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Original Article

Efficacy of isoniazid salvage therapy for latent tuberculosis infection in patients with immune-mediated inflammatory disorders – A retrospective cohort study in Taiwan

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KEYWORDS
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Abstract *Background:* Active tuberculosis (TB) in patients with latent tuberculosis infection (LTBI) was associated with use of biological agents for immune-mediated inflammatory disorders (IMIDs). For decreasing active TB, isoniazid prophylaxis therapy was administered before biologic therapy among IMID patients with LTBI. However, for patients who had been received biologics for a long time with unknown status of LTBI or exposure history of active TB, the prevalence of LTBI and efficacy of isoniazid therapy were unclear.
Method: A retrospective cohort study was conducted during 2012–2014 in a tertiary medical center in Taiwan, and the incidence case of active TB was identified by the national TB registration system on October 1, 2015.
Results: All 382 patients with 1532 person-years were followed up, the initial prevalence of LTBI by positive interferon-gamma releasing assay (IGRA+) was 17.5%. The prevalence of LTBI was increased in elder age (>20%, $p < 0.05$), chronic kidney disease (33%, $p < 0.05$), metabolic syndrome (26.3%, $p < 0.05$), but not related to the type of IMIDs or biologics. The crude incidences of TB were increased in elders (53.3/1000 person-year), abnormal chest film (49.6/1000

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person-year), administration of tocilizumab (13.6/1000 person-year), and metabolic syndrome (56.1/1000 person-year), respectively. Among patents with LTBI, the incidence of active TB was lower in patients with isoniazid therapy (9.2/1000 person-year, $p = 0.02$) than without isoniazid therapy (92.2/1000 person-years), regardless the timing of initiating isoniazid therapy ($p > 0.05$).

Conclusion: Isoniazid therapy can prevent active TB from LTBI despite of the timing of biologics administration.

Introduction

Immune-mediated inflammatory disorders (IMIDs), including rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriasis (Pso), and psoriatic arthritis (PsA), are defined as a group of inflammatory diseases related to immune dysregulation, presenting with a broad spectrum of manifestations.[1,2] Biological Disease-Modifying Antirheumatic Drugs (bDMARDs), including tumor necrosis factor inhibitors (TNFis; including etanercept [ETN], adalimumab [ADA], and golimumab [GOL]), anti-interleukin 6 receptor monoclonal antibody (anti-IL6R MAb; tocilizumab, TOC), anti-CD20 MAb (rituximab, RTX), and CTLA-4 agonist (abatacept, ABA), are recommended for IMID patients refractory to conventional synthetic (csDMARD) therapy.[3–6]

The major concern of biological agents is the increase in the incidence of infections such as tuberculosis (TB). Administration of TNFis increased the incidence of TB had been also reported.[7,8] Recent randomized controlled trials (RCTs) have shown that anti-IL6R MAb, anti-CD20 MAb, and CTLA-4 agonist possessed a lower risk of TB than TNFis.[9] In areas with a median incidence of active TB, the prevalence of latent TB infection (LTBI) ranged from 10% to 18%.[10,11] The risk of active TB is related to the LTBI status,[12,13] history of exposure to index cases within 2 years,[14] and comorbidities such as metabolic syndrome[15] and gastrectomy.[16] The current method to detect LTBI is usually based on some indirect tests, such as IFN-γ releasing assay (IGRA) and tuberculin skin test (TST) in non-Bacillus Calmette–Guérin (BCG) vaccinated area, although a definite infection with MTB is defined by autopsy.[17,18] Patients with IMIDs plan to initiating biologics treatment are recommended to receive isoniazid (INH) prophylaxis therapy (IPT) in cases of LTBI.[19] However, there were some questions to be answered. First, among patients who had undergoing biologics without active TB and unknown history of exposure to index cases, is the salvaged administration of INH therapy (IT) necessary to prevent further onset of active TB if IGRA screening showed positive results? Second, the efficacy of isoniazid therapy in bDMARD therapy with non-TNFis remains unclear in the real world.

The aim of this study was firstly evaluate the probability of LTBI in a patient cohort with IMIDs selected from a tertiary medical center with a median incidence of TB and national BCG vaccination program. Further, to investigate the incidence of active TB among patients with different risks including various types of biological agents. Finally, to evaluate the efficacy of isoniazid therapy and it's association with timing related to the biological agents.

