

RESEARCH ARTICLE

Tuberculosis screening and management of latent tuberculosis infection prior to biologic treatment in patients with immune-mediated inflammatory diseases: A longitudinal population-based analysis using claims data

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Abstract

Background and Aim: Screening for tuberculosis before treating with biologic agents is recommended in patients with immune-mediated inflammatory diseases (IMIDs). We conducted this study to identify adherence to the recommended practice in a real-world setting in Japan.

Methods: We used a community-based insurance claims database in a city in the Greater Tokyo Area in Japan. Between July 2012 and January 2019, we enrolled patients with IMIDs in the age range 15 to 74 years who had initiated biologic therapy. Tuberculosis screening was defined as (a) interferon- γ release assay and/or a tuberculin skin test (IGRA/TST) and (b) IGRA/TST and X-ray and/or CT scan (X-ray/CT) within 2 months before starting biologic agents. We analyzed the proportions of patients who underwent tuberculosis screening and their association with the patient- and treatment-related factors and treatment for latent tuberculosis infection (LTBI).

Results: Of 421 patients presumed to have initiated biologic therapy, 202 (48%) underwent IGRA/TST and 169 (40%) underwent IGRA/TST and X-ray/CT. Patients aged 65 to 74 years were more likely to undergo tuberculosis screening than those aged 45 to 64 years. Compared to infliximab, IGRA/TST was less frequently performed in patients treated with etanercept, adalimumab, golimumab, abatacept, and tocilizumab. Treatment for LTBI was provided to 67 (16%) patients. Proportions of patients receiving LTBI treatment did not significantly differ according to the screening status.

Conclusion: There was low adherence to the recommendations for tuberculosis screening and prophylactic treatment before biologic therapy. It is necessary to continue alerting clinical practitioners to the importance of screening for tuberculosis and treatment for LTBI.

KEYWORDS

autoimmune diseases, biological therapy, claims data, guideline adherence, latent tuberculosis infection

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1 | INTRODUCTION

Biologic agents, including tumor necrosis factor inhibitors (TNFi) and non-TNFi, are increasingly used as effective treatments for immune-mediated inflammatory diseases (IMiDs), such as rheumatoid arthritis (RA),¹⁻³ psoriasis,^{4,5} and inflammatory bowel diseases (IBD).^{6,7} Reactivation of tuberculosis is considered as one of the major adverse events of treatment with biologic agents, because of their strong immunosuppressive effect.⁸

Current clinical practice guidelines in Japan and other regions recommend that physicians screen for tuberculosis before initiating treatment with biologics.^{9,10} Latent tuberculosis infection (LTBI) has been diagnosed in 10% to 17% of patients with IMiDs when starting therapy with biologic agents^{11,12}; moreover, the rates of tuberculosis incidence in patients on biologic agents ranged from 172 to 457 per 100 000 patient-years in areas with moderate to high prevalence,^{13,14} and these decreased to 14% to 30% by screening for tuberculosis and preventive therapy for LTBI.^{13,15} Appropriate screening and chemoprophylaxis are crucial, especially in Japan, where the tuberculosis incidence is higher than the average (12.3 vs 6.0 per 100 000 population in 2018) reported by the Organization for Economic Co-operation and Development.^{16,17}

Studies of comprehensive postmarketing surveillances of both TNFi and non-TNFi in Japan showed almost perfect adherence to screening, and few patients developed tuberculosis (0.03%-0.14%).¹⁸⁻²¹ In contrast, a study using claims data showed that tuberculosis screening was performed in only 60% of patients who were newly prescribed TNFi in Japan.²² This implies that patients who are currently being treated with biologic agents are managed less stringently than patients treated soon after the approval of biologic agents. However, the abovementioned study used a database that covered a relatively young population and, therefore, screening status remains mainly unknown in the older population who are at a higher risk for tuberculosis.^{17,23} Furthermore, previous studies did not fully address factors that could be associated with the provision of tuberculosis screening, such as types of biologic agents, whether therapy included non-TNFi, prior prescription of methotrexate, and types of healthcare facilities.^{13,24}

This study was conducted to clarify the proportions of tuberculosis screening in patients who initiated biologic therapy, both TNFi and non-TNFi, in a large study population using a community-based health insurance claims database. Moreover, we aimed to investigate factors associated with the provision of tuberculosis screening.

