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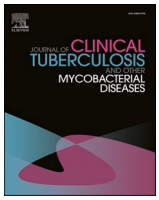

Tuberculosis screening for patients on biologic Medications: A Single-Center experience and Society guideline Review, Monroe County, New York, 2018–2021

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ABSTRACT

Rationale: Biologic medications for immune-mediated inflammatory diseases may increase the risk of tuberculosis (TB) reactivation, but data on screening for TB in low TB prevalence areas are limited.
Objective: To assess the real-world practice patterns of TB screening among prescribers of biologic medications.
Methods: We conducted a retrospective observational study at a single, university-based healthcare facility in a low TB prevalence area. We enrolled adult patients prescribed a biologic medication between October 2018 and December 2021, and collected data on demographics, biologic medications and TB test results. For patients with positive TB tests, further data including prescriber specialty and response to positive tests were obtained. We reviewed pertinent major society guidelines/ consensus statements regarding TB screening among patients treated with biologic medications.
Results: 4,085 patients were included. 3024 (74.0%) had at least one screening TB test and 42 were positive. Among patients treated with tumor necrosis factor-alpha (TNFα) inhibitors, 1779 of 2129 patients (83.6%) underwent TB testing and 25 (1.4%) were positive. Most with positive TB test results were prescribed biologic medication by gastroenterology (11 patients, 26%), dermatology (12, 29%), or rheumatology (15, 36%) providers. 32 (76%) patients had imaging and roughly half were treated for latent TB infection. Biologic medications were temporarily held for 27 patients (67%). Nine out of 13 society guidelines recommend TB screening for TNFα inhibitors but have differing recommendations for other biologic medications.
Conclusions: Significant practice pattern differences in TB screening for patients receiving biologic medications exist. Multiple society guidelines continue to recommend TB screening even for drugs with no known increased risk of TB reactivation.

1. Introduction

Since the introduction of tumor necrosis factor-alpha (TNFα) inhibitors in 1998, multiple "biologic" immunomodulatory medications have been added to the treatment armamentarium for immune-mediated inflammatory diseases (IMIDs) such as rheumatoid arthritis (RA) and inflammatory bowel disease (IBD). The categories "biologic medications" for IMIDs include inhibitors of interleukin (IL) including IL-1, IL-6, IL-12, IL-17, and IL-23, selective co-stimulation modulators, anti-cluster of differentiation 20 (CD20) monoclonal antibody, Janus kinase (JAK) inhibitors and integrin inhibitors [1–5]. Due to their immunomodulatory nature, these medications can theoretically increase a patient's risk for tuberculosis (TB) reactivation which has been best established in patients receiving TNFα inhibitors [6], but not as well for other biologics. Nevertheless, for both TNFα inhibitors and other biologics, various medical organizations recommend TB screening prior to use of these medications.

Over the course of our collective decades of diagnosing and treating

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TB, we have observed landmark improvements in TB care including development of blood-based screening tests and rapid molecular testing methods. However, as medical care advances, new challenges in TB screening arise with the widespread use of biologic medications and the availability of blood-based test for screening for TB infection. The challenges include whom, when and how to screen, how to interpret the results, and what to do with them.

Implementing optimal clinical practice for TB screening in patients receiving biologic medications is challenging for multiple reasons. Clinicians prescribing biologic medications need to estimate the value of TB screening, considering TB reactivation risk caused by the biologic medications, the local TB prevalence, and individual patients' TB risk factors, as well as the performance of the screening test in their population. The commonly available screening tests (interferon-gamma release assays (IGRA) and tuberculin skin test (TST)) depend on patients' immune response to mycobacterial antigens. These tests have inherently low diagnostic accuracy, particularly in immunocompromised patients, or in low TB prevalence areas; furthermore, they do not predict risk of TB reactivation [7–9]. While failing to screen may leave patients at increased risk for developing TB, inappropriate testing could lead to false-positive results, additional imaging and testing, and unnecessary use of preventive medications that have the potential of causing harm.

The purpose of our study was to assess the real-world practice patterns of TB screening among prescribers of biologic medications within our university-based medical facility located in Monroe County, New York (NY) State, United States (US). Monroe County is a low TB incidence region (2022 case rate was 1.6 cases of TB per 100,000 persons, with a US national average of 2.5 per 100,000 persons [10,11]). Our institution does not have a specific protocol for TB screening. We hypothesized that there was considerable variability both among prescribers and specialties in screening for TB. We aimed to assess the rate of TB screening and the prescribers' actions in response to a positive TB screening test result. We also performed a comparative review of medical society guidelines' TB screening recommendations to better understand the observed variabilities in clinical practice.

