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## Relation between Recurrence of Tuberculosis and Transitional Changes in IFN-γ Release Assays

*To the Editor*:

Although IFN-γ release assays (IGRAs) have been reported to be useful as monitoring tools during and after treatment (1–4), a relationship between IGRAs and recurrence of tuberculosis (TB) has not been studied. We evaluated the transitional changes in IFN-γ response by the QuantiFERON-TB Gold test (QFT-G; Cellestis, Carnegie, Victoria, Australia) in patients with TB from before treatment to 2 years after completion of treatment and studied a relationship between recurrence of TB and the changes in IFN-γ response. Some of the results of these studies have been previously reported in the form of an abstract (5).

Between April 2007 and April 2009, 49 Japanese patients with active TB were enrolled in a prospective cohort study at the Jikei University Daisan Hospital. All patients received treatment according to the guidelines of the Treatment Committee of the Japanese Society for Tuberculosis (6) by directly observed treatment. QFT-G was performed in all patients before the beginning of treatment (baseline [BL]) and was repeated at the completion of treatment (time 0 [T0]) and at 3, 6, 9, 12, 18, and 24 months after completion of treatment (T3, T6, T9, T12, T18, and T24, respectively). The results were evaluated according to the Centers for Disease Control and Prevention guidelines (7). The ethical committee at the Jikei University approved this study, and written informed consent was obtained from all patients. The transitional changes in IFN-γ response to early secreted antigenic target (ESAT)-6 and culture filtrate protein (CFP)-10 were calculated by subtracting BL from the observed response at other points. Chi-square and Fisher's exact tests were used to compare paired proportions. The Mann-Whitney U test was used to compare differences of average values. A $P$ value $< 0.05$ indicated statistical significance for all analyses.

The clinical characteristics and treatment regimen of the 49 patients with and without recurrence are shown in Table 1. We successfully obtained the results of culture conversion from sputum in all patients, and all patients successfully completed treatment with recovery from symptoms and significant improvement of their chest radiograph findings. Unfortunately, three patients had recurrence at 3, 4, and 7 months after completion of treatment (patients 1, 2, and 3, respectively) and underwent retreatment. None of the other patients had recurrence for 2 years after

This letter was supported by a grant-in-aid for scientific research from the Ministry of Education, Culture, Sports, Science and Technology to K.N.

Author Contributions: All authors had full access to and interpreted the data and were responsible for the decision to publish the manuscript. All authors vouch for the accuracy and completeness of the data and the analyses. Y. Kaneko and K.N. contributed to the study concept and design, data analysis and interpretation, writing of the manuscript, and editing and approval of the final manuscript. A.K., Y. Kurita, K.O., Z.S., Y.Y., T.H., A.S., Y.S., H.T., and K.K. contributed to the data collection and assembly, data analysis and interpretation, and editing and approval of the final manuscript.

**Table 1.** Clinical Characteristics of All Patients and Comparison of Clinical Variables between Patients with Recurrence and Those without Recurrence