Methods

Study cohort

Patients with IMIDs, including RA, AS, Pso, and PsA, and those aged more than 20 years were retrospectively selected from a tertiary medical center in Taiwan during 2012–2014. Patients were cross-sectionally screened with IGRA (QuantiFERON-TB Gold In-Tube) when the assay was available in the study hospital since 2012. The clinical characteristics, comorbidities, medication history, IGRA results, chest radiographs, and bDMARD therapy history were documented by chart review. The chest radiographs were reviewed by two pulmonologists with the following descriptions for suspicion of previous TB infection[16]: apical thickening, thoracic contraction, and fibronodular or reticular lesions with nodules not referring to malignancy.

Biological agents and DMARDs

Patients who were refractory to traditional therapy applied biologics according to the recommendation of the EULAR or ACR society. The biological agents included ETN, ADA, GOL, ABA, TOC, and RTX. Patients who were enrolled in companies' clinical trials were excluded. A single use of bDMARDs (single DMARDs) was defined as patients receiving one category of biologics, i.e., only one TNFi in life or switching from ETN to ADA. For patients who developed active TB, only the biological agents prior to the onset of TB were recorded.

Identification of active TB

All patients were retrospectively confirmed with active TB via the governmental registration system for TB management by October 1, 2015. In the registration system, the active TB were recorded as patient with microbiological evidence of MTB or clinical evidence with active TB who had received complete anti-TB chemotherapy. The time period of the onset of active TB was defined by the duration from the first biologic used to the date of the onset of active TB. LTBI was defined as positive IGRA (IGRA+) without evidence of active TB within 3 months of IGRA test.

INH therapy (IT)

Before the year of 2015 in Taiwan, INH prophylaxis therapy was not mandatory in patients with IMIDs and LTBI. INH therapy only could be initiated with agreement from patients after comprehensively explanation. Patients with IGRA+ result or abnormal chest films were refer to pulmonologists to exclude the active TB. If patient with LTBI status was confirmed and they agreed to receive INH therapy, the INH was prescribed with a dose of 5 mg/kg up to 300 mg/day for 6–9 months. TNFi or other biologics were initiated after at least 1 month of LTBI treatment.

For those who had been received biologics prior to IGRA screening and with LTBI, the biologics were hold until at least 1 month later of INH prescription. The dose and duration of INH therapy were the same as mentioned. In current study, INH salvage therapy (IST) was defined as the initiation of isoniazid in patients with previous biologics administration, whereas INH prophylaxis therapy (IPT) indicated the isoniazid was administrated prior to the first dose of biological agents.

Statistical analysis

Continuous variables were compared using Student's *t*-test or a nonparametric test if they were not normally distributed. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test if the accepted number was less than 5. Risk ratios (RRs) with 95% confidence intervals (95% CIs) were obtained. Survival analysis was performed using the Kaplan–Meier method, and nonparametric tests were used to analyze the differences. A p value of <0.05 was considered statistically significant.

Ethics statement

Receiving informed consent was waived due to the retrospective nature of the study, and approval was obtained from the Institutional Review Board of the Taipei Veterans General Hospital (VGHIRB No: 2015-11-005A).

Results

Study cohort

Overall 382 patients who had received bDMARD therapy were enrolled, including 245 patients with RA, 89 with AS, 30 with Pso/PsA, and 18 patients with at least 2 categories of IMIDs. Most patients were followed up for more than 1 year (87.7%), and the follow-up duration ranged from 10 months to 4.2 years, with a median of 19 months and interquartile range (IQR) of 16.7 months. Females (67.5%) and those younger than 65 years (80.2%) were predominant, and the most common comorbidity was metabolic syndrome (25.1%) (Table 1).

Prevalence of LTBI

The initial prevalence of LTBI according to IGRA+ was 17.5% and the age-specific proportion of IGRA+ was showed in Fig. 1. The prevalence of LTBI was not related to gender, type of IMIDs, type of biologics, and chest radiographs ($p > 0.05$, Table 1). However, the prevalence of LTBI was higher in patients older than 51 years and with metabolic syndrome (26.3%, $p < 0.05$), chronic kidney disease (33%, $p < 0.05$), but was slightly lower in those who received single use of bDMARDs with ADA (12.8%) and ABA (16.7%), and switching between different TNFis (10.7%) (Table 1, $p > 0.05$).

Among 354 patients who completed chest radiographs without previous anti-TB chemotherapy, 141(39.8%) were suspected with a previous TB infection according to chest radiographs. Among patients with abnormal chest radiograph, the proportion of IGRA+ were slightly higher (23%) than those of chest radiograph not suggested pulmonary TB (15%) ($p > 0.05$).