2. Methods

2.1. Current Practices Descriptive Study

This study was a single health system investigation performed at the University of Rochester Medical Center (URMC) designed to evaluate current TB screening practices in clinics treating patients with biologic medications. Patients were identified by the URMC Clinical and Translational Science Institute Informatics team through an electronic health record (EHR) query system. Patients 18 years and older prescribed a biologic medication (Table 1) at outpatient clinics between October 1, 2018 and December 31, 2021 at URMC were included. October 1, 2018 was our start date as this marked the start of URMC using Quantiferon Gold Plus® (related to the manufacturer changing methodology). Patients with hematologic malignancies or HIV infection, identified by the International Classification of Diseases 10th Revision (ICD-10) codes, were excluded.

We collected information on age, gender, race/ethnicity, smoking status, autoimmune diseases, comorbidities and TB screening tests and results. Autoimmune diseases included RA, ankylosing spondylitis, systemic lupus erythematosus, systemic sclerosis, polymyositis / dermatomyositis, Sjogren syndrome, giant cell arteritis, polymyalgia rheumatica, psoriasis / psoriatic arthritis, and IBD (Crohn's disease / ulcerative colitis). TB screening tests included IGRA (Quantiferon Gold Plus®) and TST. We calculated the proportion of patients with positive TB test results, those with negative or indeterminate TB test results, and those who did not have TB screening tests. Of note, an indeterminate result for the Quantiferon Gold Plus test is reported when either of the

Table 1
Tuberculosis screening test results among subjects being treated with a biologic medication between October 2018 and December 2021.

Variable		Positive n = 42	Negative or Indeterminate n = 2982	Not tested n = 1061	% Tested 74.1
Age		50 [28]	50 [30]	57 [28]	
Gender	Male	19 (45.2)	1284 (43.1)	432 (40.7)	75.1
Race	Caucasian	28 (66.7)	2514 (84.3)	930 (87.7)	73.2
	African-American	8 (19.0)	277 (9.3)	74 (7.0)	79.4
	Asian	4 (9.5)	39 (1.3)	17 (1.6)	71.7
	Native American or Pacific Islander	1 (2.4)	11(0.4)	5 (0.5)	70.6
Ethnicity	Not Hispanic or Latino	39 (92.9)	2766 (92.8)	1008 (95.0)	73.6
	Hispanic or Latino	2 (4.8)	148 (5.0)	29 (2.7)	83.8
Autoimmune diseases	Rheumatoid arthritis	7 (16.7)	681 (22.8)	229 (21.6)	75.0
	Ankylosing spondylitis	3 (7.1)	78 (2.6)	28 (2.6)	74.3
	Systemic lupus erythematosus	1 (2.4)	47(2.0)	15 (1.4)	76.2
	Polymyositis / dermatomyositis	0 (0)	7 (1.6)	7 (0.7)	50.0
	Sjogren syndrome	2 (4.8)	68 (2.3)	22 (2.1)	76.1
	Giant cell arteritis	0 (0)	19 (0.6)	1 (0.1)	95.0
	Psoriasis / psoriatic arthritis	11 (26.2)	712 (23.9)	120 (11.3)	85.8
	Crohn's disease / ulcerative colitis	11 (26.2)	745(31.6)	111 (10.5)	87.2
Biologic Medication	TNFα inhibitors: Adalimumab, Certolizumab pegol, Etanercept, Golimumab, Infliximab	25 (59.5)	1754 (58.8)	350 (33.0)	83.6
	Selective Co-stimulation Modulators: Abatacept	0 (0)	77 (2.6)	23 (2.2)	77.0
	Anti-CD20 monoclonal antibody: Rituximab	7 (16.7)	336 (11.3)	534 (50.3)	39.2
	IL-1 inhibitor: Anakinra	1 (2.4)	9 (0.3)	8 (0.8)	55.6
	IL-6 inhibitors: Tocilizumab, Sarilumab	0 (0)	53 (1.8)	11 (1.0)	82.8
	JAK inhibitors: Tofacitinib, Baricitinib, Upadacitinib	0 (0)	56 (1.9)	25 (2.4)	69.1
	IL-12/IL-23 inhibitor: Ustekinumab	3 (7.1)	251 (8.4)	38 (3.6)	87.0
	IL-17 inhibitors: Secukinumab, Ixekizumab, Brodalumab	2 (4.8)	90 (3.0)	11 (1.0)	89.3
	IL-23 inhibitors: Guselkumab, Tildrakizumab, Risankizumab	0 (0)	82 (2.7)	13 (1.2)	86.3
	Integrin inhibitor: Vedolizumab	4 (9.5)	271 (9.1)	46 (4.3)	85.7
TB test timing	Prior to initiation of biologic medications	20 (47.6)	1357 (45.5)		
	During continuation of biologic medications	22 (53.4)	1625 (54.5)		

