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ORIGINAL ARTICLE

Serial QuantiFERON-TB Gold In-Tube testing for psoriatic patients receiving antitumor necrosis factor-alpha therapy

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ABSTRACT

Background/Objective: Tumor necrosis factor-α (TNF-α) antagonists have become increasingly popular in the treatment of psoriasis. However, the increased risk of latent tuberculosis infection (LTBI) reactivation has also become an important issue in clinical practice. The aim of this study was to evaluate serial QuantiFERON-TB Gold In-Tube (QFT-GIT) testing for detecting LTBI among a cohort of psoriatic patients vaccinated with bacille Calmette-Guérin in a country with an intermediate burden of TB during long-term treatment with TNF-α antagonists.

Methods: We enrolled psoriatic patients treated with TNF-α antagonists who also accepted yearly serial QFT-GIT testing and regular chest X-ray examinations before and during the anti-TNF-α treatment from January 2010 to August 2014. Patients diagnosed with LTBI received chemoprophylaxis, and QFT-GIT testing was performed in these patients after completion of chemoprophylaxis.

Results: In this retrospective study, 101 patients had completed baseline and at least 1 year of follow-up. Among these patients, 60 had continued TNF-α antagonists therapy and received examinations in the 2nd year, whereas 18 had continued the therapy until the 3rd year. The conversion rate among these patients was 14.29% (13/91). In this study, 23 patients were diagnosed with LTBI according to the positive results obtained in the QFT-GIT test, with 19 of them having completed chemoprophylactic therapy. Follow-up QFT-GIT testing revealed reversion in 11 patients (57.89%) and decreased interferon-γ (IFN-γ) levels (68.42%) in 13 patients. Patients over 45 years of age tended to have a persistent positive result.

Conclusion: This study demonstrated that 14.29% of psoriatic patients undergoing long-term TNF-α antagonist therapy had a QFT-GIT conversion. Although a decreased IFN-γ level and QFT-GIT reversion were observed in most cases following prophylactic therapy, the value of QFT-GIT for evaluating the effect of LTBI prophylaxis remains controversial.

Introduction

The use of tumor necrosis factor-α (TNF-α) antagonists in psoriatic patients has become more common in recent years. However, patients treated with TNF-α antagonists are at increased risk of latent tuberculosis infection (LTBI) reactivation; therefore, screening for LTBI prior to initiating TNF-α antagonist therapy is important.[1,2] The tuberculin skin test (TST) is considered one of the standard methods of screening for TB infection. However, TST has some disadvantages. For example, false-positive results may occur in patients previously vaccinated with bacille Calmette-Guérin (BCG), which may limit its usefulness in high BCG-vaccinated populations.[3] In addition, TST is not specific for *Mycobacterium tuberculosis* infection, and cross reactivity with environmental mycobacteria may occur.[4] TST may also overestimate LTBI risk in

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psoriatic patients because the enhanced inflammatory process may cause koebnerization, which interferes with the evaluation of TST.[5] Recently, whole-blood interferon-γ release assays (IGRAs) were introduced for the diagnosis of LTBI, including the QuantiFERON-TB Gold In-Tube test (QFT-GIT; Cellestis Limited, Carnegie, Victoria, Australia) and T-SPOT TB test (Oxford Immunotec, Oxford, UK). In contrast to TST, IGRA is more specific for screening LTBI and is not affected by BCG vaccination.[6] Therefore, IGRA is considered superior to TST for detecting LTBI in countries with an intermediate to high burden of TB as well as in countries with high BCG vaccination rates.

Although there are many studies discussing a test to screen for LTBI in patients with psoriasis who have not started receiving TNF-α antagonist therapy, the long-term follow-up of LTBI in such patients is limited. The aim of this study was to evaluate the QFT-GIT test for detecting LTBI in a cohort of BCG-vaccinated patients with moderate-to-severe psoriasis, receiving long-term treatment with TNF-α antagonists in a country with an intermediate burden of TB.