Incidence of active TB

Among the 382 IMID patients with 1532 person-years at risk, the cumulative incidence and incidence rate of active TB were 18.3‰ and 4.57/1000 person-year respectively. None had recurrence of active TB in patients with a history of completed anti-TB chemotherapy. As Table 2 shown, the risk of active TB was higher in IGRA+ [75.7‰, RR(95%CI): 21(4.7–93)], and slightly increased in IGRA indeterminate [31‰, RR:8.8(0.9–87)] than in IGRA− patients (6.4‰). The positive conversion rate for IGRA was 1.6% (5 of 37), in which one of the patients was diagnosed with active TB. The remaining four patients with IGRA+ conversions had received IT, and no further active TB was diagnosed within 14.9 of person-years. In this study cohort, none of MTB strains isolated from the patients was resistant to INH or rifampicin. The characteristics of all patients who developed active TB were shown in Supp. 1.

The influence of INH therapy (IT) on TB incidence

Among 67 patients with IGRA+ at screening, 43 of them had received IT, 24 of them refused IT. Four patients received IT according to the positive conversion of IGRA, and three patients with IGRA-I received IT according to the abnormal chest film. For IGRA+ patients, the proportions of newly onset TB were 2.4% (1 of 43) and 16.7% (4 of 24) in those with or without IT, respectively ($p = 0.05$, Table 2). There were eight patients with repeated IGRA showed negative conversion of IGRA after IT.

The effectiveness for IT according to the time of initiating biologics was showed in Table 3. The incidence rate of active TB was not related to the time of initiate IT before or after starting biological agents ($p > 0.05$). Generally, all of the patients received INH therapy for 6–9 month (mean ± SD: 7 ± 3 months), and none of them discontinued INH due to side effect or other reasons. In the study cohort, none of patients with LTBI and IT permanently discontinued the biological agents.

Risks on TB incidence in IMID patients

Regarding to the single bDMARDs, patients with TOC therapy had the highest incidence of active TB (13.6/1000

Table 1 Univariate analysis for patients with IMIDs and results of IGRA at first time of screening during 2012—2014.

Variable	N	IGRA results			p value*
		Positive	Negative	Indeterminate	
		n (%)	n (%)	n (%)	
Gender					0.63
Male	124	20 (16.1)	96 (77.4)	8 (6.5)	
Female	258	47 (18)	187 (72.5)	24 (9.4)	
Age					**0.001**
≤40	93	4 (4.3)	84 (90.3)	5 (5.4)	
41—65	213	45 (20.9)	148 (69.7)	20 (9.5)	
>65	76	18 (24)	51 (66.7)	7 (9.3)	
Autoimmune disorder					0.64
RA	245	43 (17.3)	178 (72.7)	24 (9.9)	
AS	89	12 (13.5)	73 (82)	4 (10)	
Pso/PsA	30	8 (26.7)	19 (63.3)	3 (9.3)	
≧2 IMIDs[a]	18	4 (22.2)	13 (72.2)	1 (5.6)	
Host-related factors					**
Asthma	13	2 (15.4)	9 (69.2)	2 (15.4)	0.6
Lung diseases	13	2 (15.4)	10 (76.9)	1 (7.7)	0.9
CKD	6	2 (33.3)	2 (33.3)	2 (33.3)	**0.03**
ESRD with HD	1	0	1 (100)	0	0.8
Malignancy	9	2 (22.2)	6 (66.7)	1 (11.1)	0.86
Metabolic syndrome	96	25 (26.3)	61 (63.2)	10 (10.5)	**0.012**
Lipidemia	33	9 (27.3)	20 (60.6)	4 (12.1)	0.16
Chronic hepatitis	25	5 (20)	15 (60)	5 (20)	0.08
Thyroid dysfunction	4	0	4 (100)	0	0.49
GERD	50	10 (20)	35 (70)	5 (10)	0.7
Psychological complaint	3	2 (66.7)	1 (33.3)	0	0.15
TB-related factors					
History of anti-TB chemotherapy	7	1 (14.3)	6 (85.7)	0	0.85
Chest film abnormality					0.12
Suggest previous TB infection	141	33 (23.1)	94 (68)	13 (8.8)	
Not suggest previous TB infection	213	32 (15.1)	162 (75.9)	19 (8.9)	
Not available	21	0	21 (100)	0	&
INH therapy					**<0.01***
Yes	50	43 (86)	3 (6)	4 (8)	
No	332	24 (7)	280 (84.5)	28 (8.5)	
Biologics					
Single bDMARD					
ETN	131	28 (21.7)	91 (70.5)	10 (7.8)	-
ADA	125	16 (12.8)	100 (80)	8 (7.2)	0.22
GOL	4	3 (66.7)	1 (33.3)	0	0.31
TOC	3	1 (33.3)	1 (33.3)	1 (33.3)	
ABA	42	7 (16.7)	32 (76.2)	3 (7.1)	0.78
RTX	5	1 (20)	3 (60)	1 (20)	0.61
Alternative TNFi[b]	29	3 (10.7)	19 (71.4)	5 (17.9)	0.13
Sequential bDMARDs[c]					
TNFi/TOC	13	3 (25)	9 (66.7)	1 (8.3)	0.99
TNFi/ABA	11	1 (9.1)	9 (81.8)	1 (9.1)	0.62
TNFi/RTX	8	2 (14.3)	5 (71.4)	1 (14.3)	0.30

