



High risk of tuberculosis during infliximab therapy despite tuberculosis screening in inflammatory bowel disease patients in India

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Background/Aims: The data on the risk of tuberculosis (TB) reactivation with infliximab (IFX) in patients with inflammatory bowel disease (IBD) from TB endemic countries, like India, is limited. The risk of TB reactivation on IFX and its predictors in patients with IBD was assessed. **Methods:** This retrospective review included consecutive patients with IBD who received IFX, and were on follow-up from January 2005 to November 2017. The data was recorded on age/disease duration, indications for IFX, screening for latent tuberculosis (LTB) before IFX, response to IFX, incidence and duration when TB developed after IFX, and type of TB (pulmonary [PTB]/extra-pulmonary [EPTB]/disseminated). **Results:** Of 69 patients (22 ulcerative colitis/47 Crohn's disease; mean age, 35.6±14.5 years; 50.7% males; median follow-up duration after IFX, 19 months [interquartile range, 5.5–48.7 months]), primary non-response at 8 weeks and secondary loss of response at 26 and 52 weeks were seen in 14.5%, 6% and 15% patients respectively. Prior to IFX, all patients were screened for LTB, 8 (11.6%) developed active TB (disseminated, 62.5%; EPTB, 25%; PTB, 12.5%) after a median of 19 weeks (interquartile range, 14.0–84.5 weeks) of IFX. Of these 8 patients' none had LTB, even when 7 of 8 were additionally screened with contrast-enhanced chest tomography. Though not statistically significant, more patients with Crohn's disease than ulcerative colitis (14.9% vs. 4.5%, $P=0.21$), and those with past history of TB (25% vs. 9.8%, $P=0.21$), developed TB. Age, gender, disease duration, or extraintestinal manifestations could not predict TB reactivation. **Conclusions:** There is an extremely high rate of TB with IFX in Indian patients with IBD. Current screening techniques are ineffective and it is difficult to predict TB after IFX. (**Intest Res 2018;16:588-598**)

Key Words: Colitis, ulcerative; Crohn disease; Latent tuberculosis; Mantoux; Interferon-gamma release tests

INTRODUCTION

With increasing burden of IBD in India and other developing countries,^{1,2} the use of anti-tumor necrosis factor- α (anti-TNF- α) agents is also expected to increase. About one-third of the global population is infected with *Mycobacterium tuberculosis* of which the highest burden is carried by the

developing world.³ Ninety percent of this tubercular burden is shared by latent tuberculosis (LTB) which is defined as immune response against *M. tuberculosis* in the absence of clinical manifestations.⁴ Most of the individuals with LTB remain so through out their lives, however, LTB can progress to active tuberculosis (tubercular reactivation) when this immune response is lost such as human immunodeficiency infection and treatment with anti-TNF agents. TNF- α is one of key mediators in granuloma formation and maintenance, and thus control of tubercular infection.^{5,6}

The risk of tubercular reactivation is high in areas endemic for tuberculosis⁷ as suggested by comparison of nationwide registry of data bases from West⁸⁻¹² and East,¹³ and from

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retrospective cohort studies from South Korea,^{14,15} Taiwan,¹⁶ and Hong Kong.¹⁷ In a recent study from India,¹⁸ of 79 patients with UC who received infliximab (IFX), 8.8% patients developed tuberculosis after a median of 8 weeks. This has been the highest report till date on rate of tuberculosis reactivation. However, this study included only patients with UC, and majority of patients received <3 doses of IFX. Therefore, data on the rate of TB reactivation in patients with CD and among patients who have also received maintenance doses of IFX are lacking from India.

Screening for LTb is therefore recommended before a patient is started on IFX.^{15,19-22} However, >70% patients who develop TB, have screened negative for LTb with the currently recommended modalities: mantoux, interferon gamma release assays (IGRA), and chest X-ray.²²⁻²⁶ This highlights the limitations of currently available screening modalities for LTb and the need for better predictors for tubercular reactivation in these patients. The current literature on the clinical predictors for tubercular reactivation on anti-TNF agents is limited and heterogeneous and is lacking from India and most Asian countries, which are at high risk for tubercular reactivation.