Materials and methods

Patients

In this retrospective study, we enrolled psoriatic patients treated with TNF-α antagonists from January 2010 to August 2014 at Chang Gung Memorial Hospital, Linkou, Taiwan. All the patients had accepted to receive yearly serial IGRA testing and regular chest X-ray examinations before and during the anti-TNF-α treatment. All patients received at least one 12-week course of TNF-α antagonist therapy, including either etanercept or adalimumab. The medical records of these patients were reviewed to evaluate demographic information, clinical diagnosis, medication history, and laboratory data.

QuantiFERON-TB Gold In-Tube assay for latent tuberculosis infection

All the patients underwent serial testing with QFT-GIT for screening of LTBI. The antigens used in QFT-GIT are a peptide cocktail simulating the proteins ESAT-6, CFP-10, and TB7.7. The interferon-γ (IFN-γ) values were calculated by subtracting the value obtained with nil antigens, with a cutoff value of 0.35 IU/mL. A positive result was defined as an IFN-γ of nil antigens < 8.0 IU/mL and an IFN-γ response of ≥ 25% of nil antigens. A negative result was defined as an IFN-γ of nil antigens < 8.0 IU/mL and an IFN-γ response of < 25% of nil antigens or an IFN-γ response minus nil antigens < 0.35 IU/mL. Results with an IFN-γ of nil antigens > 8.0 IU/mL or IFN-γ of mitogen minus nil antigens < 0.5 U/mL were interpreted as indeterminate. Conversion of IGRA was defined as a negative IGRA at baseline and a positive IGRA at follow-up, and reversion of IGRA was defined as a positive IGRA at baseline and negative IGRA at follow-up.

Treatment and follow-up of LTBI

In this study, the diagnosis of LTBI was made on the basis of a positive QFT-GIT result and a negative chest radiograph or microbiological assay. Patients diagnosed with LTBI were referred to a pulmonologist and received chemoprophylactic therapy. During the course of chemoprophylactic therapy, all the patients underwent regular laboratory investigation of liver enzymes and bilirubin level. A follow-up QFT-GIT test was performed in these patients following completion of the chemoprophylactic therapy.

Statistical analysis

SPSS version 17 (SPSS Inc., Chicago, IL, USA) was used for all the analysis in this study. The Wilcoxon signed-rank test was used to compare the IFN-γ level before and after the prophylactic therapy. A comparison of patients with a persistent positive result and reversion of QFT-GIT after completion of chemoprophylaxis for LTBI was performed using the Fisher's exact test for categorical data.

Results

Patient characteristics

In total, 101 patients were enrolled in this study. Of these patients, 69 were men (68.3%) and the median age was 41 years (43.41 ± 11.33 years). Ninety-five patients received BCG vaccination (95%), 89 patients received etanercept (88.1%), and 12 patients received adalimumab (11.9%). Thirty-one patients also received concomitant immunosuppressant therapy during the anti-TNF-α treatment. Among these patients, methotrexate was the most commonly used drug (21.8%), and two patients were treated with more than one immunosuppressant. According to chest radiographs, none of the patients had a previous history of TB or active pulmonary lesions. The demographic data are presented in Table 1.

Outcome of serial IGRA

The patient distribution, according to the QFT-GIT status, at baseline and at follow-up, of active treatment is summarized in the study flowchart (Figure 1). In this series, all of the 101 patients completed evaluations at baseline and at least 1 year of follow-up. Among these patients, 60 (59.41%) had continued both TNF-α antagonist therapy and received examinations into the 2nd year, whereas 18 (17.82%) had continued the therapy into the 3rd year. The median cumulative durations of TNF-α antagonist therapy were 33 (31.98 ± 11.89) weeks, 26 (26.38 ± 11.74) weeks, and 26 (29.44 ± 10.12) weeks during the 1st year, 2nd year, and 3rd year of follow-up, respectively. The initial IGRA result was positive in 10 patients (9.9%), negative in 85 patients (84.2%), and indeterminate in six patients (5.9%). The serial QFT-GIT results are demonstrated in Figure 2. The conversion rate was 14.29% (13/91) in the serial QFT-GIT tests. Ten patients had QFT-GIT conversion following their second tests, whereas others had QFT-GIT conversion following their third test. All the initial indeterminate results were negative following the second QFT-GIT test, whereas two patients with initial negative results had indeterminate results at the second and third tests. No active TB infection was noted in our series.