Continuous variables are expressed as median [IQR] and categorical variables n (%).
TNF: tumor necrosis factor; CD: cluster of differentiation; IL: interleukin.

control tubes (nil or mitogen) do not produce a specified intended value. Indeterminate results with Quantiferon Gold Plus are best thought of 'uninterpretable' and usually requires repeat testing.

Manual chart review was performed for patients with positive TB screening test results to extract data on country of origin, Bacille Calmette-Guerin vaccination status, injection drug use, homelessness, TB exposure, TB testing method (IGRA or TST), ordering provider specialty, indication for testing, quantitative TB screening test result, clinical interventions performed for positive TB screening test (additional imaging, referral, latent TB infection (LTBI) or active TB disease treatment, and/or biologic therapy modification), and progression to active TB. Manual chart review was performed by two authors, with any questions or disagreements settled by a consensus meeting of all authors.

All above data were reported as median (inter-quartile range [IQR]) for continuous variables and number (percentage) for categorical variables. Basic descriptive statistics were completed using SAS 9.4 (Cary, NC) and REDCap electronic data capture tools hosted at URMC was used for data management. This study was approved by the URMC Research Subjects Review Board.

2.2. Current Guideline Review

We conducted a literature search in PubMed to identify available clinical studies and reviews describing the TB incidence associated with each of the studied biologic medications. Based on our findings, the authors developed an assessment of the risk of developing active TB and classified medications in five risk categories: 1. Increased; 2. Likely increased; 3. Likely not increased; 4. Not increased; and 5. Insufficient data. After discussion of any disagreement on rank order, the rankings presented were agreed upon by all authors.

Next, we performed a comprehensive review of major guidelines/consensus statements from global, US, and European medical societies pertinent to TB screening among patients treated with biologic medications. We also reviewed available Food and Drug Administration (FDA) drug labels for each of the biologic medications. We sorted TB screening recommendations from these documents into three categories: 1. perform testing regardless of risk factors; 2. consider testing if risk factors are present; and 3. no recommendations for or against testing. Following review of these documents, an adjudication meeting with all authors was held. Using a Mini-Delphi method [12], we assessed the strength of evidence for or against TB screening associated with each biologic medication class or lack thereof.

3. Results

3.1. Current Practices Descriptive Study

3.1.1. All Subjects

Between October 2018 and December 2021, 4,085 patients received outpatient administration of biologic medications at URMC (excluding hematologic malignancies or HIV infection). Most patients (3024, 74.0 %) had at least one screening TB test (2947 had IGRA and 77 had TST). Of these, our EHR could only confirm that 1378 patients (45.6 %) had TB screening tests before initiation of biologic medications (21 positive and 1357 negative or indeterminate), while 1646 (54.4 %) had already been on biologic medications prior to the beginning of the study period (21 positive and 1625 negative or indeterminate) (Fig. 1).

The highest rates of TB screening were observed among patients with giant cell arteritis (19 of 20 patients, 95.0 %), Crohn's disease / ulcerative colitis (756 of 867 patients, 87.2 %), and psoriasis / psoriatic arthritis (723 of 843 patients, 85.8 %). Among patients treated with TNFα inhibitors, 83.6 % (1779 of 2129 patients) underwent TB screening tests and 1.4 % (25 of 1779) were positive, though some patients may have had TB screening prior to our study period. TB screening rates and positive test rates were similar among patients treated with most other biologic medications with the exception of patients treated with rituximab (39.2 % screened of whom 2.3 % were positive) and anakinra (55.6 % screened, one was positive). These findings are summarized in Table 1.