2 | METHODS

2.1 | Study population and data source

This is a retrospective observational study that used community-based medical claims data from the National Health Insurance (NHI) association in C city, which is located in the Greater Tokyo Area, that were collected between April 2012 and January 2019. Japanese universal healthcare coverage is constituted by employment-based and

community-based health insurance plans, and the same medical fee schedule and the same co-payment rate (depending on age and income) are applied for all plans.^{25,26} The NHI, one of the community-based system, is managed by each municipality, and is offered to citizens who are younger than 75 years and ineligible for employment-based insurance: these include the self-employed, farmers, part-time workers, temporary workers, contract workers, and the unemployed or retired.^{25,27} The NHI system covers approximately 30% of the total population in Japan, and one-third of its beneficiaries are in the age range of 65 to 74 years.²⁸

The population of C city in 2012 was approximately 960 000, of which 260 000 (27%) are covered by the NHI system. The age-distribution in C city is comparable to the average in Japan.²⁹ We obtained claims data in an anonymized format in accordance with a research agreement between C city and The University of Tokyo. The monthly collected claims files contained the date of birth; sex; medical procedures and examinations; diagnostic codes according to the International Classification of Diseases, 10th Revision (ICD-10); name, dose, and dosing period of prescribed medications; and anonymized hospital codes. We combined the beneficiaries register and the claims data for each patient using a unique but anonymized identification number. The need for informed consent was waived because of the anonymized retrospective study design and the study protocol was approved by the Institutional Review Board of the Graduate School of Medicine, The University of Tokyo (approval no: 10834).

2.2 | Biologic therapy in Japan

Biologic therapy has been approved in Japan since the early 2000s. Until 2018, five TNFi, namely infliximab (IFX), etanercept (ETN), adalimumab (ADA), golimumab (GOL), and certolizumab pegol (CZP) and four non-TNFi, namely abatacept (ABT), tocilizumab (TCZ), ustekinumab (UTK), and secukinumab (SCK) have been covered by insurance. Table 1 shows the list of biologic agents covered by insurance and their indications. In general, every physician in Japan can prescribe these biologic agents at their clinical discretion. As an exception, the Japanese Dermatological Association (JDA) accredits certified facilities, mostly large general hospitals; initial administration of the biologics to patients with psoriasis is usually limited to these facilities.³⁰

2.3 | Tuberculosis in Japan

Japan has an intermediate burden of tuberculosis; in 2018, the incidence of tuberculosis was 12.3 per 100 000 population in Japan.¹⁶ The incidence of active tuberculosis has been decreasing gradually,¹⁷ but remains higher than in other developed countries, especially among the population older than 65 years. The tuberculosis incidence in C city was 18.1 per 100 000 in 2018.³¹

Japan has long included Bacille Calmette-Guérin (BCG) vaccination in the routine vaccination program and, therefore, most residents in Japan have been vaccinated with BCG in their childhood.³²

2.4 | Study cohort and variables

For this study, we defined the patients who were newly prescribed biologic agents according to the following criteria: (a) had at least one insurance claim record for any of the nine biologic agents (IFX, ETN, ADA, GOL, CZP, ABT, TCZ, UTK, and SCK) during the study period; (b) in the age range 15 to 74 years in the first month that biologic agents were prescribed; and (c) had no claims record for any of those biologic agents for at least 3 months before the initiation of biologic therapy. Patients who received biologic agents within 3 months of entry into the NHI system or the beginning of the study period were excluded. Because the maximum interval of the target biologic agents was 12 weeks, it was assumed that this 3-month pretreatment period would sufficiently exclude patients who had already initiated biologic therapy before the study period or at the point of entry into the NHI system.