The present study was designed to study the rate of tubercular reactivation on infliximab in a cohort of patients with IBD (both UC and CD), and evaluate the clinical predictors for the same.

METHODS

1. Patient Population

The present study included patients with IBD who received at least one dose of infliximab and were under follow-up at IBD Clinic, Department of Gastroenterology, All India Institute of Medical Sciences (AIIMS), New Delhi, from January 2005 to November 2017. Permission from Institutional Ethics Committee was taken (IRB No. IEC/477/7.10.2016).

2. Study Design

It was a retrospective analysis of a prospectively maintained database of patients with IBD who had received IFX. The database is maintained through a file-paper system wherein data is entered by a team of physicians running the IBD clinic. Patient files contain all dated information concerning the demographic profile, disease and its distribution, including history, medical examination, test results and follow-up symptom assessment. The following parameters were extracted from the database: demographic features, disease characteristics including location, extent, severity and behav-

ior, presence and number of extraintestinal manifestations (EIMs), complete blood count and liver and renal functions prior to infliximab, history of smoking or alcohol intake, past history of tuberculosis, any history of receiving anti-tuberculosis therapy (ATT) prior to the diagnosis of CD, prior steroids and immunomodulator use, indication for the use of infliximab, and information on screening and presence of LTb. Any missing data was confirmed by interviewing the patient in person. Patients' data was entered from the date of index infliximab dose till complete loss of response requiring switching of therapy or 30th November 2017, whichever was earlier, and data were recorded on dose and duration of infliximab received, response to infliximab, loss of response, adverse events related to infliximab therapy, development of tuberculosis after infliximab, site of tuberculosis, and mean duration of infliximab after which tuberculosis developed.

3. Definitions

1) UC

Diagnosis of UC and CD was made on the basis of European Crohn's and Colitis Organization (ECCO) guidelines.^{27,28} Disease activity in UC and CD was measured by Simple Clinical Colitis Activity Index (SCCAI)²⁹ and CDAI³⁰ respectively. Endoscopic severity in UC was assessed by Baron index.³¹ Disease extent in UC and disease location and behavior in CD was classified on the basis on Montreal classification.³²

2) Acute Severe Ulcerative Colitis

The diagnosis of Acute Severe Ulcerative Colitis (ASUC) was based on Truelove and Witts criteria defined as 6 or more stools with blood and one or more of following: hemoglobin <10.5 g/dL, ESR >30 mm/hr, fever >37.8°C, or tachycardia >90/min.³³

3) Remission

Remission for UC was defined as SCCAI <2. For CD, remission was defined as CDAI <150.³⁴

4) Response

Response for UC was defined as decrease in SCCAI by 3 points. Response in CD was defined as decrease in CDAI by 100 points.³⁴

5) Primary Non-Response

Lack of response to induction dose of infliximab

6) Secondary Loss of Response

Loss of response with maintenance dose of infliximab (af-

ter an initial response to induction dose). (1) Partial: loss of response with maintenance dose of infliximab, which was overcome by increasing the dose/frequency of infliximab and (2) complete: no response to increasing the dose/frequency, requiring switching of therapy

7) Steroid-Refractory Disease

As per ECCO guidelines, active disease despite prednisolone medication up to 0.75 mg/kg/day over a period of 4 weeks was defined as steroid-refractory disease.^{27,28}

8) Steroid-Dependent Disease

Patients who were unable to reduce steroids below the equivalent of prednisolone 10 mg/day within 3 months of starting steroids without recurrent active disease or who had a relapse within 3 months of stopping steroids.^{27,28}

9) Immunomodulator Intolerant Disease

Patients who had adverse effects on immunomodulators which necessitated withdrawal of immunomodulatory therapy.

