INT J TUBERC LUNG DIS 15(2):192–199

Interferon-inducible protein-10 as a marker to detect latent and active tuberculosis in rheumatoid arthritis

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SUMMARY

SETTING: Effective tuberculosis (TB) screening should be performed before anti-tumour necrosis factor alpha (TNF-α) treatment in rheumatoid arthritis (RA). The usefulness of the tuberculin skin test (TST) and QuantiFERON®-TB Gold (QFT-G) for detecting latent tuberculosis infection (LTBI) is limited.

OBJECTIVE: We tested the diagnostic performance of interferon-gamma (IFN-γ) inducible protein 10 (IP-10) and IFN-γ for detecting LTBI in RA patients receiving anti-TNF-α treatment.

DESIGN: IP-10 levels were determined by enzyme-linked immunosorbent assay in 56 RA patients and 18 active TB patients. TST was performed using the Mantoux method and QFT-G was performed by measuring IFN-γ levels in whole blood treated with TB-specific antigens.

RESULTS: Twenty-four (42.9%) TST-positive patients were defined as having LTBI. Significantly higher levels of baseline, early secretory antigenic target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10) stimulated IP-10 were observed in active TB patients (median 209.9 pg/ml, 899.0 pg/ml and 880.2 pg/ml, respectively) and RA patients with LTBI (165.3 pg/ml, 904.4 pg/ml and 747.5 pg/ml, respectively), compared to those without LTBI (89.3 pg/ml, 579.4 pg/ml and 515.0 pg/ml, respectively). Baseline IP-10 has high sensitivity (83.3% and 100%) and medium specificity (67.9% and 59.6%), while ESAT-6-stimulated IP-10 has high sensitivity (87.5% and 100%) and specificity (85.7% and 71.2%) for detecting LTBI and TB. The performance of IP-10 is superior to IFN-γ for detecting LTBI (TST+) and active TB.

CONCLUSION: IP-10 may be used for detecting LTBI and as a potential biomarker to identify active TB in RA patients receiving anti-TNF-α treatment.

KEY WORDS: IP-10; isoniazid prophylaxis; tuberculosis; rheumatoid arthritis; TNF-α inhibitors

AN INCREASED PREVALENCE of active tuberculosis (TB) has been reported in rheumatoid arthritis (RA) patients,[1] and the risk of TB further increases in those receiving anti-tumour necrosis factor alpha (TNF-α) treatment.[2,3] Guidelines have recommended that effective TB screening should be carried out and prophylactic treatment initiated before starting anti-TNF-α therapy if the patient has latent TB infection (LTBI).[4,5]

The tuberculin skin test (TST) has some drawbacks, including variability in test application, and low specificity due to purified protein derivative (PPD) presenting in non-tuberculous mycobacteria (NTM) as well as in bacille Calmette-Guérin (BCG) strains.[6,7] Moreover, in RA patients the application of TST for detecting LTBI is limited by the frequent presence of anergy.[8] Recent studies have shown that the QuantiFERON®-TB Gold (QFT-G) assay, which detects interferon-gamma (IFN-γ) secreted by T-cells stimulated with *Mycobacterium tuberculosis*-specific antigens, shows promise for TB screening in RA patients.[9,10] However, QFT-G faces similar sensitivity limitations and has an increased proportion of indeterminate results in immunocompromised hosts.[11,12] Other potential biomarkers capable of more accurate detection of LTBI in RA patients are therefore needed.

IFN-γ-inducible protein-10 kDa (IP-10, CXCL10 [C-X-C motif chemokine *10*]) is a pro-inflammatory chemokine involved in trafficking monocytes and T-cells to inflamed foci.[13] Active TB is associated with elevated baseline IP-10 levels,[14,15] and TB-specific antigen-stimulated IP-10 has been identified as a potential biomarker for TB infection.[16,17] IFN-γ, a member of T-helper-1 derived cytokines, plays a pivotal role in the control of TB infection.[18] We therefore hypothesised that IP-10 and IFN-γ could be used to detect

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Article submitted 12 March 2010. Final version accepted 23 July 2010.

TB infection in RA patients receiving anti-TNF-α treatment.

Our aim was to test the diagnostic performance of IP-10 and IFN-γ for detecting LTBI and active TB disease using receiver-operating characteristic (ROC) curve analysis. Due to the lack of a gold standard for LTBI, we enrolled active TB patients as controls to evaluate their diagnostic performance.

STUDY POPULATION AND METHODS

Study population

Fifty-six patients with RA[19] were enrolled before starting anti-TNF-α treatment at the Taichung Veterans General Hospital in Taiwan, where the TB notification rate was 74.6 per 100 000 population in 2002.[20] Inclusion criteria were active RA disease, defined as a score of at least 5.1 on the 28-joint disease activity score (DAS28),[21] and treatment with methotrexate (MTX) and other disease-modifying anti-rheumatic drugs (DMARDs) for at least 6 months. RA patients were excluded if they had clinically active TB infection. Eighteen patients with untreated pulmonary TB diagnosed on the basis of positive sputum culture and characteristic signs on chest radiograph were included as controls.

The Clinical Research Ethics Committee of the Taichung Veterans General Hospital approved the study protocol; informed consent was obtained from all patients.