Age was obtained as of the first month of biologic therapy. We identified a presumed primary IMID by the ICD-10 codes (M05-06 for RA, K50-K51 for IBD, and L40 for psoriasis). In addition, we used data on the type of medical institutions where the patients received their first biologic agent: hospitals that adopted the Diagnosis Procedure Combination system, which is a lump-sum payment system that was introduced in 2003 in Japan³³ (DPC hospital); non-DPC hospitals; and clinics. We obtained details on the prescription of methotrexate before the biologic therapy.

2.5 | Tuberculosis screening and treatment for LTBI

Before introducing biologic agents, screening for tuberculosis in patients with IMIDs is recommended in guidelines prepared by different academic societies in Japan and other countries. The guidelines

of the Japan College of Rheumatology (JCR) and JDA, which were available at the beginning of the study period, recommended comprehensive screening for tuberculosis infection with details of patient's medical history, chest radiography (X-ray), and a tuberculin skin test (TST), as well as chest CT and/or interferon- γ release assay (IGRA) as required.^{30,34,35} The revised version of the JCR guideline in 2017 required medical history, TST or IGRA, and chest X-ray and recommended the inclusion of CT scanning if necessary.^{36,37} Furthermore, these guidelines recommended treatment for LTBI; patients who are suspected of LTBI should undergo 6 to 9 months of chemoprophylaxis 3 weeks before the onset of the biologic treatment. Based on these guidelines, we identified patients who had undergone tuberculosis screening when evidenced by claims for (a) IGRA and/or TST (IGRA/TST) and (b) IGRA/TST and X-ray and/or CT scan (X-ray/CT) within 2 months before the first prescription of biologic agents. We specified a period of 2 months to take into account the 3 weeks of recommended treatment for LTBI.²² We identified patients who were receiving LTBI treatment as participants who had any claims records of isoniazid or rifampicin monotherapy before and/or during biologic therapy.¹⁵ We considered patients to have active tuberculosis when they were prescribed isoniazid and rifampicin, with ethambutol or streptomycin, and/or pyrazinamide for two consecutive months.

2.6 | Statistical analysis

We calculated the proportion of patients who had undergone tuberculosis screening. Chi-square test and multivariable logistic regression models were used to analyze the association between patient- and treatment-related variables and tuberculosis screening. In addition, we calculated the proportion of patients who received LTBI treatment before and/or during biologic therapy. Association between

TABLE 1 The list of biologic agents covered by insurance in Japan with their drug class, indications, and approved year

Biologic agents	Class	Immune-mediated inflammatory diseases			Approved year
		RA	IBD	Psoriasis	
Infliximab (IFX)	TNFi	+	+	+	2003
Etanercept (ETN)		+			2005
Adalimumab (ADA)		+	+	+	2008
Golimumab (GOL)		+	+ ^a		2011
Certolizumab pegol (CZP)		+			2012
Abatacept (ABT)	CTLA4-Ig	+			2013
Tocilizumab (TCZ)	IL-6 inhibitors	+			2008
Ustekinumab (UTK)	IL-12/23 antagonist		+ ^b	+	2011
Secukinumab (SCK)	IL-17 inhibitor			+	2016

Note: Plus signs indicate that the biologic agent is approved for the disease.

Abbreviations: CTLA4-Ig, cytotoxic T lymphocyte-associated antigen-4 immunoglobulin; IBD, inflammatory bowel disease; IL, interleukin; RA, rheumatoid arthritis; TNFi, tumor necrosis factor inhibitor.

^aApproved for ulcerative colitis only.

^bApproved for Crohn's disease only.

tuberculosis screening and treatment for LTBI was analyzed using the chi-square test.

Furthermore, as the JCR guideline recommends screening for tuberculosis before initiating methotrexate treatment in patients with RA,³⁸ we additionally considered tuberculosis screening before the initiation of methotrexate. For the subsample who were assumed to have initiated methotrexate before biologic therapy within the observation period, we estimated the frequencies of (a) IGRA/TST and (b) IGRA/TST and X-ray/CT within 2 months before the first prescription of methotrexate or biologic agents and repeated the same analyses. We conducted two sensitivity analyses by applying longer pretreatment and screening periods (6 months for pretreatment and 5 months for screening in one analysis, 9 months for pretreatment, and 8 months for screening in another) to obtain patients who were initiated on biologic therapy with more stringent criteria and to consider the possibility of referring screening results of more than 3 months before the commencement of biologic treatment. The *P*-values of less than .05 were considered to be statistically significant. We used Stata version 14.1 (StataCorp., College Station, Texas) for all statistical analyses.