10) Immunomodulator Refractory Disease

Patients who had active disease or relapse in spite of thiopurines at an appropriate dose for at least 3 months (i.e., azathioprine [AZA] 2–2.5 mg/kg/day or mercaptopurine 1–1.5 mg/kg/day in the absence of leucopenia.^{27,28}

11) Latent Tuberculosis

Diagnosed on the basis of positive Mantoux (>10 mm) or IGRA. Evidence of healed tuberculosis on chest X-ray or CT (pleural thickening, fibrotic scarring, calcified nodules, and calcified hilar or mediastinal lymphadenopathy) was also considered as LTb.³⁵

12) Active Tuberculosis

Pulmonary TB was diagnosed in the presence of clinical symptoms (fever/cough/anorexia/weight loss) and evidence of fresh lesions suggestive of tuberculosis on the chest X-ray/contrast-enhanced CT (CECT) chest with or without demonstration of AFB on the sputum smear examination.³⁶ Extra-pulmonary TB was diagnosed on the basis of clinical features, suggestive radiologic findings and demonstration of positive AFB/ culture for *M. tuberculosis* or caseating or non-caseating granulomas on biopsy specimens. Diagnosis of pleural TB/peritoneal TB was based on biochemical evaluation of pleural/peritoneal fluid showing a high protein content along with a high ADA content (>40 IU/mL) and

lymphocytic predominance.³⁶ Patients with evidence of TB at more than one site were diagnosed with disseminated disease.

4. Statistical Analysis

Categorical variables were expressed as percentages and continuous variables were expressed mean±SD or median (range) as appropriate. Chi-square test was used to compare categorical variables between patients who developed TB versus those who did not and Student *t*-test or Mann-Whitney *U*-test was used to compare continuous variables as appropriate. *P*<0.05 was considered as statistically significant. SPSS software version 24.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis.

RESULTS

A total of 4,352 patients of IBD were registered at IBD Clinic at All India Institute of Medical Sciences between January 2005 and November 2017. Of these, 69 patients received at least 1 dose of infliximab and were included.

1. Baseline Demographic and Clinical Features

Of the 69 patients, 22 patients were diagnosed with UC and 47 patients were diagnosed with CD. The mean age (at the time of diagnosis) of entire cohort was 35.6±14.5 years, and 50.7% patients were males. There was no significant difference between CD and UC in terms of age, gender, EIMs or disease duration (Table 1). Among patients with UC, 13 (59.1%) had E3 disease and 9 (40.9%) had E2 disease. Among patients with CD, most patients had age of diagnosis between 17 and 40 years (A2, 44.7%), colonic disease was the most common disease location (42.6%) and there was almost equal proportion of patients with inflammatory (38.3%) and stricturing disease behavior (36.2%). Seventeen patients (36.2%) were suffering from perianal disease. Of 69 patients, 28 (48.6%), 40 (58%), and 34 (49.3%) patients were on 5-aminosalicylic acid (5-ASA), steroids and immunomodulators respectively.

2. Indications for Starting Biologics

1) UC

Median duration of disease before biologics were started was 45 months (range, 1–180 months) and the median follow-up after starting biologics was 24 months (range, 2–120 months). Median SCCAI before biologics were started was 8 (range, 5–10). The major indication for starting infliximab was steroid dependent disease (n=16, 72.72%). In 11 patients

Table 1. Baseline Clinical and Demographic Features and Disease Characteristics in Patients with IBD Who Were Started on Infliximab

Characteristic	UC (n=22)	CD (n=47)
Age (yr)	36.7±9.2	35.2±16.4
Male sex	10 (45.5)	25 (53.2)
Disease duration at which biologics were started (mo)	45 (1–180)	24 (0–360)
Follow-up duration after biologics (mo)	24 (2–120)	17 (0.5–120)
Family history	2 (9.1)	1 (2.1)
Any EIMs	8 (36.4)	19 (40.4)
Peripheral arthralgia	6 (27.3)	10 (21.3)
Central arthralgia	4 (18.2)	10 (21.3)
Erythema nodosum	1 (4.5)	2 (4.3)
Pyoderma gangrenosum	1 (4.5)	1 (2.1)
Ocular	0	1 (2.1)
Aphthous ulcers	2 (9.1)	4 (8.5)
AIHA+PSC	1 (4.5)	0
AIH	0	1 (2.1)
Disease extent (UC)		-
E1	0	
E2	0	
E3	9 (40.9)	
Median SCCAI	8 (5–10)	-
Age at diagnosis (CD)	-	
A1		12 (25.5)
A2		21 (44.7)
A3		14 (29.7)
Disease location (CD)	-	
L1		4 (8.51)
L2		20 (42.56)
L3		15 (31.9)
L4		7 (14.9)
L1+L4		2 (4.25)
L3+L4		1 (2.12)
Disease behavior (CD) ^a	-	
B1		18 (38.3)
B2		17 (36.2)
B3		12 (25.5)
Perianal		17 (36.2)
Median CDAI	-	359 (140–767)
Concomitant immunosuppression		
5-ASA	14 (63.6)	16 (34)