TST and QFT-G assay for LTBI in RA patients

TB screening consisting of detailed history, chest radiograph, two-step TST and QFT-G assay was performed among all RA patients. Blood was drawn for QFT-G assay, followed by TST using the Mantoux method, performed by intradermal injection of 2 tuberculin units of PPD RT-23 (Staten Serum Institute, Copenhagen, Denmark). If the induration diameter was ⩾5 mm, the TST result was defined as positive.[22] To maximise the detection rate for LTBI, two-step TST was performed, with a second TST administered 2 weeks after a negative initial test. The QFT-G assay was performed according to the manufacturer's instructions (Cellestis Ltd, Carnegie, VIC, Australia). As recommended by a previous study,[23] the results of the QFT-G assay were considered positive if IFN-γ level was ⩾0.35 international units (IU)/ml in the antigen (early secretory antigenic target-6 [ESAT-6] and culture filtrate protein-10 [CFP-10]) stimulated wells after subtracting the level of the nil well. As there is no gold standard for the diagnosis of LTBI, RA patients with a positive TST were defined as having LTBI.

Determination of IP-10 and IFN-γ plasma levels

IP-10 and IFN-γ plasma levels were determined using enzyme-linked immunosorbent assay (ELISA; R&D Systems, Minneapolis, MN, USA). Results were expressed in pg/ml. The mean intra- and inter-assay coefficients of variation from the manufacturer of IP-10 were respectively 3.6% and 6.7%, and for IFN-γ they were respectively 3.4% and 6.0%. Stimulated levels of IP-10 were examined with modifications according to the method described in a recent report.[24] Three aliquots of heparinised whole blood were incubated with TB-specific antigens, including ESAT-6 (1.0 μg/ml), CFP-10 (1.0 μg/ml) and nil antigens. After 20 h incubation at 37°C, plasma (diluted 1:1) was aspirated from each well and IP-10 levels were determined by ELISA (R&D Systems).

Statistical analysis

Differences between groups were determined by the Kruskal-Wallis test for non-parametric analysis of variance. The most appropriate cut-off values of IP-10 and IFN-γ for detecting LTBI (TST+) or active TB disease were established using ROC curves. The diagnostic sensitivity, specificity and area under ROC curve (AUC) were determined using MedCalc statistical software version 9.3 (MedCalc Software, Mariakerke, Belgium). $P < 0.05$ was considered statistically significant.

RESULTS

Demographic data, clinical characteristics and results of TST and QFT-G assay

As illustrated in Figure 1, 24 (42.9%) RA patients had a positive TST (two-step TST in 7 patients), and 18 (32.1%) had positive QFT-G results. After exclusion of four patients with indeterminate QFT-G assay, 52 RA patients were divided into four groups: 13

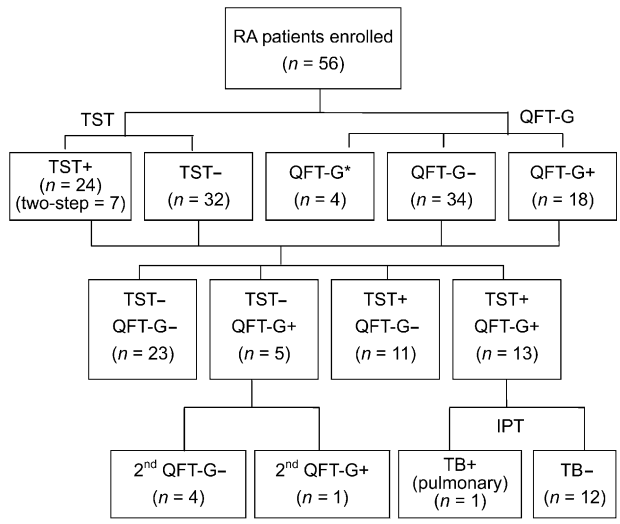

Figure 1 Flow chart showing the distribution of the results of TST and QFT-G in 56 patients with RA before starting anti-TNF-α therapy. One patient with LTBI developed active pulmonary TB after 3 months of treatment with adalimumab. *Indeterminate result. RA = rheumatoid arthritis; TST = tuberculin skin test; QFT-G = QuantiFERON®-TB Gold; + = positive; − = negative; IPT = isoniazid prophylaxis; TB = tuberculosis.

Table Demographic data and laboratory findings of four subgroups with RA according to QFT and TST results, and patients with active TB disease