Table 1 Summary of the demographic data, clinical characteristics, and treatment in our series (101 cases).

Age (y)	43.41 ± 11.33
Sex	Women: 32 (31.7)
	Men: 69 (68.3)
Patients with psoriatic arthritis	59 (58.4)
BCG vaccine	95 (95)
PASI score	14.87 ± 8.71
Treatment with TNF-α inhibitor	Etanercept: 89 (88.1)
	Adalimumab: 12 (11.9)
Combined treatment	MTX: 22 (21.8)
	Cyclosporine: 9 (8.9)
	Acitretin: 11 (10.9)
	Prednisolone: 1 (1)

Data are presented as *n* (%) or mean ± SD.
BCG = bacille Calmette-Guérin; MTX = methotrexate; PASI = Psoriasis Area Severity Index (0–72); QFT-GIT = QuantiFERON-TB Gold In-Tube; SD = standard deviation; TNF = tumor necrosis factor.

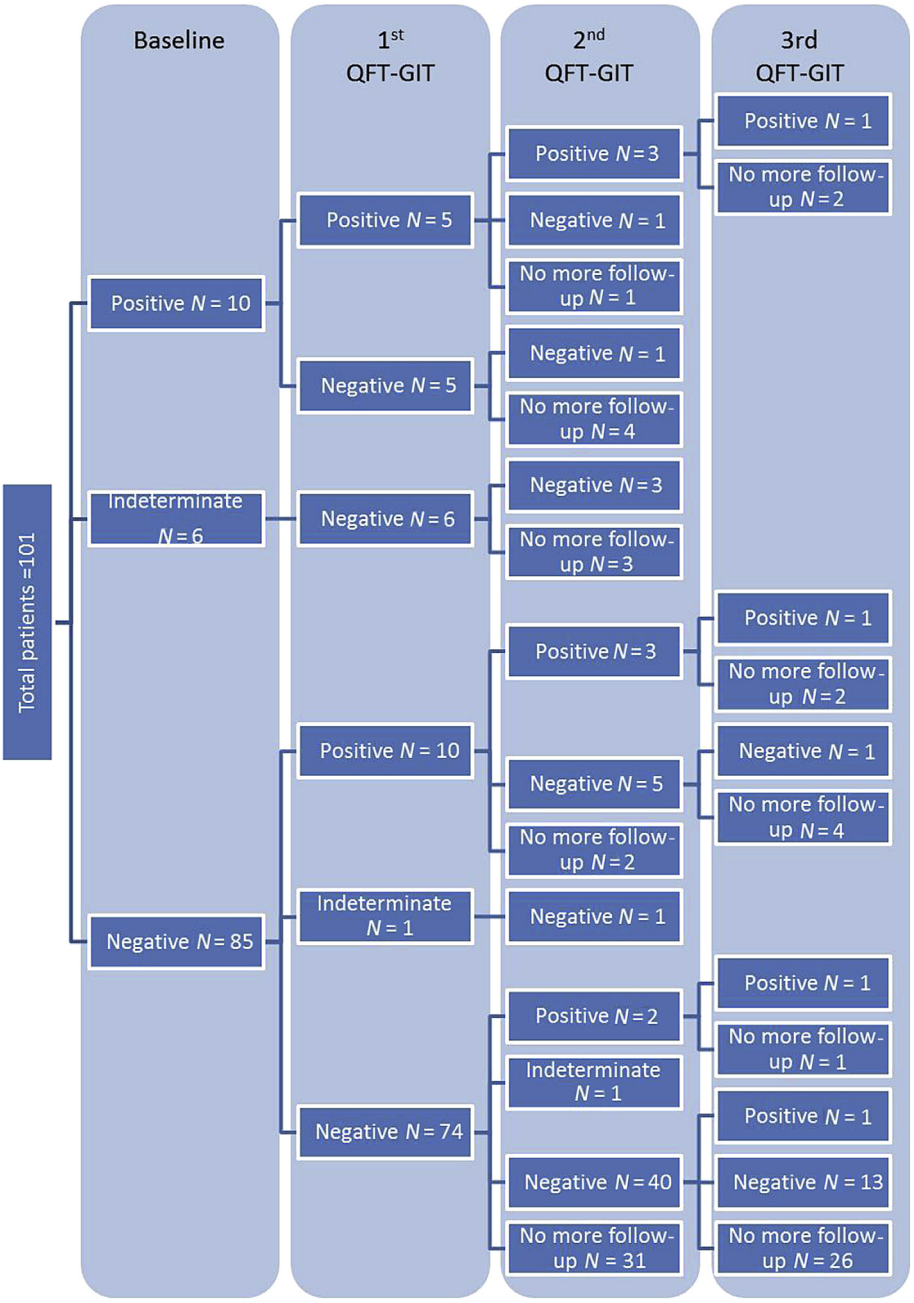

Figure 1 Flowchart distribution of QuantiFERON Gold In-Tube (QFT-GIT) test results.

Management and follow-up of patients diagnosed with LTBI

In this study, 23 patients were diagnosed with LTBI according to the positive results obtained in the QFT-GIT test. With the exception of two patients who refused to receive prophylactic therapy due to personal reasons, all the others received prophylactic therapy. Two patients developed elevated liver enzymes following a regular laboratory investigation and hence, only received a 4-month course of prophylactic therapy with 300 mg of daily isoniazid (INH). In total, 19 patients had