3.1.2. Subjects with Positive IGRA Screening Tests

TB Screening tests were positive in 42 patients (1.0 % of the total cohort), all of which were by IGRA. Five patients had documented history of residence in countries other than the US (India, China, Ethiopia, Italy and the United Kingdom). The ranges for TB1 and TB2 were 0–10.00 and 0.27–8.24 (IU/mL) and median [IQR] 0.67 [0.40–2.13]

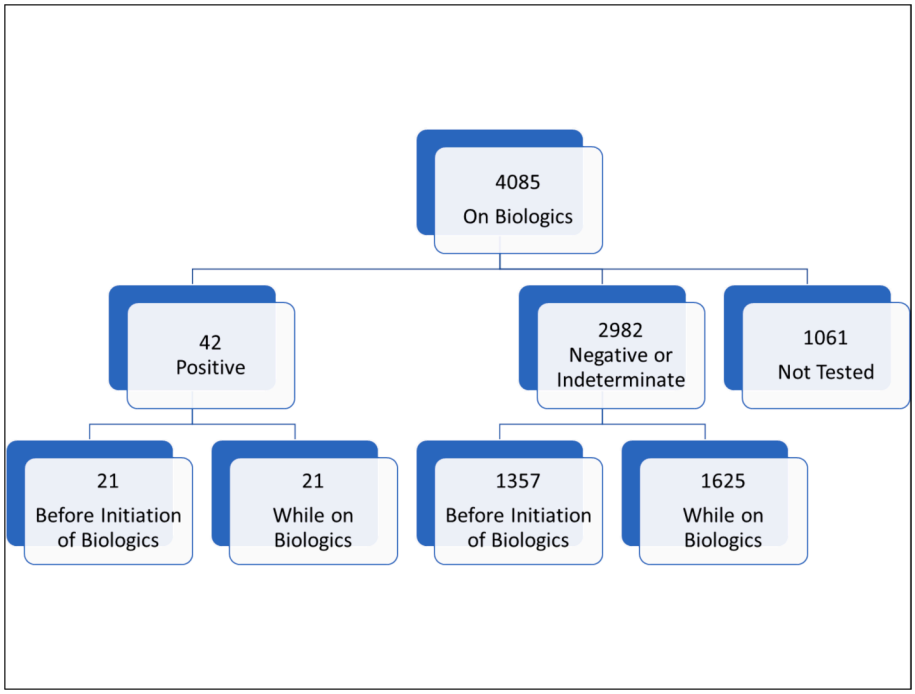

Fig. 1. Results and timing of tuberculosis screening for patients being treated with a biologic medication between October 2018 and December 2021.

and 0.77 [0.48–2.31] respectively. Most patients in the study received biologics from gastroenterology (11, 26 %), dermatology (12, 29 %), or rheumatology (15, 36 %) providers. Most patients (67–91 %) across all specialties had imaging documented in our system. Twenty-two of the 42 positive patients had documentation of treatment for LTBI. None of the 42 patients with positive tests developed active TB as of August 2022 by chart review. Based on additional chart review, biologic medications were temporarily held for 27 (4: adalimumab; 2: etanercept; 2: golimumab; 9: infliximab; 1: abatacept; 4: rituximab; 3: ustekinumab; 1: vedolizumab) of 42 patients testing positive on TB screening (67 %) due to concern for conversion to active TB. Typically, biologic medications were resumed one to three months after treatment of LTBI, which is consistent with recommendations from major society guidelines such as one from American College of Rheumatology (ACR) [13]. These findings are summarized in Table 2.

3.2. Current Guideline Review

We identified several recent review articles summarizing TB incidence rates by different biologic medications. TB incidence rate was highest for patients receiving TNFα inhibitors. Specifically, patients receiving infliximab and adalimumab had TB incidence rates of 52.5–2558 and 90–215 per 100,000 person-year, respectively. Patients receiving JAK inhibitors also had high incidence rates (200–210 for tofacitinib, 150–230 for baricitinib). Other medications were generally associated with lower incidence rates or lacked data [1,4,5].

We reviewed 19 guidelines / consensus statements by 13 organizations (one global, nine US, and three European) relevant to TB screening among patient treated with biologic medications, of which 12 had specific recommendations for TB screening. These included guidelines / consensus statements from World Health Organization (WHO) [14], American Thoracic Society (ATS) / Infectious Diseases Society of America (IDSA) / Centers for Disease Control (CDC) [15], United States Preventive Services Task Force (USPSTF) [16], European Respiratory Society (ERS) [17], European Society of Clinical Microbiology and Infectious Diseases (ESCMID) [2,18–21], ACR [13,22–25], European Alliance of Associations for Rheumatology (EULAR) [26], American College of Gastroenterology (ACG) [27,28], American Academy of

Table 2
Characteristics of patients with positive tuberculosis screening test results among patients being treated with biologic therapy between October 2018 and December 2021.