(Continued to the next)

Table 1. Continued

Characteristic	UC (n=22)	CD (n=47)
Steroids	16 (72.7)	24 (51)
Immunomodulators	10 (10.5)	24 (51)

Values are presented as mean±SD, number (%), or median (range). E1, proctitis; E2, left sided colitis; E3, pancolitis; A1, <17 years; A2, 17–40 years; A3, >40 years; B1, inflammatory; B2, stricturing; B3, penetrating; L1, terminal ileal; L2, colonic; L3, ileocolonic; L4, upper gastrointestinal. ^aSeventeen patients had overlap between perianal and other disease behavior.

EIM, extraintestinal manifestation; AIHA, autoimmune hemolytic anemia; PSC, primary sclerosing cholangitis; AIH, autoimmune hepatitis; SCCAI, Simple Clinical Colitis Activity Index; 5-ASA, 5-aminosalicylic acid.

(50%), ASUC not responding to the intravenous steroids was the reason to start infliximab therapy. Five patients with ASUC had steroid dependent disease prior to onset of ASUC.

2) CD

Median disease duration before starting biologics was 36 months (range, 0–360 months), and median follow-up duration after biologics were started was 19 months (range, 0.5–120 months). Median CDAI before starting infliximab was 359 (range, 140–767). The indications for starting infliximab therapy were steroid dependence (n=22, 46.8%), steroid refractory disease (n=6, 12.8%), perianal disease (n=16, 34%), fistulising disease (n=6, 10.6%), and postoperative recurrence of disease (n=6, 12.76%). Nine patients had overlap between more than one indication.

3. Response to Infliximab

1) UC

Median number of infliximab doses in patients with UC was 6.7 weeks (range, 2–35 weeks) given over a period of 36.5 weeks (range, 2–262 weeks). Five patients (22.7%) had a primary non-response, and 17 patients (77.3%) went into remission after the induction dose. The follow-up and treatment response in patients on maintenance dose is described in Fig. 1.

2) CD

Median number of IFX doses in patients with CD was 9.9 weeks (range, 2–52 weeks) given over a period of 61 weeks (range, 2–398 weeks). Five patients (10.6%) had primary non-response, 4 (8.5%) had partial response and 38 (80.8%) had remission after the induction dose. The follow-up and treatment response in patients on maintenance dose is described in Fig. 2.