completed the whole course of prophylactic therapy (Table 2). Among these patients, 10 (52.63%) received a 9-month course of INH therapy, whereas three cases (15.79%) received a 6-month course of INH therapy. Four patients had initially received INH and then shifted to a 4-month course of rifampicin (RIF) therapy (600 mg/d) because of elevated liver enzymes, hepatotoxicity, or allergy to INH. In addition, two cases had a previous history of peripheral neuropathy; therefore, they received a 4-month course of RIF therapy to avoid possible INH neurotoxicity. In our series, these patients received the QFT-GIT test within 1–6 months of completing the prophylactic therapy. Follow-up QFT-GIT testing revealed reversion in 11 patients (57.89%) and decreased IFN-γ levels (68.42%) in 13 patients. The longitudinal change in IFN-γ level is shown in Figure 3. There was no significant change in the level of IFN-γ before and after chemoprophylaxis ($p = 0.22$). Moreover, when comparing the persistent positive and reversion groups (Table 3), no significant differences were observed in either sex, anti-TB regimen, IFN-γ level at first result, the time that LTBI had been diagnosed, or the type of TNF-α antagonist used.

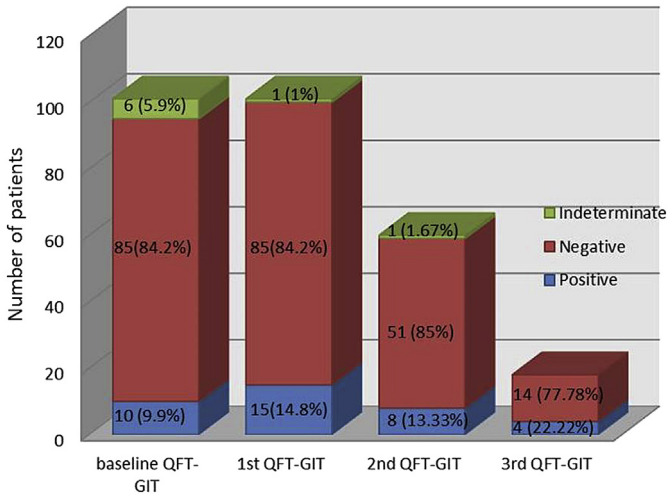

Figure 2 Results of serial QuantiFERON-TB Gold In-Tube (QFT-GIT) tests.