(*continued on next page*)

Table 1 (*continued*)

Variable	N	IGRA results			p value*
		Positive	Negative	Indeterminate	
		n (%)	n (%)	n (%)	
History of non-TNFi biologics[d]					
TOC and TNFi/TOC	16	4 (25)	10 (62.5)	2 (12.5)	0.75
ABA and TNFi/ABA	53	8 (15.1)	41 (77.4)	4 (7.5)	0.61
RTX and TNFi/RTX	13	3 (16.6)	8 (66.7)	2 (16.6)	0.22
Total	**382**	**67 (17.5)**	**283 (74.1)**	**32 (8.4)**	

[a] Patients who presented with more than 2 categories of IMIDs.
[b] Alternative TNFi: Patients who received different kinds of TNFi therapy due to non-tuberculosis reasons.
[c] Sequential use of biologics from TNFis to non-TNFis, including TOC, ABA, and RTX.
[d] Patients with a history of non-TNFi biologics prior to new-onset TB, the number of patients included sequential use of bDMARDs from TNFi to non-TNFi.
Abbreviations: ABA: abatacept, AS: ankylosing spondylitis, F: female, IGRA: interferon-gamma releasing assay, INH: isoniazid, M: male PsA: psoriatic arthritis, Pso: psoriasis, RA: rheumatoid arthritis, RTX: rituximab, TB: tuberculosis, TNFi: tumor necrosis factor inhibitors, TOC: tocilizumab.
*: p-values were obtained by overall Chi-square test. ** P-values were obtained for patients compared to those who without the diseases.
&: not included in Chi-square analysis.
-: Baseline for comparison in chi-square test.
&: Patients not included in statistics.

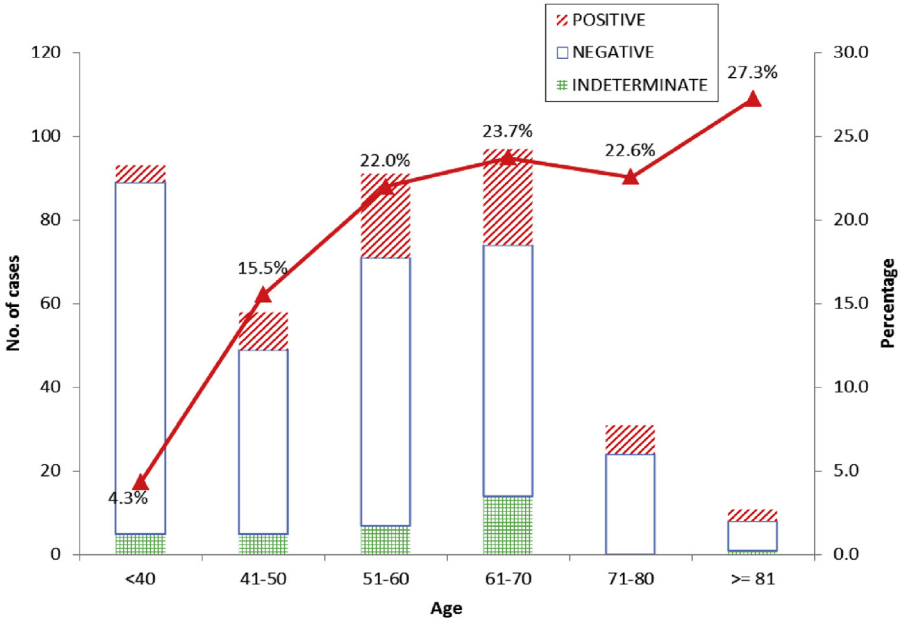

Figure 1. Age specific IGRA positive rate for patients who receive first time of IGRA screening.

