated in the future. Alternatively, because the pathogenesis of TB is driven by immune responses (30), it is presumed that underlying LTBI may modulate immune responses and potentially alter disease progression of CD. So far, there is a paucity of information about this issue. A dedicated study aiming to investigate the effect of LTBI on disease progression in patients with CD will be required.

Notably, our study found that the duration of ATT exceeding 4.5 months resulted in a higher likelihood of disease progression than ATT less than 4.5 months or non-ATT treatment. This finding differed from a previous study (8), which reported that the probabilities of disease progression remained constantly high, irrespective of the duration of ATT. The disparity may be because of the different sample sizes and designs between the 2 studies. Given the profibrotic effects of antitubercular agents, it is postulated that the longer exposure of drugs will have a higher chance of harmful effects. Combining the results from our previous study (13) and this one, the issue about how to achieve a favorable benefit-risk profile for prophylactic ATT in patients with CD when commencing biological therapy needs to be reconsidered. If LTBI exists, prophylactic ATT is needed, but the duration should not exceed 4.5 months. Non-TNF biologics such as vedolizumab (31) or ustekinumab (32) with a lower rate of TB activation are the preferred choices. If the evidence of LTBI is inadequate, prophylactic ATT should not be recommended. Nevertheless, considering the potential risk of TB activation, a regular monitoring of TB during biological therapy is still required.

The multivariate analysis also showed that longer duration of anti-TNF therapy was a protective factor against disease progression, which was similar to a previous study that longer treatment durations were associated with a lower likelihood of disease progression (33). It is known that inflammation is the prerequisite for fibrosis, and TNF-α is a potent proinflammatory cytokine. It is justifiable that longer treatment with inhibitors of TNFs could delay the formation of a stricture by relieving intestinal inflammation in the early stage (34). In addition, our study showed that complicated disease phenotypes developed later in patients who started early treatment with immunomodulators. Indeed, a similar finding was observed by Ramadas et al. (35), who found that thiopurine use within the first year of CD diagnosis was associated with a reduced risk of disease progression. In another study by Safroneeva et al. (36), initiation with immunomodulators within 2 years of CD diagnosis was associated with a reduced risk of stricture compared with those initiating immunomodulators after 2 years of diagnosis.

Our study had several limitations. First, the retrospective design could induce selection bias when collecting information. To minimize the selection bias, this study was performed in multiple centers. Moreover, to negate the confounders from baseline characteristics such as age, disease location, and smoking, the PS methodology was performed to select an appropriately matched subset of patients. Second, because the predominant regimen of ATT in this study was INH monotherapy, we could not deduce that other antitubercular agents such as RFP also accelerate disease progression. Therefore, the impact of other types of antitubercular agents such as RFP and ethambutol on disease progression in CD should be investigated in the future. Finally, as our study was conducted retrospectively, one may argue that the endoscopic or radiological follow-up examinations are not pre-established, and hence, the time intervals may vary among patients. However, a standardized follow-up schedule was established in the 3 IBD centers. For example, colonoscopy and cross-sectional imagings were recommended annually for most of the patients in remission, which may have reduced the heterogeneity in our study.

In conclusion, our study showed that prophylactic ATT with duration over 4.5 months may accelerate disease progression in patients with CD receiving anti-TNF treatment. This reinforced the opinion that targeted TB chemoprophylaxis rather than universal chemoprophylaxis should be recommended when initiating anti-TNF therapy in TB-endemic regions. However, the findings, especially the optimal duration of ATT, need to be validated in future prospective studies.

CONFLICTS OF INTEREST

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Specific author contributions: M.H.C., F.L., J.T., and L.N.Y.: study conception. F.L., J.T., L.N.Y., J.Y.T., F.H., and J.S.H.: data collection. F.L., J.T., and L.N.Y.: data analysis. F.L., J.T., and L.N.Y.: manuscript drafting. R.M., M.H.C., B.L.C., Y.H., Z.R.Z., Q.C., X.G., and Q.Y.: manuscript editing. All authors reviewed and commented on the manuscript and approved the final version.

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Study Highligts

WHAT IS KNOWN

- ✓ Antitubercular agents possess profibrotic effects.
- ✓ There are no studies to investigate the profibrotic effect of antitubercular agents in patients with Crohn's disease (CD) receiving anti-tumor necrosis factor (anti-TNFs) treatment.

WHAT IS NEW HERE

- ✓ Prophylactic antitubercular therapy (ATT) with a duration over 4.5 months may accelerate disease progression in CD patients receiving anti-TNFs treatment.
- ✓ Prophylactic ATT should be administered to CD patients with proven latent TB infection, and the duration should be less than 4.5 months.

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