| | Patients without Recurrence *(N = 46)* | Patients with Recurrence *(N = 3)* | *P* Value | OR (95% CI) |
|---|---|---|---|---|
| Variables for clinical characteristics of patient | | | | |
| Age, yr (mean ± SD) | 54.4 ± 22.3 | 34.3 ± 8.5 | | |
| Sex, male/female, n (%) | 31/15 | 3/0 | | |
| Smoking history, n (%) | 26 (56.5) | 1 (33.3) | | |
| Underlying disease, n (%) | 20 (43.5) | 0 (0) | | |
| COPD, n (%) | 4 (8.7) | 0 (0) | | |
| Diabetes mellitus, n (%) | 2 (4.3) | 0 (0) | | |
| Malignancy, n (%) | 4 (8.7) | 0 (0) | | |
| Past history of TB treatment, n (%) | 2 (4.3) | 0 (0) | | |
| Baseline laboratory data | | | | |
| WBC count, cells/ml (mean ± SD) | 6,480 ± 1,516 | 6,233 ± 702 | | |
| Lymphocyte count, cells/ml (mean ± SD) | 1,196 ± 368 | 1,467 ± 153 | | |
| Albumin, g/dl (mean ± SD) | 3.61 ± 0.63 | 4.17 ± 0.17 | | |
| Detailed diagnosis on TB | | | | |
| Pulmonary TB, n (%) | 36 (78.3) | 3 (100) | | |
| Pulmonary TB and TB pleuritis, n (%) | 2 (4.3) | 0 (0) | | |
| Pulmonary TB and bronchial TB, n (%) | 1 (2.2) | 0 (0) | | |
| TB pleuritis, n (%) | 5 (10.9) | 0 (0) | | |
| TB lymphangitis, n (%) | 2 (4.3) | 0 (0) | | |
| Location of lesions | | | | |
| Bilateral, n (%) | 15 (32.6) | 2 (66.7) | | |
| Unilateral, n (%) | 29 (63.0) | 1 (33.3) | | |
| TB lymphangitis in mediastinum, n (%) | 2 (4.3) | 0 (0) | | |
| Cavitation, n (%) | 18 (39.1) | 2 (66.7) | | |
| Treatment regimen | | | | |
| 2HREZ/4HRE, n (%)* | 30 (65.2) | 3 (100) | | |
| 2HREZ/7HRE, n (%)† | 8 (17.4) | 0 (0) | | |
| 9HRE, n (%)‡ | 5 (10.9) | 0 (0) | | |
| 6REZL/6REL, n (%)§ | 2 (4.3) | 0 (0) | | |
| 6RZLS/6RL, n (%)‖ | 1 (2.2) | 0 (0) | | |
| Variables for considerable clinical items as risk factors for recurrence | | | | |
| Age, yr (mean ± SD) | 54.4 ± 22.3 | 34.3 ± 8.5 | 0.17 | |
| Sex, male/female (n) | 31/15 | 3/0 | 0.54 | 3.44 (0.17–70.98) |
| Immunosuppressive state, n (%)¶ | 3 (6.5) | 0 (0) | >0.99 | 0.56 (0.02–13.25) |
| Lymphocyte count < 1,000 /ml, n (%) | 11 (23.9) | 0 (0) | >0.99 | 0.76 (0.44–9.20) |
| Albumin < 3.5 g/dl, n (%) | 22 (47.8) | 0 (0) | 0.24 | 0.16 (0.01–3.18) |
| Extra pulmonary TB, n (%) | 7 (15.2) | 0 (0) | >0.99 | 0.75 (0.04–16.13) |
| Positive sputum culture at 2 mo after beginning of treatment, n (%) | 6 (13.0) | 0 (0) | >0.99 | 0.89 (0.04–19.32) |
| Presence of cavities on chest X-ray, n (%) | 18 (39.1) | 2 (66.7) | 0.56 | 3.00 (0.25–35.59) |
| Infected with TB resistant to INH or RFP, n (%) | 3 (6.5) | 0 (0) | >0.99 | 0.56 (0.02–13.25) |
| Increase of the IFN-γ level from baseline to T0, n (%) | 1 (2.2) | 3 (100) | <0.001 | 212.30 (7.21–6,243.00) |

*Definition of abbreviations*: CI = confidence interval; COPD = chronic obstructive pulmonary disease; EB (E) = ethambutol; INH (H) = isoniazid; LVFX (L) = levofloxacin; OR = odds ratio; PZA (Z) = pyrazinamide; RFP (R) = rifampicin; SM (S) = streptomycin; TB = tuberculosis; WBC = white blood cells.
*INH, RFP, EB, and PZA for the initial 2 months and then INH, RFP, and EB for the following 4 months.
†INH, RFP, EB, and PZA for the initial 2 months and then INH, RFP, and EB for the following 7 months.
‡INH, RFP, and EB for 9 months.
§RFP, EB, PZA, and LVFX for the initial 6 months and then RFP, EB, and LVFX for the following 6 months.
‖RFP, PZA, LVFX, and SM for the initial 6 months and then RFP and LVFX for the following 6 months.
¶This patient was treated with corticosteroid.

completion of treatment. The transitional changes in IFN-γ response to ESAT-6 and CFP-10 in all patients are shown in Figure 1A. IFN-γ response in most patients decreased from BL to T0, and afterward did not increase over the T0. However, for ESAT-6, IFN-γ response in three patients increased from BL to T0, and all three patients suffered recurrence. For CFP-10, IFN-γ response in four patients increased from BL to T0, and three of them suffered recurrence. In contrast, all patients with no increase in IFN-γ response to either ESAT-6 or CFP-10 from BL to T0 (n = 45) did not suffer recurrence. The rate of the positive QFT-G is shown in Figure 1B. It decreased significantly from BL (93.9%) to T0 (63.3%; $P < 0.001$) and then decreased gradually from T0. The transitional changes in IFN-γ levels at BL, T0, follow-up points to recurrence, and the completion of retreatment in three patients