	RA patients (n = 52)				
	TST−/QFT− (n = 23) n (%) or mean ± SD	TST+/QFT− (n = 11) n (%) or mean ± SD	TST−/QFT+ (n = 5) n (%) or mean ± SD	TST+/QFT+ (n = 13) n (%) or mean ± SD	TB patients (n = 18) n (%) or mean ± SD
Age, years	59.3 ± 11.1	52.4 ± 14.2	66.0 ± 10.9	60.3 ± 8.5	61.4 ± 12.6
Females	20 (87.0)	10 (90.9)	3 (60.0)	10 (76.9)	14 (77.8)
BCG vaccination	21 (91.3)	10 (90.9)	5 (100)	12 (92.3)	16 (89.0)
RF positivity	17 (73.9)	10 (90.9)	4 (80.0)	12 (92.3)	—
Anti-CCP positivity	18 (78.3)	9 (81.8)	4 (80.0)	11 (84.6)	—
ESR, mm/1st h	56.5 ± 33.4	58.1 ± 28.0	60.6 ± 49.8	45.2 ± 20.3	—
DAS28	6.96 ± 0.72	6.87 ± 0.79	7.34 ± 0.90	6.61 ± 0.49	—
Daily steroid dose, mg	6.74 ± 1.91	6.82 ± 1.62	7.00 ± 2.09	6.35 ± 1.65	—
Used DMARDs					
Methotrexate	21 (91.3)	10 (90.9)	4 (80.0)	12 (92.3)	—
Sulfasalazine	22 (95.6)	11 (100)	5 (100)	13 (100)	—
Hydroxychloroqine	23 (100)	11 (100)	5 (100)	12 (92.3)	—
Ciclosporine	13 (56.5)	6 (54.5)	3 (60.0)	7 (53.8)	—
TNF-α inhibitors					
Etanercept	10 (43.5)	1 (9.1)	1 (20.0)	5 (38.5)	—
Adalimumab	13 (56.5)	10 (90.9)	4 (80.0)	8 (61.5)	—

RA = rheumatoid arthritis; QFT = QuantiFERON-TB; TST = tuberculin skin test; TB = tuberculosis; − = negative; + = positive; SD = standard deviation; BCG = bacilli Calmette-Guérin; RF = rheumatoid factor; anti-CCP = anti-cyclic citrullinated peptide antibodies; ESR = erythrocyte sedimentation rate; DAS28 = 28-joint disease activity score; DMARD = disease-modifying anti-rheumatic drug; TNF-α = tumour necrosis factor alpha.

(25.0%) who had concordant TST+/QFT-G+ results received isoniazid prophylaxis (IPT); 23 (44.2%) had concordant TST−/QFT-G− results; 11 (21.2%) had TST+/QFT-G− results; and 5 (9.6%) had TST−/QFT-G+ results. A significantly greater TST induration was observed in RA patients with TST+/QFT-G+ results (median 15 mm, interquartile range [IQR] 10–19) than those with TST+/QFT-G− results (median 10 mm, IQR 9–11, $P < 0.05$).

No significant differences in age, proportion of females, proportion with BCG vaccination, positive rate of rheumatoid factor or anti-cyclic citrullinated peptide antibodies, doses of prednisolone or MTX, or disease activity were observed among the four subgroups of RA patients (Table).

Baseline IP-10 and IFN-γ levels in patients with RA and active TB disease

As shown in Figure 2, significantly higher baseline IP-10 levels were observed in RA patients with LTBI (median 165.3 pg/ml, IQR 109.5–218.7) and patients with active TB disease (median 209.9 pg/ml, IQR 183.0–355.6) than in RA patients without LTBI (median 89.3 pg/ml, IQR 71.0–126.6, $P < 0.005$ and $P < 0.001$, respectively). Baseline IP-10 levels were significantly higher in patients with active TB than in RA patients with LTBI ($P < 0.05$). After stratification of RA patients according to TST/QFT-G results, significantly higher baseline IP-10 levels were observed in RA patients with TST+/QFT-G+ results (median 200.6 pg/ml, IQR 163.4–296.8) than in those with TST−/QFT-G− results (median 89.3 pg/ml, IQR 70.9–131.0, both $P < 0.01$) and those with TST+/QFT-G− results (median 111.4 pg/ml, IQR 93.1–174.4, both $P < 0.05$). Significantly higher baseline IP-10 levels were also found in those with TST+/QFT-G− results than in those with TST-/QFT-G− results ($P < 0.05$). However, there was no significant difference in baseline IFN-γ level between RA patients with LTBI and active TB patients, between RA patients with LTBI and those without LTBI, or among the four subgroups of RA patients.

Stimulated levels of IP-10 in patients with RA and active TB disease

To determine whether TB-specific antigens could enhance IP-10 levels, plasma IP-10 levels were assessed after 20 h incubation with ESAT-6 and CFP-10. As shown in Figure 3, significantly higher levels of ESAT-6- and CFP-10-stimulated IP-10 were observed in RA patients with LTBI (median 904.4 pg/ml and 747.5 pg/ml, respectively) and patients with active TB disease (median 899.0 pg/ml and 880.2 pg/ml, respectively) than in RA patients without LTBI (median 579.4 pg/ml and 515.0 pg/ml, respectively, all $P < 0.001$). Significantly higher levels of CFP-10-stimulated IP-10 were observed in active TB patients than in RA patients with LTBI ($P < 0.05$). No significant difference in levels of stimulated IP-10 was observed between samples incubated with ESAT-6 and CFP-10.