	All participants	Gastroenterology	Dermatology	Rheumatology
	n = 42	n = 11	n = 12	n = 15
Male gender	19 (45)	8 (73)	3 (25)	5 (33)
Race				
White/Caucasian	28 (67)	7 (64)	7 (58)	11 (73)
Black/African American	9 (21)	1 (9)	4 (33)	4 (27)
Asian	4 (10)	3 (27)	1 (8)	0
American Indian/Alaskan native	1 (2)	0	0	0
Ethnicity				
Not Hispanic/Latino	39 (93)	11 (100)	11 (92)	13 (87)
Hispanic/Latino	2 (5)	0	0	2 (13)
Unknown	1 (2)	0	1 (8)	0
Previous TB treatment	11 (26)	1 (9)	5 (42)	3 (20)
Smoking history				
Never	20 (48)	8 (73)	3 (25)	7 (47)
Former	12 (29)	2 (18)	5 (42)	5 (33)
Active	10 (24)	1 (9)	4 (33)	3 (20)
Silicosis	0	0	0	0
Foreign born	5 (12)	1 (9)	1 (8)	2 (13)
BCG	2 (5)	0	1 (8)	1 (7)
IV drug use	1 (2)	0	1 (8)	0
Close contact to TB infected person	0	0	0	0
Prior immunosuppressants	33 (79)	9 (82)	7 (58)	13 (87)
Systemic corticosteroids	11 (26)	2 (18)	2 (17)	4 (27)
Other immunosuppressants	24 (57)	8 (73)	6 (50)	9 (60)
Biologic Medication*				
Adalimumab (TNFα inhibitor)	6 (14)	0	3 (25)	2 (13)
Etanercept (TNFα inhibotor)	4 (10)	0	1 (8)	3 (20)
Golimumab (TNFα inhibitor)	3 (7)	0	0	3 (20)
Infliximab (TNFα inhibitor)	10 (24)	5 (45)	2 (17)	3 (20)
Abatacept (Selective Co-stimulation Modulator)	1 (2)	0	0	1 (7)
Rituximab (Anti-CD20 monoclonal antibody)	7 (17)	0	1 (8)	3 (20)
Ustekinumab (IL-12/IL-23 inhibitor)	5 (12)	1 (9)	4 (33)	0
Risankizumab (IL-23 inhibitor)	1 (2)	0	1 (8)	0
Vedolizumab (Integrin inhibitor)	5 (12)	5 (45)	0	0
Management of positive LTBI test				
DOH referral	25 (60)	5 (45)	11 (92)	7 (47)
Other specialist referral	11 (26)	6 (55)	1 (8)	1 (7)
No referral	9 (21)	1 (9)	1 (8)	7 (47)
Imaging test	32 (76)	10 (91)	10 (83)	10 (67)
Treatment for TB	22 (52)	4 (36)	6 (50)	6 (40)
Change in biologic medication				
Held	27 (64)	7 (64)	9 (75)	7 (47)
Changed to alternative	2 (5)	0	0	2 (13)
No change	12 (29)	4 (36)	2 (17)	6 (40)

TB: tuberculosis; BCG: bacilli Calmette-Guerin; IV: intravenous; TNF: tumor necrosis factor; CD: cluster of differentiation; IL: interleukin; LTBI: latent tuberculosis infection; DOH: department of health.
*No patients receiving the following medications studied had positive TB screening tests: certolizumab pegol (TNFα inhibitor); anakinra (IL-1 inhibitor); tocilizumab or sarilumab (IL-6 inhibitors); tofacitinib, baricitinib or upadacitinib (JAK inhibitors); secukinumab, ixekizumab or brodalumab (IL-17 inhibitors); or guselkumab or tildrakizumab (IL-23 inhibitors).

Dermatology (AAD) / National Psoriasis Foundation (NPF) [29] and United States and Canadian Hidradenitis Suppurativa Foundations [30]. FDA drug labels were found for all 21 biologics studied, of which 19 comment on TB risk and screening recommendations.

Table 3 presents a summary of previous clinical data, recommendations of the guidelines / consensus statements / FDA drug labels, along with the results from our institution. More complete narratives extracted from the guideline / consensus statements are provided in Table S1 in the online supplement.