3 | RESULTS

Of the approximately 670 000 beneficiaries who were covered by the NHI of C city during at least a part of the observation period, 1017 patients had at least one claim record of biologic agents. Of these, we identified 421 patients who were newly prescribed biologic agents after July 2012. Table 2 shows the patient characteristics of our study population (mean age 59.1 years, standard deviation [SD] 13.9 years; female 311 [74%]). Most of the patients (85%) were presumed to have RA. We found that ETN (26%) and IFX (21%) were the most commonly prescribed biologic agents. Approximately half of the patients (49%) received methotrexate before they started biologic therapy. More than half of the patients (53%) started biologic therapy in DPC hospitals, whereas 32% started treatment in clinics.

Table 3 shows the proportions of patients who underwent tuberculosis screening. Overall, 202 (48%) patients underwent IGRA/TST and 169 (40%) underwent IGRA/TST and X-ray/CT. The proportions of patients who underwent tuberculosis screening did not significantly differ by the specified age groups and were 50% at the upper limit among the highest age group. Screening frequencies for different biologic agents varied from 75% (UTK) to 27% (ADA) for IGRA/TST, and from 67% (CZP) to 22% (ADA) for IGRA/TST and X-ray/CT. Patients who received methotrexate before biologic treatment showed lower frequencies for tuberculosis screening than patients who did not.

Table 4 shows the results of multivariable logistic regression analyses. Patients in the age range 65 to 74 years were more likely to undergo IGRA/TST than those in the range 45 to 64 years (adjusted odds ratio [OR] 1.68, 95% confidence interval [CI] 1.06-2.67), but the result was not statistically significant for IGRA/TST and X-ray/CT (adjusted OR 1.35, 95% CI 0.85-2.14). Compared to IFX, tuberculosis

TABLE 2 Baseline characteristics of the patients who started biologic therapy

Variable	<i>n</i>	%
Age, years		
15-44	70	17
45-64	135	32
65-74	216	51
Sex, female	311	74
Diagnosis ^a		
Rheumatoid arthritis	357	85
Inflammatory bowel disease	76	18
Psoriasis	32	8
Other	3	1
Biologic agent		
Infliximab (IFX)	87	21
Etanercept (ETN)	110	26
Adalimumab (ADA)	55	13
Golimumab (GOL)	51	12
Certolizumab pegol (CZP)	12	3
Abatacept (ABT)	37	9
Tocilizumab (TCZ)	54	13
Ustekinumab (UTK)	8	2
Secukinumab (SCK)	7	2
Methotrexate prescription, yes	207	49
Hospital type ^b		
DPC hospital	221	53
Non-DPC hospital	66	16
Clinic	133	32
Period (Fiscal year)		
2012-2015	219	52
2016-2018	202	48

Abbreviation: DPC, diagnosis procedure combination.

^aIncluding duplication.

^bMissing 1.

screening with IGRA/TST was less frequently performed in patients treated with ETN, ADA, GOL, ABT, and TCZ (adjusted OR 0.35, 95% CI 0.16-0.77; OR 0.15, 95% CI 0.06-0.36; OR 0.22, 95% CI 0.10-0.52; OR 0.28, 95% CI 0.11-0.71; OR 0.41, 95% CI 0.18-0.92). Moreover, screening with IGRA/TST and X-ray/CT was significantly less frequently performed for ADA than for IFX (adjusted OR 0.29, 95% CI 0.12-0.71). Primary IMIDs and hospital types were not significantly associated with the performance of tuberculosis screening.