Kinetics of plasma IP-10 and IFN-γ levels in RA patients with LTBI

During follow-up of RA patients receiving anti-TNF-α treatment, one LTBI patient developed active

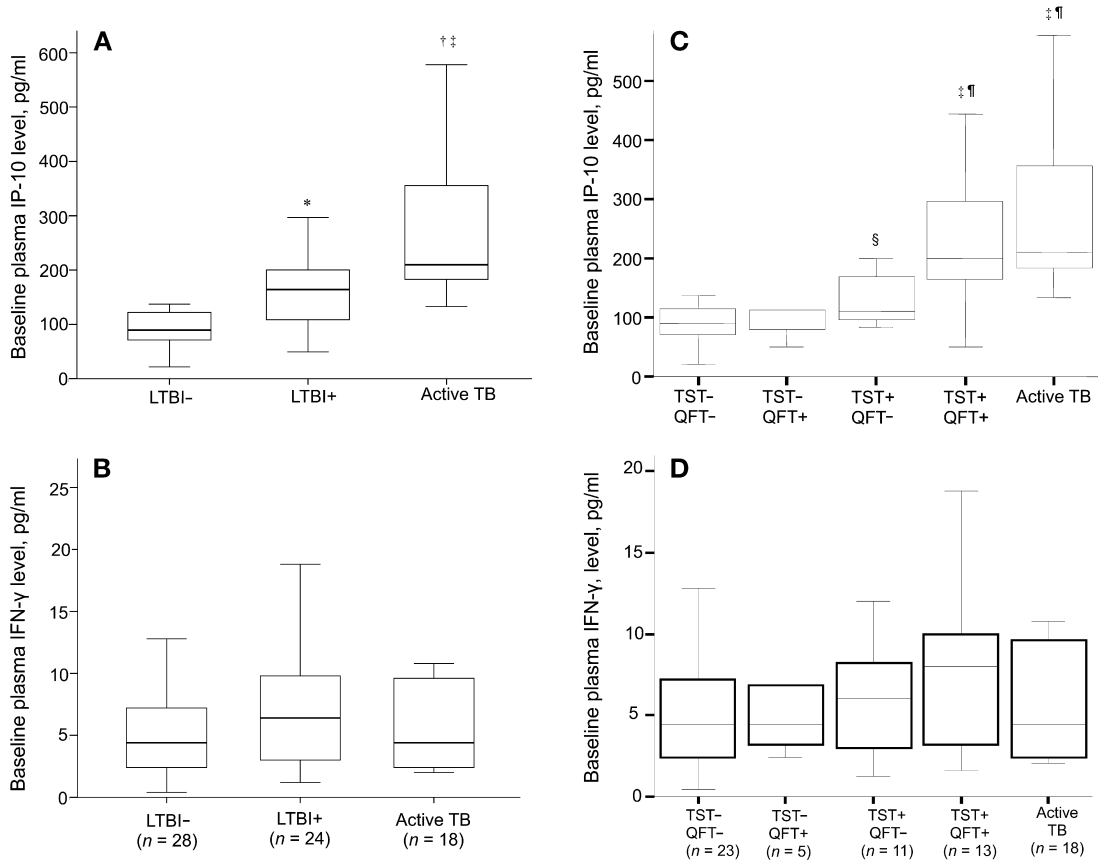

Figure 2 Baseline plasma levels of IP-10 (**A**) and IFN-γ (**B**) in active TB patients and RA patients with and without LTBI, based on TST results. After stratification of RA patients according to TST/QFT-G results, IP-10 (**C**) and IFN-γ (**D**) plasma levels in active TB patients, RA patients with TST+/QFT-G+, TST+/QFT-G−, TST−/QFT-G+ and TST−/QFT-G− results. IP-10 and IFN-γ plasma levels were determined using ELISA; results were expressed in pg/ml. Data are presented as box-plot diagrams, with the box encompassing the range of levels from the 25th to the 75th percentile. Horizontal line = median value; horizontal lines above and below = maximum and minimum values for each group. *$P < 0.005$, †$P < 0.001$ vs. RA patients without LTBI or those with TST−/QFT-G− results; ‡$P < 0.05$ vs. those with LTBI or those with TST+/QFT-G− results; §$P < 0.05$, ¶$P < 0.01$. IP-10 = IFN-inducible protein 10; LTBI = latent TB infection; TB = tuberculosis; IFN-γ = interferon gamma; TST = tuberculin skin test; − = negative; + = positive; QFT-G = QuantiFERON®-TB Gold; RA = rheumatoid arthritis; ELISA = enzyme-linked immunosorbent assay.