4. Discussion

We examined the clinical practice patterns of TB screening prior to, and during biologic medication administration for patients with IMIDs, and evaluation of those with positive TB screening results, at our health system in a low TB prevalence setting. We found that TB screening rates for patients receiving biologics were highly variable depending on medication category. Aside from patients on rituximab (39.2 % screened), more than half of patients on other types of biologics received screening. Also, we observed considerable variability across medical specialties in the evaluation and management of positive TB screening tests. We did not observe any cases of active TB in our population. Most of the major guidelines / consensus statements recommend TB screening prior to initiation of TNFα inhibitors. In addition, ESCMID recommends TB screening for IL-6 inhibitors and suggests screening for IL-1 inhibitors, JAK inhibitors, IL-12/23 inhibitors, and IL-17 inhibitors. Both

Table 3
Summary of biologic medications with indications, TB risk, guideline recommendations and our data.

Medication Category	Name	IMID indications per FDA labels	Incidence*	TB risk**	WHO, ERS, ACG	ATS/ IDSA/ CDC, USPSTF	ESCMID	ACR, EULAR	AAD/ NPF	FDA label	Evidence Level**	Our data (% tested)
TNFα inhibitors	Adalimumab	RA, JIA, PsO/ PsA, SpA, Crohn's	90–215	Increased							Strong	83.6
	Certolizumab pegol	RA, Crohn's	474.29	Increased							Strong	
	Etanercept	RA, JIA, PsO/ PsA, SpA	9.3–80	Increased							Strong	
	Golimumab	RA, PsA, SpA	172.13	Increased							Strong	
	Infliximab	Crohn's, UC, RA, SpA, psoriasis/PsA	52.5–2558	Increased							Strong	
Selective Co-stimulation Modulators	Abatacept	RA, JIA	0–230	Likely not increased							Weak	77.0
Anti-CD20 monoclonal antibody	Rituximab	RA, GPA / MPA	0–32	Likely not increased							Weak	39.2
IL-1 inhibitor	Anakinra	RA	N/A	Insufficient data							Weak	55.6
IL-6 inhibitors	Tocilizumab	RA, GCA, JIA	0–230	Likely not increased							Weak	82.8
	Sarilumab	RA	0	Insufficient data							Weak	
JAK inhibitors	Tofacitinib	RA, PsA, UC	200–210	Likely increased							Weak	69.1
	Baricitinib	RA	150–230	Likely increased							Weak	
	Upadacitinib	RA, PsA	N/A	Insufficient data							Weak	
IL-12/IL-23 inhibitors	Ustekinumab	Psoriasis/PsA, Crohn's	0–22.12	Not increased							Weak	87.0
IL-17 inhibitors	Secukinumab	PsO/PsA, SpA	0–5	Not increased							Weak	89.3
	Ixekizumab	PsO/PsA, SpA	0	Likely not increased							Weak	
	Brodalumab	PsO	N/A	Insufficient data							Weak	
IL-23 inhibitors	Guselkumab	PsO	N/A	Likely not increased							Weak	86.3
	Tildrakizumab	PsO	N/A	Likely not increased							Weak	
	Risankizumab	PsO/PsA, Crohn's	N/A	Likely not increased							Weak	
Integrin inhibitor	Vedolizumab	UC, Crohn's	7–100	Likely not increased							Weak	85.7

*Per 100,000 patient-years. **Author consensus.

Blue cells: Guideline recommendations for TB screening tests. Orange cells: Consider testing if clinical and/or epidemiologic risk factor is present. White cells: No specific recommendations.

TNF: tumor necrosis factor; CD: cluster of differentiation; IL: interleukin; IMID: immune mediated inflammatory disease; FDA: Food and Drug Administration; RA: rheumatoid arthritis; JIA: juvenile idiopathic arthritis; PsO: plaque psoriasis; PsA: psoriatic arthritis; SpA: axial spondyloarthropathy; UC: ulcerative colitis; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; TB: tuberculosis; WHO: World Health Organization; ERS: European Respiratory Society; ACG: American College of Gastroenterology; ATS: American Thoracic Society; IDSA: Infectious Disease Society of America; CDC: Center for Disease Control and Prevention; USPSTF: United States Preventive Services Task Force; ESCMID: European Society of Clinical Microbiology and Infectious Disease: ACR: American College of Rheumatology; EULAR: European Alliance of Associations for Rheumatology; AAD: American Academy of Dermatology; NPF: National Psoriasis Foundation.