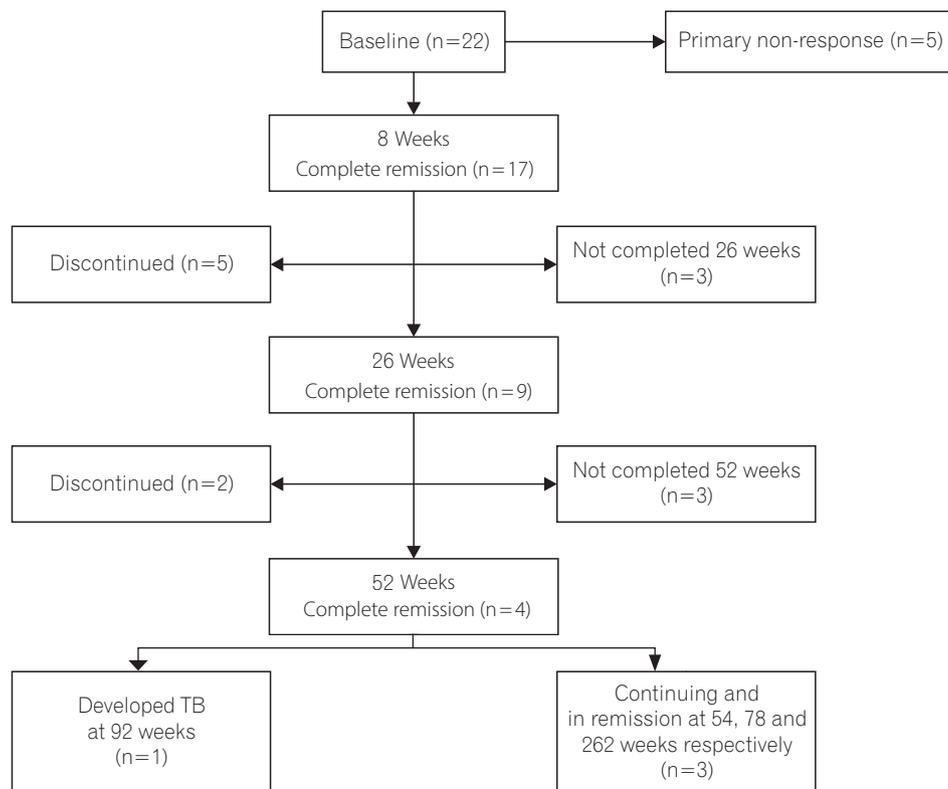


Fig. 1. Flowchart demonstrating response to infliximab in patients with UC. TB, tuberculosis.

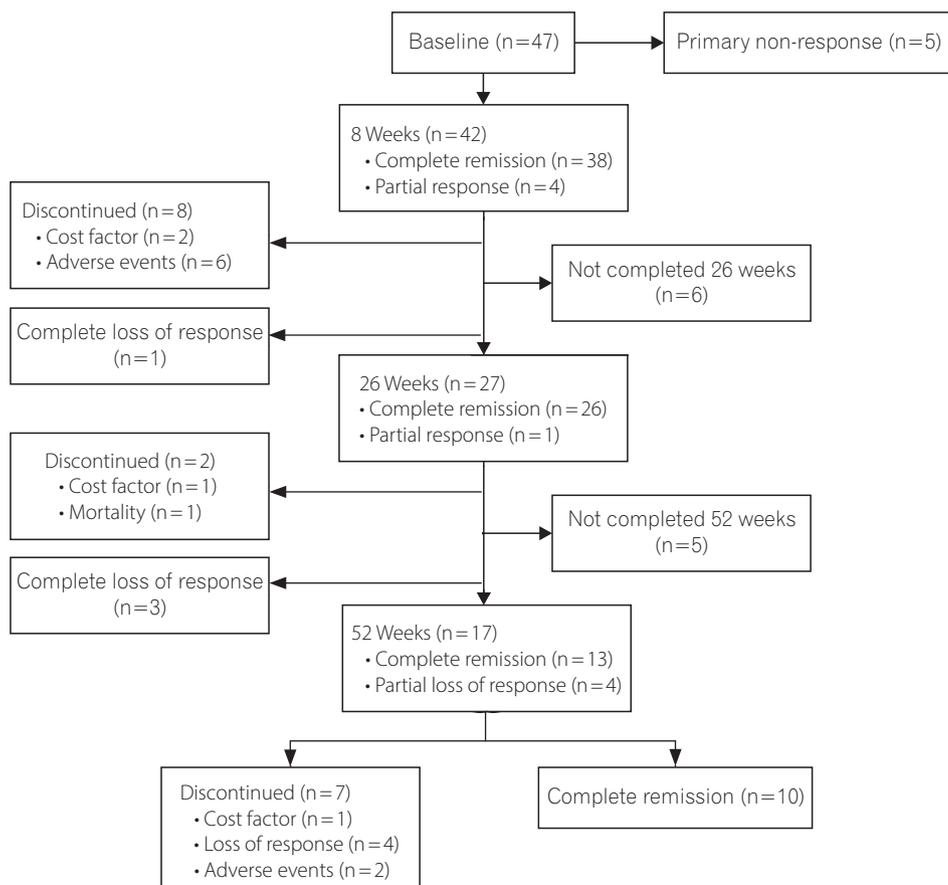


Fig. 2. Flowchart demonstrating response to infliximab in patients with CD.