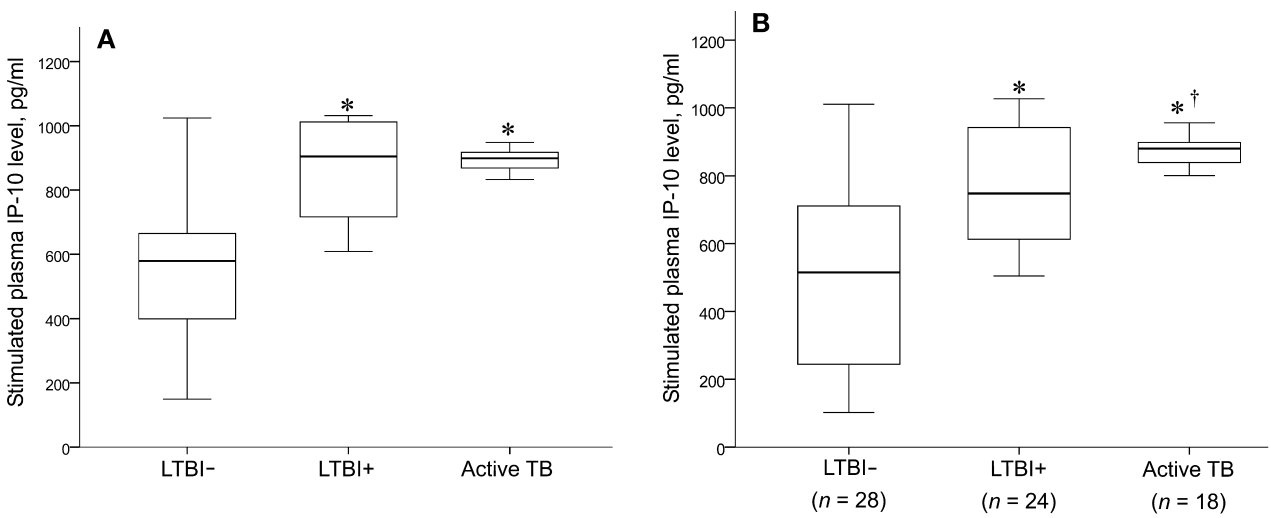

Figure 3 Plasma IP-10 levels after stimulation with TB-specific antigens ESAT-6 (**A**) and CFP-10 (**B**) in RA patients without LTBI, RA patients with LTBI, and patients with active TB disease. Data are presented as box-plots. *$P < 0.001$ vs. RA patients without LTBI; †$P < 0.05$ vs. RA patients with LTBI. ESAT-6 = early secretory antigenic target 6; IP-10 = interferon-inducible protein 10; LTBI = latent TB infection; TB = tuberculosis; CFP-10 = culture filtrate protein-10; RA = rheumatoid arthritis.

pulmonary TB despite IPT. High levels of baseline and ESAT-6-stimulated IP-10 (166.3 pg/ml and 1023.8 pg/ml, respectively) were observed in this patient in contrast to the other LTBI patients who did not develop active TB (range 80.6–164.3 and 819.8–1015.7 pg/ml, respectively). The kinetics of IP-10 and IFN-γ in this patient showed that baseline IP-10 levels paralleled the occurrence of active TB and clinical remission of TB after anti-tuberculosis treatment (Figure 4A). By contrast, there was no significant change in baseline IP-10 levels in the seven RA patients with LTBI who did not develop active TB during a 10-month follow-up period after anti-TNF-α treatment (Figure 4B).

Diagnostic performance of IP-10 and IFN-γ for LTBI and active TB

The diagnostic performance of IP-10 and IFN-γ using the ROC-derived cut-off points are illustrated in Figure 5. For detecting LTBI, the sensitivity (83.3%) and specificity (67.9%) of baseline IP-10 level at the 99.0 pg/ml cut-off point exceeded those of baseline IFN-γ level (50.0% sensitivity and 67.9% specificity). For detecting active TB disease, the sensitivity (100%) and specificity (59.6%) of baseline IP-10 level at the 132.8 pg/ml cut-off point exceeded those of baseline IFN-γ level (94.4% sensitivity and 17.3% specificity). ESAT-6-stimulated IP-10 level at the 691.6 pg/ml cut-off point and CFP-10-stimulated IP-10 level at the 586.3 pg/ml cut-off point had high sensitivity (87.5% and 91.7%, respectively) and specificity (85.7% and 60.7%, respectively) for detecting LTBI. ESAT-6-stimulated IP-10 level at the 826.3 pg/ml cut-off point and CFP-10-stimulated IP-10 level at the 684.7 pg/ml cut-off point had high sensitivity (both 100%) and specificity (71.2% and 55.8%, respectively) for detecting active TB disease.

DISCUSSION

The present study is the first attempt to evaluate the potential utility of IP-10 for detecting LTBI in RA patients before starting anti-TNF-α treatment. Our results show that baseline and stimulated levels of plasma IP-10 were significantly higher in RA patients with LTBI and active TB patients compared to those without LTBI. With ROC-derived cut-off values, high sensitivities of baseline and stimulated IP-10 were observed for detecting LTBI and active TB disease.

A recent meta-analysis showed that QFT-G has high specificity (96%) whereas TST has low and highly variable specificity in BCG-vaccinated populations.[25] There were fewer positive QFT-G than positive TST results (32.1% vs. 42.9%) in our RA patients before starting anti-TNF-α treatment (Figure 1). Among the 24 RA patients with a positive TST, the median TST induration in QFT-G-positive patients was significantly greater than in the QFT-G-negative patients.