person-year, $p < 0.05$), followed by ADA (6.3/1000 person-year) and ETN (1.8/1000 person-year) (Table 2, Fig. 2). Other single bDMARDs presented with zero incidence of TB. In patients with history of receiving TOC, the positive LTBI status was the predictor of active TB after administration with TOC ($p < 0.05$, Suppl 1).

Overall, age older than 65 years, abnormal chest radiographs, and metabolic syndrome were risks related to onset of TB in univariate Kaplan-Meir analysis ($p < 0.05$, Suppl 2). In patients without INH therapy, the risk of active TB was higher in patients with IGRA+ ($p < 0.01$), abnormal chest radiographs ($p < 0.01$), age older than 65 years, and metabolic syndrome ($p < 0.05$, Suppl 3). Corticosteroid, methotrexate, and other combinated medications revealed no influence on the onset of active TB in study cohort ($p > 0.05$).

Discussion

This retrospective observational study of patients with IMIDs demonstrated the heterogeneous medication of bDMARDs in real life. The strength of this study was that most patients were followed up for more than 1 year, with the longest follow-up duration under biologics for more than 10 years. Three important findings were observed in

Table 2 Univariate analysis for incidence of tuberculosis in the study population.

Variable	N	Active TB (n)	Cumulative incidence (1/1000 person)			Incidence rate (1/1000 person-year)			
			n/N (‰)	OR	p-value	p-y at risk (PY)	n/PY (‰)	RR	p-value
Gender									
Male	124	2	16.1	0.8 (0.2—4.2)	0.58	508.6	3.9	0.8 (0.1—4.1)	0.42
Female	258	5	19.6	1.00	-	1023.2	4.8	1.00	-
Age									
≤40	93	1	10.7	1.00	-	381.9	2.6	1.00	-
41—65	213	2	9.4	0.9 (0.1—9.6)	0.6	877.1	2.3	0.9 (0.08—9.6)	0.3
>65	76	4	53.3	4.9 (0.7—34)	0.12	272.8	14.6	5.6(0.8—390	**0.05**
Type of disorder									
RA	245	5	20.6	1.00	-	976.8	5.1	1.00	-
AS	89	1	11.2	0.5 (0.07—4.4)	0.5	372.6	2.7	0.5 (0.06—4.3)	0.31
Pso/PsA	30	1	33.3	1.6 (0.2—13)	0.5	95.8	10.4	2.0 (0.2—16.6)	0.26
≧2 IMIDs	18	0	0	0	0.7	86.5	0	0	0.33
TB-related factor									
History of anti-TB chemotherapy	7	0	0.0	0	NA	27.6	0.0	0	0.49
Chest film abnormality									
Suggest previous TB infection	141	7	49.6	NA	**0.001**	566.5	12.3	6.99	**<0.001**
Not suggest previous TB infection	213	0	0	1.00	-	886.4	0	1.00	-
Not available	21	0	0	NA	NA	51.33	0	0	0.086
IGRA									
Positive	67	5	75.7	21 (4.7—93)	**0.001**	291	17.2	13.8	**<0.001**
Negative	283	1	6.4	1.00	-	1134.9	0.8	1.00	-
Indeterminate	32	1	31	8.8 (0.9—87)	0.2	106.1	9.4	10.7 (1.2—98)	**0.08**
IGRA+									
With INH	43	1	23.2	1.00	**0.05**	192.3	5.2	1.00	-
Without INH	24	4	166.7	7.2 (0.8—60)	-	93.3	42.8	8.2 (1.2—51)	**0.009**
IGRA conversion with INH	4	0	0	0	0.9	14.9	0	0	0.023
Type of bDMARDs									
ETN $	131	1	7.7	1.00	-	550.8	1.8	1.00	-
ADA	125	3	24	3.1 (0.3—26)	0.29	478.4	6.3	3.4 (0.4—29)	0.15
GOL	4	0	0	0	0.86	6.9	0	0	0.49
TOC	3	1	33.3	43 (8.5—217)	**0.045**	7.35	13.6	75 (18—304)	**0.01**
ABA	42	0	0.0	0	0.57	72.9	0.0	0	0.44
RTX	5	0	0	0	0.85	28.8	0.0	0	0.47
Alternative TNFi[a]	29	0	0.0	0	0.64	191.5	0.0	0	0.37
History of non-TNFi biologics[c]									
TOC and TNFi/TOC[b]	16	3	18.7	24 (5.3—109)	**<0.01**	73.8	40.6	22.3 (4.7—106)	**0.003**
ABA and TNFi/ABA	53	0	0.0	0	0.29	247.6	0.0	0	0.34
RTX and TNFi/RTX	12	0	0	0	0.05	68.9	0	0	0.11
Host-related factors*									
Metabolic syndrome	107	6	56.1	2.2	0.16	359.7	16.7	3.3	**0.025**
CKD	6	1	166.7	6.6	**0.03**	23.0	43.5	5.98	0.09
Total	382	7	18.3			1531.8	4.57		