Table 2. Patient Characteristics and Type of Tuberculosis in Patients Who Developed Tuberculosis on Infliximab Therapy

Patient no.	Baseline demographic and clinical characteristics					Screening for TB before biologics				Characteristics of TB				
	Age (yr)	Sex	Disease type	Disease location (CD)	Disease behavior (CD)	Past history of TB	ATT before diagnosis of CD	Mantoux	Chest X-ray	IGRA	CECT chest	Site	Duration of IFX at which TB developed (wk)	No. of doses of IFX at which TB developed
1	37	M	CD	L3	B1	No	No	Yes	Yes	No	Yes	PTB	24	5
2	24	F	UC (E2)	-	-	Yes	No	Yes	Yes	Yes	Yes	EPTB	94	14
3	64	M	CD	L3	B2	No	No	Yes	Yes	No	No	Disseminated	14	4
4	28	F	CD	L2	B1	Yes	No	Yes	Yes	No	Yes	Disseminated	6	3
5	15	M	CD	L4	B1	No	No	Yes	Yes	No	Yes	Disseminated	92	13
6	18	M	CD	L1	B2	No	Yes	Yes	Yes	Yes	Yes	Disseminated	14	4
7	25	F	CD	L2	B1	No	No	Yes	Yes	Yes	Yes	EPTB	14	4
8	55	M	CD	L3+L4	B2	No	Yes	Yes	Yes	Yes	Yes	Disseminated	62	10

L1, terminal ileal; L2, colonic; L3, ileocolonic; L4, upper gastrointestinal; B1, inflammatory; B2, stricturing; B3, penetrating. TB, tuberculosis; ATT, anti-tubercular therapy; IGRA, interferon gamma release assay; CECT, contrast-enhanced CT; IFX, infliximab; M, male; PTB, pulmonary tuberculosis; F, female; EPTB, extra-pulmonary tuberculosis.

4. Adverse Events on Infliximab

Of 69 patients who received IFX, 8 developed TB, 1 developed herpes zoster, 1 had in-growing toe nails with recurrent infections, 2 developed pneumonia, 1 developed varicella, 2 had leg abscess, and 2 patients developed infusion reaction. Overall rate of adverse events on IFX was 24.6%, and overall rate of infectious complication was 21.7%. One patient with CD died after he developed pneumonia and sepsis after 46th weekly dose of infliximab.

5. Tuberculosis after Infliximab

1) Screening for TB

Eight patients (11.6%) developed tuberculosis after infliximab therapy, of which 1 had pulmonary tuberculosis, 2 had extra-pulmonary TB (1 had mediastinal adenopathy, 1 had peritoneal tuberculosis) and 5 had disseminated TB (Table 2). Median duration after the first dose of infliximab to detection of tuberculosis was 19 weeks (range, 6–94 weeks). Three patients developed tuberculosis after 52 weeks of infliximab therapy. Of these 8 patients, 7 had CD and 1 had UC.

All the patients who developed tuberculosis had undergone screening for LTb before starting infliximab therapy. A chest X-ray and Mantoux test was done for all of these patients, while IGRA was done in 4 of 8 patients. CECT was done in 7 of 8 patients as an additional precautionary screening investigation. None of the patients had any evidence of LTb. Two patients had a past history of tuberculosis, while 2 patients had received anti-tubercular therapy before a conclusive diagnosis of CD was made.

2) Predictors of Tuberculosis after Infliximab Therapy

Though not statistically significant, more patients with CD than UC (14.9% vs. 4.5%, $P=0.211$), and more patients with past history of TB (25% vs. 9.8%, $P=0.208$), developed TB after IFX (Table 3). Among patients with CD, none of the patients with perianal disease (0% [perianal disease, $n=17$] vs. 23.3% [non-perianal disease, $n=30$], $P=0.028$) or penetrating disease (0% [B3 disease, $n=12$] vs. 20% [B1 and B2 disease, $n=35$], $P=0.26$) developed tuberculosis. No other baseline factor including age of onset of disease, gender, disease duration, or presence of EIMs could predict the development of TB after infliximab in patients with IBD.