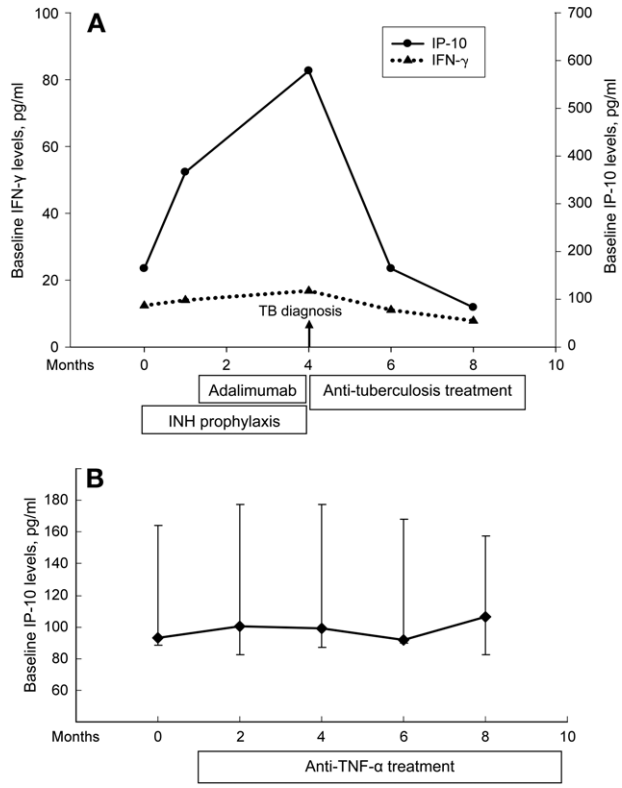

Figure 4 **A.** Kinetics in plasma levels of IP-10 and IFN-γ in an RA patient with LTBI who developed active TB 3 months after treatment with adalimumab despite INH prophylaxis. **B.** Kinetics in plasma IP-10 levels in seven RA patients with LTBI who did not develop active TB during the 10-month follow-up after anti-TNF-α treatment. Data are presented as median and 25th–75th percentiles. IP-10 = interferon-inducible protein 10; IFN-γ = interferon gamma; TB = tuberculosis; TNF-α = tumour necrosis factor alpha; RA = rheumatoid arthritis; LTBI = latent TB infection; INH = isoniazid.

In the absence of a history of contact with active TB, the discordant results of TST+/QFT-G− in our patients seem to be due to universal BCG vaccination and the high prevalence of NTM in Taiwan.[26] Our results support a recent study showing that QFT-G has a better diagnostic performance than TST in detecting LTBI in immunocompromised patients.[27] A higher specificity of QFT-G would help to avoid unnecessary IPT. The discordant TST−/QFT-G+ results in our RA patients might be caused by false-positive QFT-G or occur in a LTBI patient with false-negative TST.[8] Borderline positive QFT-G results (median IFN-γ 0.44 IU/ml in ESAT-6-stimulated wells and 0.38 IU/ml in CFP-10-stimulated wells) were observed among these discordant results, and QFT-G reversion was found in 4/5 patients at 6-month follow-up (Figure 1), suggesting a high possibility of false-positive QFT-G in RA patients with discordant results. In agreement with the results of recent studies,[28,29] none of our patients with discordant results developed active TB during a 2-year follow-up. However, in the absence of long-term follow-up data, we should interpret discordant TST and QFT-G results with caution.