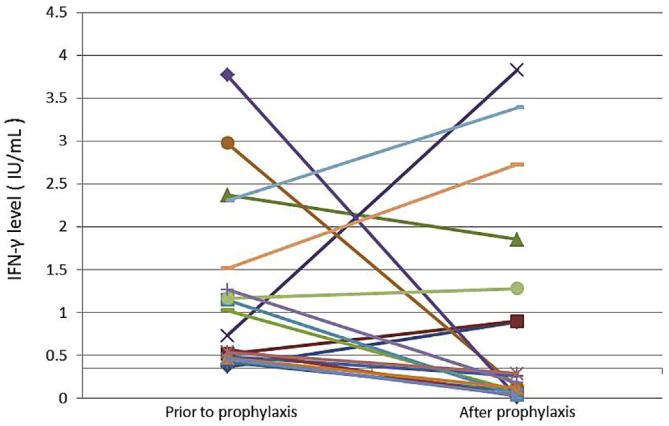

Figure 3 Interferon-γ (IFN-γ) response to *Mycobacterium tuberculosis*-specific antigens measured before and after chemoprophylaxis.

However, we found that patients over the age of 45 years tended to have a persistent positive result ($p = 0.02$). Interestingly, one patient who had not received prophylactic therapy and two patients who only received a 4-month course of INH treatment due to elevated liver enzymes also had reversion following subsequent QFT-GIT tests.

Discussion

In recent years, TNF-α antagonists have become increasingly popular in the treatment of psoriasis and other rheumatoid diseases although the increased risk of LTBI reactivation has also now become an important issue in clinical practice. Taiwan is a country with an intermediate burden of TB with an annual incidence of 57/100,000 and mortality rate of 2.8/100,000. According to Matulis et al,[7] those living in countries with a high prevalence of TB had a higher risk of developing LTBI. Therefore, screening for LTBI before and during the treatment with TNF-α antagonists is essential to prevent adverse effects of the medication and control an infectious disease. According to previous studies, the mechanisms by which TNF-α antagonists interfere with anti-TB immunity may be related to blocking TNF-mediated immune responses, inhibiting phagolysosomal maturation, inducing monocyte apoptosis, and reducing IFN-γ secretion by memory T cells.[8] Among the TNF-α antagonists, patients treated with adalimumab had a greater risk of developing TB than those treated with etanercept.[9] The median time of developing TB in patients treated with adalimumab and etanercept were 3–8 months and 11.2 months, respectively.[10,11] Therefore, the recommended interval of screening for LTBI during the TNF-α antagonist therapy was at least 12 months.

TB screening is recommended prior to initiating TNF-α antagonist therapy and at yearly intervals, thereafter.[12] TB infection screening should include detailed medical history, chest X-ray, and either TST or IGRA tests. The medical history should include TB infection risk factors such as residence in a country with a burden of TB, travel to endemic areas, substance abuse, or health care

Table 2 Treatment and follow-up of LTBI patients.