Among all of our patients, 67 (16%) received treatment for LTBI. Older patients were more likely to receive LTBI treatment than younger patients (*P* for trend = .001; Table S1). The proportions of patients receiving LTBI treatment did not significantly differ according to the screening status. Of the 219 patients who did not undergo IGRA/TST, 186 (85%) did not receive LTBI treatment (Table 5). One patient, who

TABLE 3 Proportions of patients underwent tuberculosis screening

	All n	IGRA/TST			IGRA/TST and X-ray/CT		
		n	%	P ^a	n	%	P ^a
Overall	421	202	48		169	40	
Age, years				.12			.64
15-44	70	37	53		28	40	
45-64	135	55	41		50	37	
65-74	216	110	51		91	42	
Sex				.35			.68
Female	311	145	47		123	40	
Male	110	57	42		46	42	
Diagnosis ^b				.36			.40
Rheumatoid arthritis	357	170	48		144	40	
Inflammatory bowel disease	76	42	55		34	45	
Psoriasis	32	19	59		15	47	
Other	3	1	33		1	33	
Biologic agent				<.001			.02
Infliximab (IFX)	87	58	67		43	49	
Etanercept (ETN)	110	51	46		46	42	
Adalimumab (ADA)	55	15	27		12	22	
Golimumab (GOL)	51	19	37		16	36	
Certolizumab pegol (CZP)	12	8	67		8	67	
Abatacept (ABT)	37	16	43		14	38	
Tocilizumab (TCZ)	54	26	48		23	43	
Ustekinumab (UTK)	8	6	75		5	63	
Secukinumab (SCK)	7	3	43		2	33	
Methotrexate prescription				.02			.05
Yes	207	87	42		73	35	
No	214	115	54		96	45	
Hospital type ^c				.46			.58
DPC hospital	221	111	50		91	41	
Non-DPC hospital	66	33	50		29	44	
Clinic	133	58	44		49	37	
Period (Fiscal year)				.44			.42
2012-2015	219	109	50		92	42	
2016-2018	202	93	46		77	38	

Abbreviations: CT, computed tomography; DPC, diagnosis procedure combination; IGRA, interferon- γ release assays; TST, tuberculin skin test; X-ray, radiography.

^aChi-square test.

^bIncluding duplication.

^cMissing 1.

had undergone IGRA/TST and X-ray/CT but did not receive LTBI treatment, developed active tuberculosis during the study period.

The proportions of patients who underwent screening and the results of regression analyses when considering a prior prescription of methotrexate are shown in Tables S2 to S4. Overall screening frequencies increased to 57% for IGRA/TST and 49% for IGRA/TST and

X-ray/CT. The results of the logistic regression analysis were mostly consistent with the main analyses.

Sensitivity analyses using the 6- and 9-month period before treatment (381 patients and 360 patients, respectively) showed higher proportions of patients who underwent IGRA/TST (58% for 6 months; 62% for 9 months) and IGRA/TST and X-ray/CT (48% for 6 months;

Variables	IGRA/TST		IGRA/TST and X-ray/CT	
	Adjusted OR	95% CI	Adjusted OR	95% CI
Age, years				
15-44	1.29	0.65-2.57	0.94	0.47-1.88
45-64	Ref		Ref	
65-74	1.68*	1.06-2.67	1.35	0.85-2.14
Sex				
Female	1.12	0.67-1.87	1.13	0.68-1.87
Male	Ref		Ref	
Diagnose				
Rheumatoid arthritis	Ref		Ref	0.63-2.62
Other	0.86	0.42-1.76	1.29	
Biologic agent				
Infliximab (IFX)	Ref		Ref	
Etanercept (ETN)	0.35*	0.16-0.77	0.81	0.38-1.73
Adalimumab (ADA)	0.15*	0.06-0.36	0.29*	0.12-0.71
Golimumab (GOL)	0.22*	0.10-0.52	0.45	0.19-1.03
Certolizumab pegol (CZP)	0.95	0.24-3.76	2.37	0.61-9.23
Abatacept (ABT)	0.28*	0.11-0.71	0.62	0.24-1.57
Tocilizumab (TCZ)	0.41*	0.18-0.92	0.82	0.37-1.81
Ustekinumab (UTK)	1.33	0.25-7.23	1.51	0.33-6.95
Secukinumab (SCK)	0.31	0.06-1.58	0.30	0.05-1.69
Methotrexate prescription				
Yes	0.70	0.44-1.12	0.72	0.45-1.15
No	Ref		Ref	
Hospital type				
DPC hospital	Ref		Ref	
Non-DPC hospital	1.41	0.76-2.60	1.45	0.79-2.67
Clinic	1.32	0.77-2.26	1.15	0.67-2.00
Period (fiscal year)				
2012-2015	Ref		Ref	
2016-2018	1.24	0.78-1.96	1.14	0.72-1.79