ACR and EULAR recommend TB screening for selective co-stimulation modulators, anti-CD20 monoclonal antibody, IL-6 inhibitors, and JAK inhibitors. AAD/NPF recommends TB screening for IL-12/23 inhibitors, IL-17 inhibitors, and IL-23 inhibitors. However, ATS/IDSA/CDC recommends that clinicians do not perform TB screening if the patient is "unlikely to be infected" and USPSTF recommends screening only high-risk individuals. FDA drug labels for most of the studied biologics recommend TB screening, except that they suggest considering TB screening for vedolizumab and that there is no mention of TB screening for rituximab and anakinra.

To our knowledge, there are few studies on TB screening practice patterns for biologics across a wide variety of medical specialties. This paucity of existing data makes our study one of the first in the US to focus on the screening rates and the management of positive test results in patients taking biologics for non-malignant diseases.

We observed that the TNFα inhibitors are the most frequently prescribed biologic medications at our institution. TNFα inhibitors have been shown to increase the risk of reactivation TB disease [6]. Though the risk of reactivation TB in the setting of TNFα inhibitors is based on strong evidence, there is little data available on the risk of TB for other biologic agents.

Though this study focused on the practice patterns of blood-based tests for TB screening, to provide thoughtful screening recommendations, we must acknowledge the limitations of these tests, particularly in our low prevalence population. Blood-based tests have low sensitivity and specificity in low prevalence population, and are frequently falsely positive [7,31,32]. For example, in a military population in South Carolina, United States, the participants were tested with 2 different IGRAs and TST simultaneously and 77 % of those with positive test results were positive by only one of the three tests (likely false positive) [31]. These tests are unable to predict the risk of developing active TB. Annual screening with these tests in different populations have clearly shown high rates of false-positive conversions and reversions [33]. Previous studies conducted in other low prevalence settings (including Denver, Colorado and Melbourne, Australia) have shown that screening for TB in all patients with human immunodeficiency virus (HIV), regardless of risk exposure, may result in a lower predictive value [34,35]. Ya et al. showed that only 0.2 % of patients with psoriasis treated with TNFα inhibitors developed "true" LTBI upon retesting in a study from a low TB prevalence population (Cleveland, Ohio, US) [36].

An additional challenge to understanding the TB screening landscape is the paucity of data describing real-world TB screening practice patterns specifically for biologic medications. Within the US, Fine et al. from Providence, Rhode Island, US, recently reported TB screening rate in IBD and non-IBD patients receiving biologic medications. In their study including 188 patients, 83 % of IBD patients vs 56 % of non-IBD patients received TB screening. Of these patients, 65 % had at least two follow-up surveillance tests for TB. Three or more surveillance TB tests were performed in 40 % of patients with IBD (GI) versus only 13 % of non-IBD (non-GI specialty) patients [37]. While this inter-specialty difference also appears to be the case at our institution (Table 2), the overall TB screening rate appears to be higher at our center, suggesting there may be significant variability within an institution as well as across different regions and health systems.

The relatively high rate of performance of TB screening for patients receiving biologics at our center demonstrates fairly good adherence to society guidelines. However, variability in the approach to patients on certain medications like Rituximab or less commonly used medications (JAK inhibitors) still exist. Based on guideline review and clinical experience, we recommend the following:

1. We agree with the widespread consensus recommendation of initial TB screening for patients starting treatment with TNFα inhibitors.
2. We also suggest initial screening for patients starting JAK inhibitors due to the likely increased risk of active TB and the majority of guidelines support screening.
3. Before recommendations can be made on other biologics, more data are needed to assess the risk of TB reactivation from the specific biologic class.
4. As additional biologics come to market, the decision on whether TB screening is needed should be made at the point of FDA approval to avoid gaps in medication approval and TB screening guidelines.
5. After an initial negative TB assessment, annual retesting of patients with low risk of TB exposure should be avoided. Instead, clinician education on risk assessment and updated testing recommendations are needed.
6. At our institution, we suggest that prescribers of biologic medications use an EHR documentation template to determine whether initial and subsequent TB screening is advised (Table 4).
7. The follow up of positive testing results after TB screening must be consistent and thorough. The fact that our documented follow up of positive results is less than 100 % is a concern and should serve as a call to action to health systems across the country to ensure excellence in follow up.