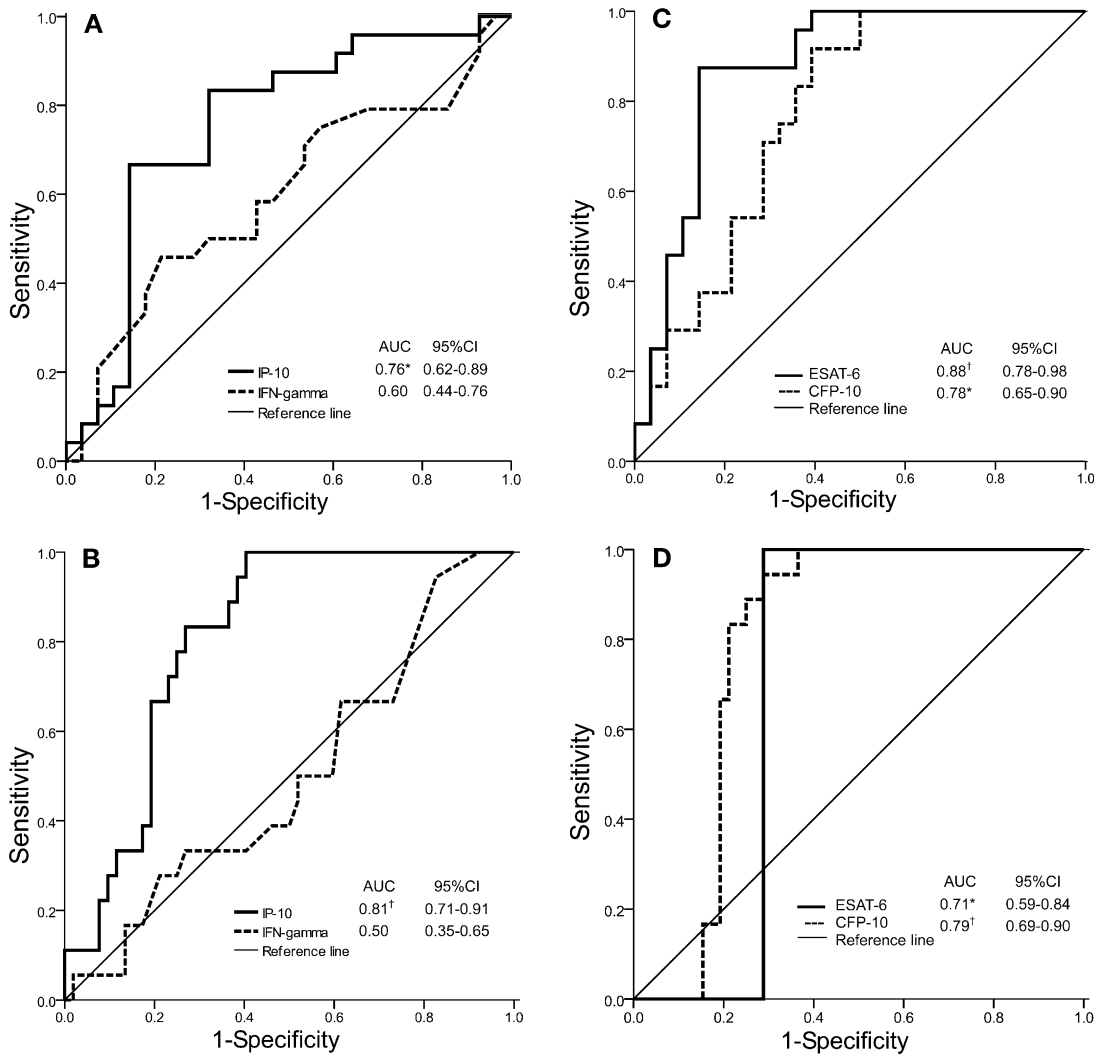

Figure 5 ROC curves comparing baseline levels of IP-10 and IFN-γ for predicting LTBI (TST+) (**A**) and active TB disease (**B**), and ROC curves comparing ESAT-6- and CFP-10-stimulated levels of IP-10 for predicting LTBI (TST+) (**C**) and active TB disease (**D**) in RA patients. *$P < 0.005$. †$P < 0.001$ determined by χ^2 test with Yate's correction of contingency or Fisher's exact test. LTBI = latent TB infection; AUC = area under ROC curve; CI = confidence interval; IP-10 = IFN-γ inducible protein 10; IFN-γ = interferon gamma; TB = tuberculosis; ESAT-6 = early secretory antigenic target 6; CFP-10 = culture filtrate protein 10; ROC = receiver operating characteristic; TST+ = tuberculin skin test positive; RA = rheumatoid arthritis.

Preliminary case-control studies have identified IP-10 as a potential diagnostic biomarker for LTBI.[17,30,31] We showed that baseline IP-10 levels were significantly higher in RA patients with LTBI than in those without LTBI, similar to the results of a recent study.[32] Consistent with the findings of another recent study,[17] the levels of stimulated IP-10 were significantly higher in our RA patients with LTBI than in those without LTBI, suggesting that IP-10 might serve as a potential biomarker capable of discriminating between RA patients with and those without LTBI. Using the ROC-derived cut-off point 691.6 pg/ml, the high sensitivity and specificity of ESAT-6-stimulated IP-10 levels for detecting LTBI indicated that it might be used as an adjunct to TST or QFT-G for detecting LTBI in RA patients. The disparity in the levels of stimulated IP-10 between our study and prior studies[24,30] may be due to the differences in patient characteristics, the detection methods and the different dilutions of the samples.

Because sputum smear microscopy cannot detect extra-pulmonary TB, which is frequent in RA patients receiving anti-TNF-α treatment,[3,4] we need new diagnostic markers for active TB, with improved detection rates. However, neither TST nor QFT-G allows early discrimination between LTBI and active TB.[33,34] Consistent with the results of recent case-control studies,[15,16] we have shown that significantly higher levels of baseline and stimulated IP-10 were observed in active TB patients than in RA patients without LTBI. However, similarly to the findings reported by Whittaker et al.,[17] we showed that IP-10 levels could not distinguish between active TB and LTBI. Using a ROC-derived cut-off point, the high

sensitivity of baseline and stimulated IP-10 levels for detecting active TB suggests that IP-10 might be a potential marker for detecting this disease. Although low specificity was observed for IP-10 in detecting active TB, it still has a role as part of a panel of diagnostic markers.

In line with a recent report[35] and the possibility of INH resistance, one of our RA patients who had LTBI and received IPT still developed active TB after 3 months of anti-TNF-α treatment. The kinetics of IP-10 levels showed progressively increased IP-10 levels before the development of active TB, while no significant change in IP-10 levels was found in those who did not develop active TB. Our finding was supported by the observation that IP-10 levels substantially increased in exposed household individuals at the onset of TB.[14] Progressively increased IP-10 levels in RA patients receiving anti-TNF-α treatment may represent ongoing and enhancing immune response to *M. tuberculosis* infection. The hypothesis that increased IP-10 levels are related to active TB is further supported by the effect of anti-tuberculosis treatment on IP-10 levels in our patients and in previous reports.[14] We showed higher levels of baseline and stimulated IP-10 in the patient who developed active TB compared to those who did not. However, the predictive value of IP-10 for the development of active TB from LTBI in RA patients remains unclear.