The cumulative incidence and incidence rate were obtained since the first dose of biological agents.
Bold text represented the statistical significance with p-values ≤ 0.05.
Abbreviations: ABA: abatacept, AS: ankylosing spondylitis, bDMARD: biological Disease-Modifying Antirheumatic Drugs, F: female, IGRA: interferon-gamma releasing assay, INH: isoniazid, M: male, OR: odds ratio, PsA: psoriatic arthritis, Pso: psoriasis, p-y: person-year, RA: rheumatoid arthritis, RR: relative risk, RTX: rituximab, TB: tuberculosis, TOC: tocilizumab, TNFi: tumor necrosis factor inhibitors.
-: Baseline for comparison in univariate analysis by chi-square test.
*: Only the statistical significant risks for incidence of active TB were shown.
[a] Alternative TNFi: Patients who received different kinds of TNFi therapy due to non-tuberculosis reasons.
[b] Sequential use of biologics from TNFi to non-TNFis, including TOC, ABA, and RTX.
[c] Patients with a history of non-TNFi biologics prior to new-onset TB, the number of patients included sequential use of bDMARDs from TNFi to non-TNFi.

Table 3 Effectiveness of isoniazid therapy in patients LTBI prior to or after initiating biological agents.

INH therapy	N	abnormal CXR[a] n (%)	Active TB n (%)	Incidence rate[c]			
				p-y	Incidence (‰ p-y)	RR (95%CI)	P-value
IGRA (+) or (+) conversion							
No INH therapy	24	13 (54.2)	4 (16.6)	43.4	92.2	1.00	—
With INH therapy	50	27 (54.0)	1 (2.0)	108.8	9.2	0.29 (0.09–0.9)	0.02[b]
Prophylaxis	15	8 (53.3)	0	34.3	0.0	0 (-)	<0.01[b]
Salvage	35	19 (54.3)	1 (2.8)	74.5	13.4	0.14 (0.02–0.9)	0.04[b]

[a] Chest radiography that suggesting previous TB infection was characterized to abnormal CXR.
[b] p-value was obtained when the incidence of active TB was compared to those who were IGRA (+) without INH therapy.
[c] The cumulative incidence was estimated since the first time of IGRA screening.
Abbreviations: CXR: chest radiography, IGRA: interferon-gamma releasing assay, INH: isoniazid, TB: tuberculosis, p-y: person-year.