DISCUSSION

The therapeutic armamentarium for patients of IBD in developing countries including India, is expanding with the inclusion of biologics, especially the anti-TNF agents, possibly

Table 3. Comparison of Disease Characteristics between Patients with IBD Who Developed Tuberculosis after Infliximab versus Who Did Not

	Among all patients		Among patients with CD	
	Patients who developed tuberculosis after biologics	P-value	Patients who developed tuberculosis after biologics	P-value
Diagnosis		0.211	-	-
UC	1/22 (4.5)			
CD	7/47 (14.9)			
Sex		0.479		0.295
Male	5/35 (14.3)		5/25 (20.0)	
Female	3/34 (8.8)		2/22 (9.5)	
Past history of tuberculosis		0.208		0.896
None	6/61 (9.8)		6/41 (14.6)	
Yes	2/8 (25.0)		1/6 (16.7)	
ATT received before Crohn's diagnosis established		0.839		0.519
No	4/34 (12.1)		5/33 (15.2)	
Yes	2/13 (14.3)		1/13 (7.7)	
Screening for tuberculosis before biologics		0.518		0.668
Not done	0/3 (0)		0/1 (0)	
Done	8/65 (12.3)		7/45 (15.6)	
Presence of latent tuberculosis		0.312		0.230
No	8/62 (12.9)		7/40 (17.5)	
Yes	0/7 (0)		0/7 (0)	
Presence of EIMs		0.384		0.488
No	6/42 (14.3)		5/28 (17.9)	
Yes	2/27 (7.4)		2/19 (10.5)	
Perianal disease		-		0.028
No	-		7/30 (23.3)	
Yes	-		0/17 (0)	

Values are presented as number/number (%).

ATT, anti-tubercular therapy; EIM, extraintestinal manifestation.

due to increasing disease burden and improving economy. In the Indian IBD survey,³⁷ published 5 years back, only 3 of 374 patients (0.8%) had received biologics, whereas in the present study 69 of 4,352 patients (1.58%) received anti-TNF agents over the last 12 years, of which the majority (74%) have received it after 2011. With the increasing use of anti-TNF agents, the physicians treating IBD in these regions, especially India, need to be aware of their efficacy and the side effect profile which would help them making treatment decisions for their patients. Present study describes the results and adverse events, especially tuberculosis, of IFX from a tertiary care centre from North India. The significant findings which emerge out from this study include, good response

rates of IFX in Indian patients with UC, quite high rate of TB after IFX in Indian patients with IBD, inefficacy of screening modalities for latent TB and higher chance of TB in patients with CD as compared to UC.

Of 22 patients with UC, 77% went into remission after induction dose, and of those who continued IFX, none had a loss of response. Even those who stopped IFX after induction dose (n=8), continued to remain in remission on 5-aminosalicylic acid±AZA. Similar findings were reported from a retrospective study from another North Indian center³⁸ and from a 3-center study from India.¹⁸ In the first study,³⁸ of 28 patients, 24 (85.6%) responded by 8 weeks and 56% remained colectomy free by 2 years. In the other study,¹⁸ 79

patients received a median of 3 doses of IFX, and over a follow-up period of 2 years, bowel disease remained quiescent and none of the patients required colectomy. These findings indicate a good clinical response in Indian patients with UC, only with the induction dose of IFX. The results of IFX in CD, matched that of Western literature with a primary non-response rate of 10.6% and secondary loss of response rate of 21% at 1 year.²⁷

In a recent 3-center study from India,¹⁸ 8.8% patients (7/79) with UC developed TB after a median of 3 doses of IFX with a median time lag of 8 weeks. Present study also yielded significantly high rates of TB reactivation, with 8 of 69 patients (11.6%) developing tuberculosis at a median of 19 weeks (range, 6–94 weeks), which was longer than previous study, possible due to longer exposure to IFX, the median IFX doses in patients who developed TB were 8.8, with 55% and 38% patients continuing IFX beyond 6 months and 1 year respectively. This reconfirms significantly higher rates of TB reactivation in countries endemic for TB, in fact, the present and the previous report have documented the highest rate of TB reactivation in patients with IBD on IFX. Less than 10% of cases of TB reactivation have been reported from Europe and North America, with Asia and Africa accounting for rest of the burden.³⁹ Reports from other Asian countries including Turkey⁴⁰ and South Korea^{14,15} have also documented moderately high rates of TB ranging from 1.2% to 4.7%. Like the previous studies from India and other Asian countries, present study also reports higher rates of EPTB (25% vs. 20%–81%) and disseminated TB (63% vs. 20%–56%). All tuberculosis cases could be successfully treated and there was no mortality due to TB.