There are some limitations in our study. The sample size was too small to draw a definitive conclusion, especially for detecting active TB disease. Our preliminary results require confirmation in larger studies to determine an appropriate cut-off point for IP-10 in detecting LTBI in RA patients. Although the QFT-G version we employed is now no longer in use, its diagnostic performance is similar to that of QuantiFERON®-Gold In-Tube, as shown in a recent meta-analysis.[25]

In conclusion, our results show that IP-10 might be a potential adjunct to TST or QFT-G for detecting LTBI (TST+) in RA patients before anti-TNF-α treatment. Serial determination of plasma IP-10 level may help to identify RA patients with a high risk of developing active TB disease when receiving anti-TNF-α treatment.

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RÉSUMÉ

CONTEXTE : Un dépistage efficient de la tuberculose (TB) devrait être réalisé avant traitement contre le facteur de nécrose tumorale alpha (TNF-α) pour la polyarthrite rhumatoïde (RA). L'utilisation du test cutané tuberculinique (TST) et du test QuantiFERON®-TB Gold (QFT-G) pour la détection d'une infection TB latente (LTBI) est limitée.

OBJECTIF : Tester la performance de la protéine-10 (IP-10) inductible par l'interféron gamma (IFN-γ) et celle de l'IFN-γ dans la détection de la LTBI en cas de RA sous traitement anti-TNF-α.

SCHEMA : On a déterminé les niveaux de l'IP-10 par titrage avec immunoadsorbant lié à une enzyme (ELISA) chez 56 patients atteints de RA et dans 18 cas de TB active. Le TST a été pratiqué selon la méthode de Mantoux et le QFT-G a été pratiqué en mesurant les niveaux d'IFN-γ dans le sang complet traité au moyen d'antigènes spécifiques à la TB.

RESULTATS : On a défini comme atteints de LTBI 24 patients (42,9%) dont les TST étaient positifs. On a observé des niveaux significativement plus élevés d'IP-10 non stimulée, stimulée par ESAT-6 et stimulée par CFP-10 chez les patients atteints de TB active (valeur médiane respectivement 209,9, 899,0 et 880,2 pg/ml) ainsi que chez les patients atteints de RA et de LTBI (165,3, 904,4 et 747,5 pg/ml) par comparaison avec ceux sans LTBI (89,3, 579,4 et 515,0 pg/ml). Pour la détection de la LTBI et de la TB, l'IP-10 non stimulée a une sensibilité élevée (83,3% et 100%) et une spécificité moyenne (67,9% et 59,6%), tandis que l'IP-10 stimulée par ESAT-6 a une sensibilité élevée (87,5% et 100%) et une spécificité élevée (85,7% et 71,2%). La performance de l'IP-10 est supérieure à l'IFN-γ pour la détection de la LTBI (TST+) et de la TB active.

CONCLUSION : L'IP-10 peut être utilisée pour la détection de la LTBI et comme marqueur biologique potentiel pour l'identification d'une TB active chez les patients atteints de polyarthrite rhumatoïde sous traitement anti-TNF-α.

RESUMEN

MARCO DE REFERENCIA: Es preciso llevar a cabo una detección sistemática eficaz de la tuberculosis (TB) antes de comenzar el tratamiento de la artritis reumatoide (RA) con anticuerpos dirigidos contra el factor de necrosis tumoral α (TNF-α). La información que aportan la prueba cutánea de la tuberculina (TST) y la prueba QuantiFERON®-TB Gold (QFT-G) en la detección de la infección tuberculosa latente (LTBI) es limitada.

OBJETIVO: Evaluar el rendimiento diagnóstico de la determinación del interferón gama (IFN-γ) y de la proteína 10 inducida por el IFN-γ (IP-10) en la detección de la LTBI en pacientes con RA que reciben tratamiento dirigido contra el TNF-α.

MÉTODO: Se determinaron las concentraciones séricas de IP-10 mediante pruebas del ensayo inmunoabsorbente ligado a la enzima (ELISA) en 56 pacientes con RA y 18 pacientes con TB activa. Se llevó a cabo la TST con el método de Mantoux y se realizó la prueba QFT-G con determinación de la concentración de IFN-γ en sangre estimulada con antígenos específicos de la TB.

RESULTADOS: Se diagnosticó la LTBI en 24 pacientes (42,9%) que presentaron TST positiva. En los pacientes con TB activa se encontraron concentraciones significativamente más altas de IP-10 basal e inducida por la estimulación con ESAT-6 y CFP-10 (mediana 209,9, 899,0 y 880,2 pg/ml, respectivamente) y también en los pacientes con RA e LTBI (165,3, 904,4 y 747,5 pg/ml), en comparación con los pacientes sin LTBI (89,3, 579,4 y 515,0 pg/ml). La concentración inicial de IP-10 ofreció una alta sensibilidad diagnóstica (83,3% en la LTBI y 100% en la TB activa) y una especificidad intermedia (67,9% para la LTBI y 59,6% para la enfermedad activa); la concentración de IP-10 tras estimulación con ESAT-6 ofreció alta sensibilidad (87,5% en la LTBI y 100% en la TB activa) y alta especificidad (85,7% en la LTBI y 71,2% en la TB activa). El rendimiento diagnóstico de la IP-10 es superior al del IFN-γ en la detección de la LTBI (con TST positiva) y de la tuberculosis activa.

CONCLUSIÓN: Se puede utilizar la determinación de la IP-10 en la detección de la LTBI en pacientes con RA que reciben tratamiento dirigido contra el TNF-α.