As our study was performed within a single healthcare system, it is possible that our relatively low number of positive screening tests was because the EHR query did not capture relevant data such as TB screening test performed at outside facilities, or variability in the manual entry of TST results. Also, IGRA result reporting was variable and made it impossible to reliably separate negative and indeterminate results during the EHR query. We focused the individual chart review on patients with positive TB testing, so we did not have data on prior TB testing for the large number of negative and indeterminate IGRA results. Therefore, it is possible that we underestimated the number of patients who were tested prior to initiation of biologic therapy. Similarly, we had limited chart review data on the timing and exact LTBI treatment regimens of patients with positive tests as the New York State County Health Department records (where LTBI treatment primarily occurs) were not

Table 4
Suggested approach to Tuberculosis screening in patients receiving biologic medications.

A. Initial Screening Prior to Starting Biologic Therapy	
Initial Risk Assessment	
Non-US born individual**	yes / no
Residence or Travel > 30 days in a TB-endemic country over past year	yes / no
Close contact with someone with active TB	yes / no
Health care worker with known exposure or ongoing transmission within the healthcare facility	yes / no
Initial TB Testing Recommendations	
Any "yes" response: TB testing and consider a second test if initial result negative	
All "no" responses: TB testing with a single test	
B. Annual Re-Screening of Patients Receiving Biologic Therapies	
Annual Risk assessment	
Residence or Travel > 30 days in a TB-endemic country over past year	yes / no
Close contact with someone with active TB	yes / no
Health care worker with known exposure or ongoing transmission within the healthcare facility	yes / no
Annual TB Testing Recommendations	
Any "yes" response: TB testing and consider a second test if initial result negative	
All "no" responses: No annual retesting	

*Any country other than the United States, Canada, Australia and New Zealand, and those in Northern or Western Europe.
Modeled after recommendations by Centers for Disease Control and Prevention (https://www.cdc.gov/tb/publications/ltbi/default.htm; https://www.cdc.gov/tb/topic/testing/healthcareworkers.htm#:~:text=All%20U.S.%20health%20care%20personnel,known%20exposure%20or%20ongoing%20transmission).

available for review. In general, the interval from LTBI treatment initiation to biologic therapy was one to three months.

Though our study period (2018–2021) included two years of the global COVID-19 pandemic, due in part to a rapid shift to telemedicine and other adaptations, we did not see a drop in our LTBI testing numbers with biologic therapy across years of our study. Our results should be interpreted only in the context of a low TB prevalence setting. For instance, Iba et al. (2020) reported a low proportion of TB screening for individuals receiving biologics for IMIDs in Tokyo, Japan area, where the TB incidence rate (10.1 / 100,000 in 2020) is higher than in the US (2.5 / 100,000) [10,38,39]. Given the difference in prevalence between different areas worldwide, it is reasonable to consider more aggressive retesting policy in areas with an increased rate of new TB infection.

Finally, we did not include certain novel biologics (like belimumab, or other agents used for non IMIDs indication such as oncology or allergy). An iterative process to reach future consensus, whether as part of FDA approval or not, is needed for these medications given the continuous development of novel biologic medications.

In conclusion, our study suggests significant inter-specialty practice patterns in TB screening of patients with IMIDs receiving biologic medications. The lack of TB testing of these patients may leave individuals at risk for developing TB while incorrect interpretation and management of test results may expose patients to risks of unnecessary preventive treatment. In order to create more consistent and well-informed TB screening practices for patients receiving immune modulating biologic medications, more research is needed to assess the utility and cost-effectiveness of TB screening in low TB prevalence settings. In addition to the existing specialty-specific guidelines, a multidisciplinary consensus is needed for TB screening and subsequent evaluation of patients treated with biologic immunomodulatory medications.

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Ethical Statement

The study was determined to be minimal risk and approved by the University of Rochester Medical Center Research Subject Review Board for exemption, where informed consent was waived.

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CRediT authorship contribution statement

Tetsuro Maeda: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Margaret Connolly:** Writing – review & editing, Writing – original draft, Software, Project administration, Investigation, Funding acquisition, Formal analysis, Data curation. **Kelly Thevenet-Morrison:** Writing – review & editing, Formal analysis, Data curation. **Paul Levy:** Writing – review & editing, Supervision, Conceptualization. **Mark Utell:** Writing – review & editing, Supervision. **Sonal Munsiff:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization. **Daniel Croft:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Margaret Connolly reports financial support was provided by National Institutes of Health. Daniel Croft reports financial support was provided by National Institute of Environmental Health Sciences. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jctube.2024.100460.

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