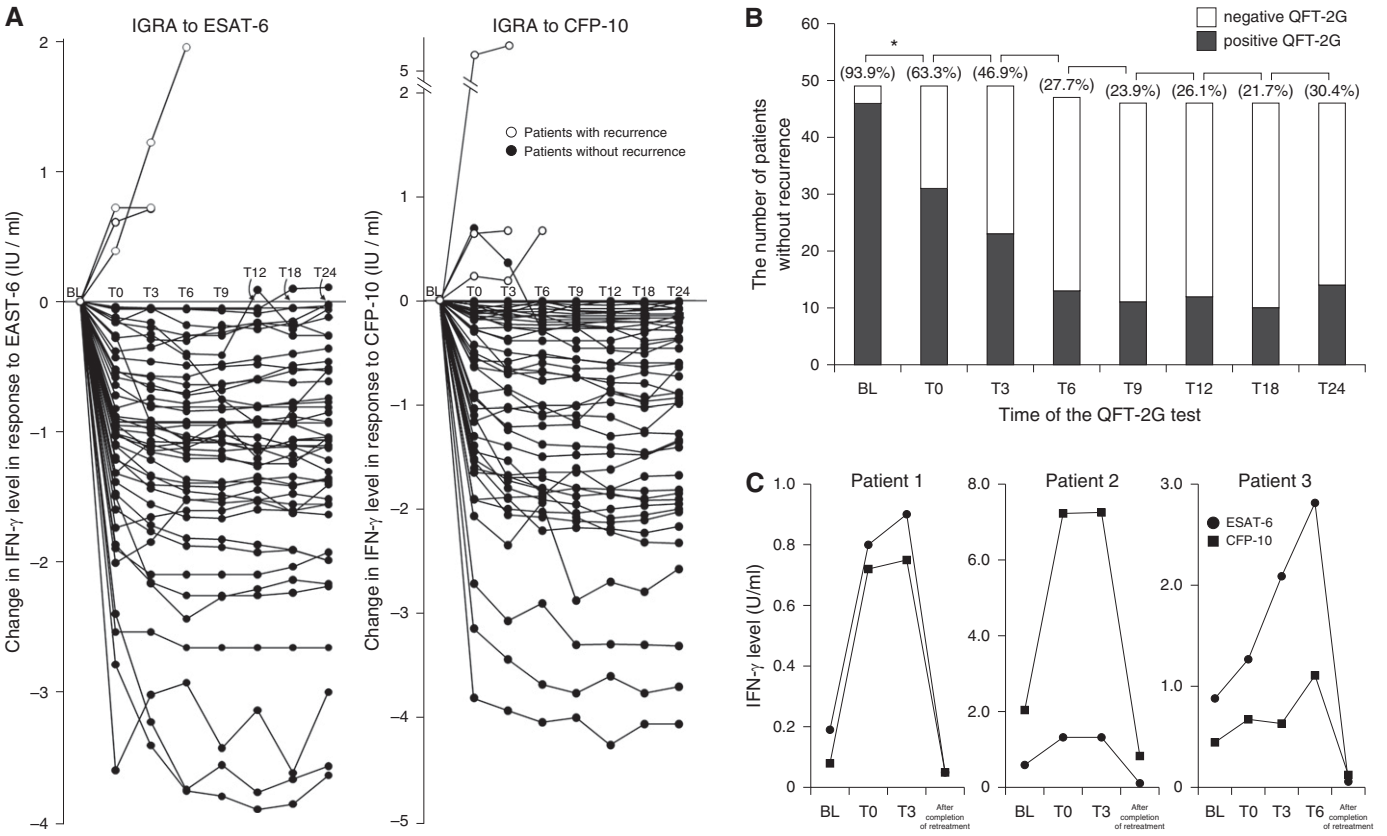


**Figure 1.** (*A*) Transitional changes in the IFN-γ response to early secreted antigenic target-6 and culture filtrate protein-10 from baseline to 24 months after completion of treatment in all patients. (*B*) The number of patients with negative (*open bars*) and positive (*solid bars*) QuantiFERON-TB Gold test results from baseline to 24 months after completion of treatment. The patients with recurrence are excluded at the time of recurrence and later. The parenthetical number indicates the percentage ratio of patients with positive QuantiFERON-TB Gold test results among all patients without recurrence at each time. The serial two values in the percentage ratio of positive QuantiFERON-TB Gold test were compared by chi-square test. *Statistical significance, with $P$ value $< 0.05$. (*C*) Transitional changes in the IFN-γ level to early secreted antigenic target-6 and culture filtrate protein-10 in each patient with recurrence from baseline to the time after completion of retreatment. IGRA = IFN-γ release assay.

with recurrence are shown in Figure 1C. Because they showed no resistant TB strains, they were retreated with the same set of drugs for 9 or 12 months. Their IFN-γ levels to both TB antigens increased until recurrence but decreased after retreatment. Furthermore, they had no recurrence again more than 2 years after retreatment. We performed univariate analysis on 10 considerable clinical items as a candidate of the risk factor for recurrence, which are shown in Table 1. As the result, increase in IFN-γ response to either ESAT-6 or CFP-10 from BL to T0 was the only factor with statistical significance (odds ratio, 212.30; $P < 0.001$).