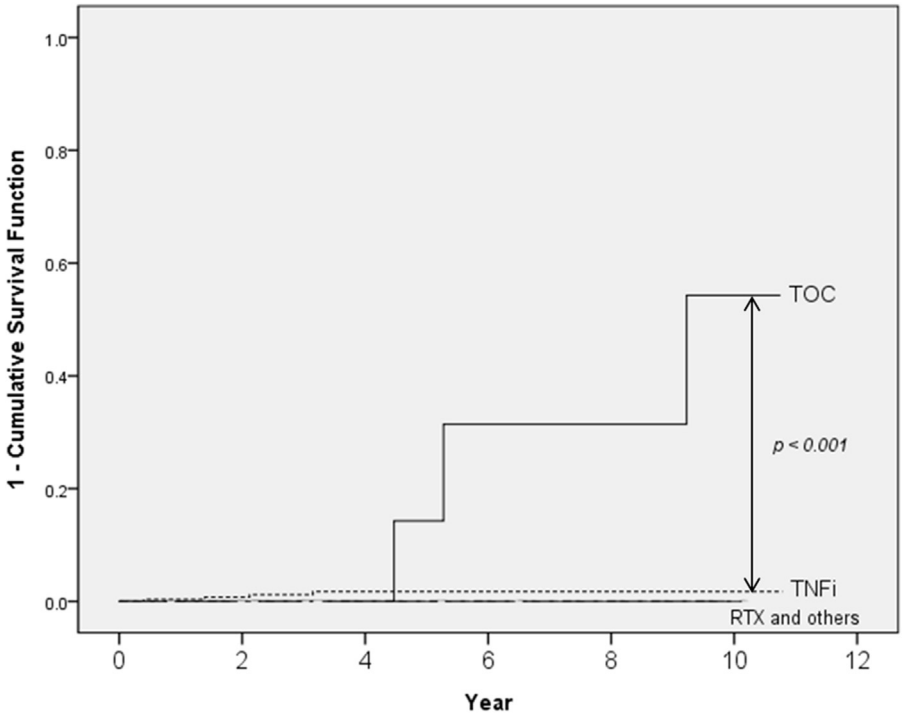

Figure 2. Incidence of active TB in patients with IMIDs who received biologics therapy. New onset of active TB among patients with history of non-TNFi treatments were shown by different lines in the plot. P value was obtained when compared to the patients who received TNFi therapy. The analysis was performed using Kaplan-Meir Method, and p-value less than 0.05 was demonstrated (Log-rank test). **Abbreviations:** ABA: abatacept, TNFi: tumor necrosis factor inhibitors, TOC: tocilizumab, RTX: rituximab.

our cohort. First, the effectiveness of isoniazid therapy in LTBIs was demonstrated despite the isoniazid was prescribed before or after bDMARDs therapy. The second finding was that active TB may happen in patients with IGRA-Indeterminate results after the initiation of biological agents. Further, we observed that patients with a history of TOC use and the association with high incidence of TB in patients with LTBI.

In Taiwan, the incidences of TB ranged from 79 to 53/100,000 person-year during the year 2005 and 2012. We found that the high proportion (39%, 141/354) of abnormal chest film in patients with IMIDs, and 23% (33/141) of the patients with abnormal chest film were IGRA+. The high frequencies of previous TB infection or LTBI were also in other median TB incidence countries.[20] However, there were less than 100% of patients remained IGRA+ after anti-TB chemotherapy or after INH prophylaxis therapy.[21] Therefore, the positive rate of IGRA could be lower than the percentage of abnormal chest film. Further, a national-wide survey showed previous TB infection early in life might increase the risk of RA in future.[22] The association between tuberculosis and arthritis could be explained by dysregulated immune response after infection with MTB that further investigation is warranted.[23]

The national BCG vaccination program for live births was started in 1965 with covering rate greater than 98% in Taiwan. We estimated the BCG coverage rate as 95–98% among patients younger than 51 years old, which accounted for 41.9%

of study population, thus the estimated BCG coverage rate was 41.1% of overall population. Due to the unavailability of TST in the study hospital, and TST results could interfere by BCG vaccination and in old ages, we used IGRA and chest radiographs for surveying the likelihood of MTB infection. In our cohort, the prevalence of LTBI was 17.5% (IGRA+) and indeterminate IGRA results was 8.6%, which is similar to a previous result in central Taiwan.[11] Patients younger than 51 years of age had a lower IGRA positive rate (9.3%) than those elder than 51 years of age (23%, $p < 0.05$). This observation was compatible with the BCG vaccination program since year 1965. The other factors associated with positivity of IGRA included the exposure of GOL or TOC, suggesting that the choice of biologics is confounded by the LTBI status.

For patients with active TB, it could not differentiate reactivation from LTBI or new infection of MTB unless molecular typing for *mycobacterium* was performed; the onset of active TB was therefore recorded according to the national-wide register system. The overall incidence of active TB were 4.57/1000 person-year, 3.2/1000 person-year in patients undergoing TNFi, and 8.6/1000 person-year in patients undergoing non-TNFi, respectively. The incidences were lower to the previous findings in patients with RA[11,24] in Taiwan. The reason could be explained by some of patients with LTBI had receive INH therapy, which resulted in the lower incidence of active TB in our cohort.

The INH prophylaxis therapy for LTBI prior to biological agents and regular follow up with IGRA test per 6 months were recommended by the society of rheumatology in Taiwan since 2015. Before the year of 2015, the IGRA test was only supported once before bDMARDs therapy by non-government funding source. Because of the expensiveness for the IGRA in Taiwan, there was only 43 of patients had serial IGRA testing. Therefore, the serial IGRA results were lacking in current study.