Note: Multivariable logistic regression analysis.

Abbreviations: CI, confidence interval; CT, computed tomography; DPC, diagnosis procedure combination; IGRA, interferon-gamma release assays; OR, odds ratio; Ref, reference; TST, tuberculin skin test; X-ray, radiography.

* $P < .05$.

TABLE 4 Factors associated with the performance of tuberculosis screening

	Total	IGRA/TST				P^a	IGRA/TST and X-ray/CT				P^a
		Not done		Done			Not done		Done		
		n	%	n	%		n	%	n	%	
Total	421	219	100	202	100		252	100	169	100	
Treatment for LTBI											
Not received	354	186	85	168	83	.62	212	84	142	84	.98
Received	67	33	15	34	17		40	16	27	16	

Abbreviations: CT, computed tomography; IGRA, interferon-gamma release assays; LTBI, latent tuberculosis infection; TST, tuberculin skin test; X-ray, radiography.

^aChi-square test.

TABLE 5 Proportions of patients who received treatment for LTBI according to tuberculosis screening status

50% for 9 months) than those in the main analyses. Logistic regression models showed similar trends to the main results (Tables S5-S12).

4 | DISCUSSION

Using a community-based health insurance claims database, we investigated the real-world situation of tuberculosis screening among patients who received biologic therapy and the factors that were associated with the provision of tuberculosis screening. The proportion of patients who underwent tuberculosis screening was approximately 50%, which was much lower than the proportion reported in post-marketing surveillance reports.^{18-20,39} The overall screening frequency with IGRA/TST was 48%, which was lower than in a previous study (66%) that used an employment-based claims database that covered a relatively young population²² as well as the proportions reported from other countries. In a Spanish study using a registry of patients treated with TNFi, 88% were screened with TST.¹³ In addition, this proportion was lower than the reported percentage in hospital-based studies of IBD in Korea (74% with IGRA)⁴⁰ and the United States (65% with TST).²⁴ The proportion decreased to 40% when combined with X-ray/CT. These results were lower than the proportions reported in post-marketing surveillances of ETN (99%)²⁰ and ADA (89%)³⁹ in Japan, indicating that there was low adherence to guidelines in a real-world setting. It is noteworthy that the observed low adherence was derived from the beneficiaries of NHI—a population with a high proportion of older patients or generally with a high risk for developing tuberculosis.

Tuberculosis screening was less performed in patients who received ETN, ADA, GOL, ABT, and TCZ compared to those who received IFX. After IFX was approved as the first TNFi, the risk of tuberculosis reactivation was identified and a warning was provided to physicians worldwide.⁸ In post-marketing surveillance of IFX in Japan, the tuberculosis incidence decreased after the warning (11 in 2000 patients to 3 in 3000 patients).⁴¹ Lower tuberculosis incidences in post-marketing surveillance of TNFi that were approved after IFX might have resulted from the successful screening program.^{20,39} Furthermore, ABT was shown to have the least risk of serious infection.⁴² This information may have altered physician awareness of tuberculosis risk toward an optimistic approach.

We assumed that patients with psoriasis might manifest a higher proportion of tuberculosis screening because the JDA regulated this aspect in its policy. However, there was no significant difference in screening frequency according to IMiDs. Further investigation is needed to clarify the effect of strict regulation on the prescription of biologic agents. Moreover, we assumed that patients treated in DPC hospitals, where they had better access to instruments such as IGRA or radiography, had a higher probability of being screened for tuberculosis, although the proportion did not significantly differ according to the types of medical institutions.