Case	Sex	Age	BCG vaccine	TNF-α antagonists	Anti-TB	Anti-TB duration (mo)	IFN-γ level (IU/mL) before chemoprophylaxis	IFN-γ level (IU/mL) after chemoprophylaxis	Reversion
1	M	56	Y	Enbrel	INH	9	0.37	0.89	N
2	M	60	N	Enbrel	INH→RIF	1.5 + 4[a]	0.52	0.9	N
3	F	38	Y	Enbrel	INH	6	2.37	1.85	N
4	M	57	Y	Enbrel	INH→RIF	2 + 4[b]	0.73	3.83	N
5	M	41	Y	Enbrel	INH	9	0.42	0.08	Y
6	M	57	Y	Enbrel	INH	9	2.98	0.13	Y
7	M	65	Y	Enbrel	INH	6	0.49	0.26	Y
8	M	38	Y	Humira	INH	9	0.57	0.03	Y
9	M	31	Y	Enbrel	INH	9	1.03	0.08	Y
10	M	35	Y	Enbrel	INH	6	3.77	0.01	Y
11	M	54	Y	Enbrel	INH→RIF	0.5 + 4[a]	1.15	0.04	Y
12	M	40	Y	Enbrel	INH	9	0.47	0.12	Y
13	M	32	Y	Enbrel	INH	9	0.46	0.04	Y
14	M	39	Y	Enbrel	INH	9	0.54	0.29	Y
15	F	49	Y	Enbrel	INH	9	1.17	1.28	N
16	F	25	Y	Enbrel	INH→RIF	2 + 4[c]	1.27	0.18	Y
17	M	54	Y	Enbrel	RIF	4	2.31	3.39	N
18	F	46	Y	Enbrel	RIF	4	1.52	2.73	N
19	F	48	Y	Enbrel	INH	9	0.52	0.35	N

A = adalinumab; AST = aspartate aminotransferase; ALT = alanine transaminase; BCG = bacille Calmette-Guérin; E = etanercept; IFN = interferon; INH = isoniazid; LTBI = latent tuberculosis infection; QFT-GIT = QuantiFERON-TB Gold In-Tube; RIF = rifampicin; TB = tuberculosis; TNF = tumor necrosis factor; TST = tuberculin skin test.

[a] Patient 2 and Patient 11 changed LTBI prophylaxis from INH to RIF due to elevated liver enzyme level.

[b] Patient 4 changed LTBI prophylaxis from INH to RIF due to acute hepatitis (AST: 237 IU/mL and ALT: 486 IU/mL).

[c] Patient 16 changed LTBI prophylaxis from INH to RIF due to allergy to INH.

Table 3 Comparison of persistent positive result and reversion of QFT-GIT in patients who were treated with chemoprophylaxis.

	Persistent positive group ($N = 8$)	Reversion group ($N = 11$)	p
Age (y)			0.02 *
> 45	7	3	
≤ 45	1	8	
Sex			0.111
Male	4	10	
Female	4	1	
Anti-TB therapy			0.171
INH	4	9	
INH→RIF	2	2	
RIF	2	0	
TNF regimen			> 0.99
Etanercept	8	10	
Adalimumab	0	1	
IFN-γ level at first positive result (IU/mL)			> 0.99
> 1	4	6	
≤ 1	4	5	
Diagnosis of LTBI			0.170
Initial examination	6	2	
Subsequent examination	4	7	

* Significant at $p < 0.05$.
IFN = interferon; INH = isoniazid; LTBI = latent tuberculosis infection; QFT-GIT = QuantiFERON-TB Gold In-Tube; RIF = rifampicin; TB = tuberculosis; TNF = tumor necrosis factor.

employment that may result in contact with patients who have TB.[12] In addition, it is necessary to ascertain whether the patient had any symptoms related to TB infection, including cough, loss of body weight, night sweats, and fever. Currently, TST and IGRA are the two available methods for detection of LTBI. Although some studies showed consistent results between the two tests, systemic review and meta-analysis showed that the specificity of IGRAs was superior to TST.[11] The odds ratio for positive TST results in patients who received BCG vaccination varied from three to 25, whereas IGRA was not influenced by BCG vaccination.[6] Taiwan launched the neonatal BCG vaccination program in 1965, and the coverage rate was above 97% after 2001.[13] The coverage rate (95%) of BCG vaccinations in our series was similar to the nationwide data; therefore, IGRA is more specific and suitable for detection of LTBI in this study.