Of 69 patients, 7 (10%) were positive for latent TB, all received chemo-prophylaxis, and none developed active TB on follow-up. The efficacy of chemo-prophylaxis for LTB in this setting has been shown in several reports from Asia as well as West,⁴¹ with studies indicating decline in TB reactivation rate by 65% to 70%.⁴²⁻⁴⁴ The failure of LTB treatment could be due to resistance to drugs or new infection developing after LTB treatment has been completed. None of the patients who developed active TB (n=8) had evidence of LTB on screening. All patients were screened with Mantoux and chest X-ray, IGRA was additionally done in 4 of 8 patients and CECT chest was done in 7 of 8 patients. In the other Indian study¹⁸ also, Mantoux test was negative in all, and IGRA was negative in 3 patients in which it was carried out. Similarly, studies from South Korea¹⁵ and multicentre study from GETAID centres²² have shown that >70% of TB cases develop in those who are negative for latent TB at initial screening.

These findings highlight the inefficacy of screening strategies for latent TB in this group of patients. Possible reason could be exposure to immunosuppression in these patients, which could lead to false negative results on immunological tests for latent TB. More than 50% patients in the present and previous study¹⁸ were on steroids/immunomodulators. Strategies to improve LTB detection rates would include boosting the Mantoux/IGRA response rates by 2-step testing, and development of next-generation immunological tests with different targets. Other strategy could be chemoprophylaxis for all, especially if annual risk of TB is higher than drug induced hepatotoxicity, which would be the scenario in TB endemic countries like India. With the rates of TB reactivation exceeding 10%, especially in LTBI negative individuals, the number needed to prevent one case of active TB would be <10.

The rate of TB reactivation was much higher in patients with CD (14.9% vs. 4.5%, $P=0.21$) and in patients with past history of tuberculosis (25% vs. 9.8%). Of 7 patients with CD who developed TB, none had penetrating or perianal disease. However, the numbers are small, and definite conclusions cannot be drawn on this aspect. The possibility of these patients having intestinal TB (and therefore the higher chance of TB reactivation) is negated by the fact that 2 patients had already received ATT before diagnosis of CD was made and had demonstrated symptomatic response after CD specific therapy. In other patients, there was no diagnostic dilemma between CD and ITB, and patients had a definite diagnosis of CD on the basis of clinical, endoscopic, radiological and histological features. Moreover, there was no worsening of intestinal symptoms after IFX, and only one patient who developed TB had a primary non-response to IFX. This patient had disease duration of 40 years with ileocolonic and steroid dependent disease. Few studies have looked at the baseline predictors of TB reactivation on IFX.^{12,14,15} The results from these studies have been heterogeneous and include type of anti-TNF (IFX>adalimumab [ADA]), irregular chemo-prophylaxis of LTB and TLC <5,000. In the present study, though not statistically significant, disease subtype (CD>UC) and past history of TB seemed to be factors associated with risk of TB, but these results need to be confirmed further with a larger sample size, and from other centres.

This study is limited by a smaller sample size, but this small sample size has also provided clinically significant results which give us a direction to be extremely cautious before using anti-TNF, and which provoke use to probe further into the mechanisms, clinical and laboratory predictors of TB reactivation, and better ways of preventing TB. Smaller sample size is also a reflection of sparing use of IFX in India,

which although is increasing with increasing disease burden. We did not include data on ADA which would have allowed us to compare TB reactivation rates between IFX and ADA. However, the number of patients who received ADA at our centre was quite small in comparison to number of patients on IFX, and therefore we have analysed the data on ADA in combination with other centres and it would be published as a separate manuscript. We did IGRA in 50% of our patients only because of its inhibitory cost. It has been shown that the immunosuppression has less effect on the results of IGRA than Mantoux, but we did CECT chest in 7 of 8 patients, and therefore, the measures used for detection of LTB were rigorous, as per the currently available recommendations. In conclusion, we re-confirm that there is a high chance of TB reactivation with the use of IFX for IBD in India. The presently available screening modalities are ineffective and this study lays a roadmap for further research into immunological, genetic and serological predictors for TB reactivation in patients on IFX and thereby fill up the large diagnostic gap which exists with currently available diagnostic modalities.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTION

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