This is the first report of a prospective study regarding IGRAs for a long-term period of 2 years after completion of treatment. Among all cases of recurrence, the rate of early recurrence within 2 years after completion of treatment was reported to be more than 50% in a Japanese paper (8). Dutt and colleagues reported that 15 of 730 patients with TB treated with short-course regimen had recurrence in the follow-up period for 7 years, and the rate of recurrence within 2 years in the 7-year follow-up was 73% (9). Therefore, patients with TB who completed treatment should be followed carefully at least for 2 years, so as to not miss early recurrence. Although there have been a few reports on IGRAs followed for 6 months or less after TB treatment (1, 2, 10–12), these observation periods were not long enough. Three of the 49 patients in the present study showed positive increase in IFN-γ response to both antigens from BL to T0, and all three patients had recurrence. Conversely, 45 patients with no increase in IFN-γ response to either ESAT-6 or CFP-10 did not have recurrence. All three patients with recurrence successfully completed retreatment, and TB has not recurred more than 2 years after retreatment. Taken together, the positive increase in IFN-γ response to both antigens from BL to T0 could be an important predictive marker for recurrence. We could monitor the change in IFN-γ response from BL to T0 and consider the extension of the treatment period in patients with increase in their IFN-γ response. There are two limitations in the present study. First, the sample size was too small to allow multivariate analysis. To evaluate usefulness of IGRAs as monitoring tools for recurrence, it will be necessary to perform a long-term study on a larger scale in the future to clarify the relation between recurrence of TB and the other IGRAs (the QuantiFERON-TB Gold In-Tube test [QFT-GIT] and the T-SPOT.TB test [Oxford Immunotec Ltd., Summertown, UK]), because QFT-GIT has higher sensitivity

than QFT-G (13) and has recently replaced QFT-G worldwide. Second, we managed treatment in the present study according to a Japanese guideline (6). In the context of this guideline, we did extend the duration of treatment for 3 months in patients with TB with diabetes mellitus and immunosuppressive therapy.

In conclusion, we found a relation between the transitional changes in IFN-γ response and recurrence of TB by following the QFT-G test for 2 years after completion of treatment. When there is an obvious increase in IFN-γ response to TB antigens at completion of treatment compared with those at the beginning of treatment in patients with TB, the risk for recurrence of TB should be considered. ■

**Author disclosures** are available with the text of this letter at www.atsjournals.org.

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## Attitudes about Low-Dose Computed Tomography Screening for Lung Cancer: A Survey of American Thoracic Society Clinicians

*To the Editor*:

The National Lung Screening Trial (NLST) demonstrated a 20% reduction in lung cancer mortality with annual low-dose computed tomography (LDCT) screening among high-risk individuals (1). Yet LDCT screening can also cause harm. Although several organizations recommend screening (although in different populations) (2–4), others do not (5).

With both Medicare and private insurers set to begin coverage in 2015, LDCT screening is expected to disseminate widely into practice. Whether implementation is successful, appropriate, and cost-effective will depend on clinicians' attitudes and behaviors regarding screening (6). To address this issue, we surveyed an international sample of practicing clinicians who see patients with pulmonary disease.

### Methods

We surveyed clinician (MDs, NPs, PAs) members of the American Thoracic Society (ATS) Clinical Problems and Respiratory Cell and Molecular Biology Assemblies (the parent assemblies of the Section of Thoracic Oncology) who regularly see outpatients. ATS sent three emails between March and April 2014 inviting participation in

Supported by National Institutes of Health Grant K07 CA138772 (R.S.W.).

Author Contributions: R.S.W. had full access to the data and takes responsibility for the data integrity and the accuracy of the data analysis. Study concept and design: M.K.G., S.W., L.M.S., and R.S.W.; acquisition, analysis, or interpretation of data: R.S.W.; drafting of the manuscript: J.S. and R.S.W.; critical revision of the manuscript for important intellectual content: all authors; statistical analysis: J.S. and R.S.W.; obtained funding: R.S.W.; and study supervision: M.K.G., S.W., L.M.S., and R.S.W.