The purpose of isoniazid prophylaxis therapy is to prevent onset of active TB in contact with exposure history to index case within 2 years.[25] Herein we demonstrated the IT was effective in patients who had been received bDMARDs, regardless of history for exposure to index case. It could provide the evidence to start IT in patients with LTBI who had been received bDMARDs prior to the IGRA screening. However, the effectiveness of IT for patients with LTBI and sequential bDMARDs was uncertain. In our cohort, a case with 9 months of IT was failure to prevent onset of active TB after starting TOC therapy.

Furthermore, time to initiating bDMARDs after starting latent TB chemotherapy was controversial.[26] Guidelines from UK suggested starting bDMARDs after complete prophylaxis LTBI therapy,[27] others suggested at least 3–4 weeks of INH or rifampicin prior to biological agents.[28] In our cohort, the shortest duration of IT prior to bDMARDs was 2 weeks, and some patients may extend to 2–3 months of IT before starting bDMARDs. Further investigation could be considered to find out the minimal requirement of time duration for prophylaxis anti-TB therapy prior to biological agents.

The increased risk of tuberculosis after administration with different TNFis had been discussed. Patients who received ADA would have a 3-4 times of risk for active TB than ENT.[26] This observation was also presented in our patient cohort (OR = 3.1, $p = 0.15$, Table 2), although without statistical significance which could be attributed to a limited population size.

In current study, we found that patients in the TOC treatment subgroup also had a higher incidence of TB than patients with TNFi monotherapy. The onset of active TB (<1.5 year) after the administration of TOC following long-term TNFi therapy (>3.5 year) has not been reported.[29–32] There were some reasons to be considered. Traditionally, patients who received TOC therapy usually presented a higher disease activity,[33] that lead to more frequently administration of concomitant corticosteroid than TNFi, which the former was also related to increase the risk of active TB.[34] However, in our subgroup observation, co-administration of corticosteroid, methotrexate (MTX), or adjustment of corticosteroid or MTX were not related to the onset of active TB (Supp 1) in patients who received TOC. The status of LTBI was the significant factors to predict onset of active TB. The second explanation was related to the immunopathophysiology of the active TB in corresponding to the biological agents. The role of TNF-α in the control of TB via the activation of macrophages which lead to and maintain the TB granuloma has been well established.[7,8] IL-6 is also directly related to the anti-MTB microbicidal effect in macrophages.[35–37] An IL-6 knock-out animal model revealed disease progression of TB due to the deleterious effects of type 1 IFN and impaired innate immunity.[38] In summary, the inhibition by TNFis and IL-6R MAb may both act on macrophages, neutrophils, and the type 1 IFN lineage, leading to the risk of the progression of active TB. Further extended post-marketing survey or animal trials designed to co-administration or sequential use of TNF-a blockers and IL-6R MAb in control of MTB infection was need be considered.

The strengths of current study were the identification of initial LTBI status according to laboratory results in a cross-sectional survey, definition of active TB via the governmental registration system, and the chest image finding to confirm the status of previous TB infection, which were irreplaceable by database survey.[24,39,40] There are some limitations in this retrospective cohort study. First, there was a lack of a fixed follow-up duration for each patient so that the person-years under risk may be uneven between groups. Second, the heterogeneous clinical characteristics resulted in the influence of comorbidities and medications on the risk of active TB. As a result we did not analyze the risk of TB for each medication in DMARDs, such as MTX, corticosteroid, and sulfasalazine that need to be more detailed analyzed in future investigation. Finally, the limited number of patients in subgroups that multivariate analysis was not performed.

In conclusion, the prevalence of LTBI among patients with IMIDs in a median TB incidence area was approximately 20% by IGRA. The incidence of active TB was not only observed among patients with IGRA+ but also among those with IGRA-indeterminate results. The risk factors related to the increase of active TB in IMIDs included elders before BCG vaccination era, metabolic syndrome, and the likelihood of previous TB infection, and isoniazid were effective for the prevention of active TB regardless it was prophylaxis or salvaged administrated. Subgroup analysis showed that the anti-IL6R MAb may be related to a progressive form of active TB, particularly in patients with LTBI.

Conflicts of interest

This study was supported by academic grants 103DHA0100371 and 105DHA0100478 by Taipei Veterans General Hospital. Otherwise, the author has declared no conflicts of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jmii.2017.04.001.

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