A number of previous studies have demonstrated higher percentages of indeterminate QFT-GIT results in the immunocompromised rather than in the immunocompetent patients (21.4% vs. 9.6%, $p = 0.021$).[14] However, in this study, indeterminate results at baseline examination were only found for six patients (5.9%) in agreement with Chiu et al,[15] who also described a low rate of indeterminate results.[15] These findings may be associated with the relatively low percentage of patients receiving other immunosuppressive agents. In comparison with other serial IGRA for monitoring LTBI in patients who received TNF-α antagonists, the conversion rate in our series was 14.29%, which is similar to the findings of other studies in Korea (12.1%) and in Italy (11.6%) where the TB burden was intermediate and low, respectively.[16,17] The conversion of QFT-GIT may be attributed to new TB infection, cross reactivity with other species of *Mycobacterium*, or laboratory bias. Indeed, few patients also had a change in QFT-GIT status between indeterminate and negative results and reversion without prophylactic therapy. These findings are similar to previous studies, which demonstrated that patients who received long-term biologic therapy experienced dynamic changes in the IFN-γ level in response to TB.[18,19]

Currently, there are several therapies available for LTBI, including either a 9- or 6-month course of INH, a 4-month course of RIF, or a 3-month course of INH plus RIF. Most of our patients diagnosed with LTBI received chemoprophylaxis. Among these patients, five of 19 patients (26.31%) who received prophylactic INH therapy had elevated liver enzymes, whereas two discontinued the chemoprophylaxis. Three also shifted to RIF therapy as hepatotoxicity was less common in patients receiving RIF than in those receiving INH.[20] After chemoprophylactic therapy, the IFN-γ level decreased in 13 (68.42%) patients, whereas 11 (57.89%) patients developed reversion in the subsequent QFT-GIT test. The reversion rate in patients who received INHP in the present study was higher than that (30.54%) in a meta-analysis that estimated the pooled percentage of reversion after 3–6 months of follow-up.[21] In addition, the reversion rate in our study was also higher than that in the study of Sauzullo et al[19] who demonstrated only an 8% reversion rate in psoriatic patients receiving TNF-α antagonist following INHP for LTBI. The difference may be related to different LTBI prophylactic regimens or the time points of testing with QFT-GIT. Although the higher rate of reversion and decreased level of IFN-γ were demonstrated in our study, no significant change in the IFN-γ level before and after chemoprophylaxis was observed. In the study by Johnson et al,[22] there was also no significant difference in the IFN-γ level decline between the INHP group and the observation group. In comparison, among patients with persistently elevated IFN-γ levels and reversion following chemoprophylaxis, we found those aged less than 45 years were more likely to have IGRA reversion. This result is similar to the study of Bartalesi et al[23] who demonstrated that patients who were older, had larger TST size, or a higher baseline level of IFN-γ were less likely to achieve reversion, although no significant correlation of baseline IFN-γ level and reversion occurred in our series. Bartalesi et al[23] suggested that TB infection in younger patients is more likely to have occurred recently without remote infection, with these patients tending to achieve lower levels of IFN-γ following treatment. However, the present study did not show a significant association between reversion rate and the time that LTBI has been diagnosed. Therefore, the actual mechanism is still unclear.

In conclusion, this study has described the long-term follow-up of psoriatic patients receiving TNF-α antagonist therapy. We found that 14.29% of psoriatic patients who had undergone long-term TNF-α antagonist therapy had QFT-GIT conversion. No active TB infection had been noted in our series. Although decreased IFN-γ levels and QFT-GIT reversion were observed in most patients following chemoprophylaxis, the value of QFT-GIT for evaluating the effect of LTBI prophylaxis remains controversial. Thus, the current screening and management of LTBI may be effective in patients receiving TNF-α antagonists therapy. However, a larger, controlled prospective study is warranted before QFT-GIT is introduced for clinical practice in the long-term screening of psoriatic patients receiving TNF-αantagonist therapy.

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