The screened proportion increased slightly when combined with the screening status before initiation of methotrexate, indicating that some patients had been screened for tuberculosis before

methotrexate was prescribed in accordance with the guidelines.³⁸ In sensitivity analyses with longer pretreatment and screening periods, patients screened for tuberculosis increased by approximately 10%. This suggests that some physicians referred to test results of more than 3 months preceding therapy onset with biologic agents. Although optimal timing of screening is not specified in the guidelines, physicians should be cautious about false-negative test results or increased risk of undetected tuberculosis infection that arise from a longer interval between screening and starting biologic treatment.

Our study has several limitations. First, not all patients who were considered to start biologic treatment were included; the test results were not available in claims data and, therefore, we could not identify patients who were not treated with biologic agents due to positive screening results. This might have resulted in an underestimation of the frequency of tuberculosis screening. However, this would not greatly affect the results, given the low prevalence of active tuberculosis in C city. Second, it might have resulted in an underestimation of the frequency of screening because the physicians could suspect that patients had LTBI by medical history taking or reviewing the positive test results long before biologic therapy. This impact, however, would be limited because the frequency of LTBI treatment was not high (only 15%) among those who did not undergo IGRA/TST. Third, patients who had been previously treated for LTBI did not require tuberculosis screening before the current biologic treatment. However, this effect could be small because the proportion of such patients was relatively small, as reported previously.⁴³ Thus, we believe that our findings of low adherence to the guidelines would not be altered despite the abovementioned limitations. Fourth, we could not obtain information on medical history from the claims data. Moreover, the claims data did not distinguish the body parts on X-ray/CT. Therefore, the number of patients who received X-ray/CT may have been overestimated although it would not alter our findings of low adherence to the guidelines. Fifth, the database has not been validated for this study, although the validity of diagnoses and procedures are checked mainly through the review process of insurance claims. Medical fee claims are subject to guidance and audit, and individuals or organizations will be penalized for improper claims. While the accuracy of testing and treatment documentation may be questioned, we considered them to be exactly recorded because there is an incentive to precisely record procedures to secure reimbursement. The disease names for which biologic agents are indicated are subject to review, so diagnoses are also likely to be documented on the claims. Finally, although the study population was community-based and proportionately representative of Japanese residents, the present results might not apply to the general population. Our study population had a higher risk of LTBI than the general population because the incidence rate of tuberculosis in C city was relatively higher than the Japanese average,³¹ and community-based insurance covered beneficiaries with higher age and lower socioeconomic status²⁵ compared to employment-based insurance. There might be regional differences in practice, while the previous study did not specify the region. Those aged 75 and older might show a higher proportion of screening because of the

increased risk of LTBI although they have a lower opportunity of using biologic agents.

The strength of our study was that we could simultaneously assess patients who had different IMIDs and were treated at all levels of medical institutions to identify whether they were appropriately screened for tuberculosis in a real-world setting using a community-based health insurance claims database. Moreover, we could comprehensively show screening frequencies according to a wide range of age, IMIDs, biologic agents, and hospital types within a long study period.

These findings raise the importance of continuing alerting physicians to the screening for tuberculosis and prophylactic treatment for LTBI before starting biologic treatment. There are several options to improve adherence to the guidelines, including point of care reminders⁴⁴ and audit and feedback.⁴⁵ Financial incentives can also be an effective approach,⁴⁶ while the balance between the other medical care should be considered.⁴⁷ To determine effective measures, we also need to investigate the physician's knowledge and perception of the guidelines.⁴⁸

In summary, our findings suggest that not many patients underwent recommended tests to screen for tuberculosis and prophylactic treatment. Therefore, it is necessary to continue alerting clinical practitioners to the importance of screening for tuberculosis and prophylactic treatment for LTBI before the initiation of biologic agents for the treatment of IMIDs.

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CONFLICT OF INTEREST

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All authors have read and approved the final version of the manuscript.

Arisa Iba had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

TRANSPARENCY STATEMENT

Arisa Iba affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analyzed during the current study are not publicly available due to ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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