Introduction

QuantiFERON TB Gold Plus (QFT-Plus) was approved as an IVD on February 5, 2018 in Japan, and sales began on June 1. Here, I will introduce recent findings on the clinical significance of QFT-Plus.

1. Sensitivity of QFT-Plus in immune compromised patients

HIV / AIDS is a disease which causes severe cellular immune function deterioration from CD4 T cells depletion. As a result, tuberculosis is much more frequent among those co-infected with both pathogens. Telisinghe et al. examined the sensitivity (positive rate) of QFT-Plus in active TB and compared results of individuals from with and without HIV infection in adults in Zambia 1). Furthermore, they compared it with the past study 2) using QFT-3G in the same cohorts. The results demonstrated that sensitivity of QFT-Plus was not affected by HIV infection and was less susceptible to the reduction in the number of CD4 T cells in the subject compared to QFT-3G (Table 1).

QFT-Plus seems to be able to maintain a certain level of sensitivity compared to QFT-3G even if the number of CD4 T cells declines because CD8 T cells signal is involved in addition to CD4 T cells signal.

Table 1. Comparison of sensitivity between QFT-3G and QFT-Plus in immunocompromised patients

	QFT-3G [1)] n = 112	QFT-Plus[2)] n = 108
Sensitivity		
HIV-positive	63%(37/59)	85% (58/68)
HIV-negative	84%(31/37)	80% (32/40)
CD4 T cells counts / µl		
<100	23% (3/13)	50% (4/8)
100–199	70% (14/20)	91% (10/11)
200–349	74% (17/23)	85% (17/20)
≥350	88% (43/49)	92% (23/25)

Cases without information about HIV infection and CD4 T cells counts were not included in the table. Data cited from reference1),2)

2. Measurement results of QFT-Plus in rheumatoid arthritis

Rheumatoid arthritis (RA) is an autoimmune disease and is treated with immunosuppressant drugs. Accurate diagnosis of LTBI is needed as RA patients undergoing treatment are a type of immunesuppressive condition that is at high risk of developing tuberculosis. Igari et al. conducted an LTBI study QFT-Plus on RA patients 3). Sixty three percent of the patients in this study were taking steroids, 53% on biologic agents, and 76% on methotrexate.

The positive rate of QFT-Plus was 9.7% (15/154) in 154 of patients with RA (median age 66.5 years), And Matsumura et al., also conducted QFT-3G in a similar cohort in the past. The positive rate of QFT-3G was 8.3% (19/230) in 230 of RA patients (median: 64 years old). The positive rate of QFT-Plus was higher than that of QFT-3G. Patients with CD4 T-cells ≧ 650 /μL and CD8 T-cells ≧ 400 /μL had significantly higher positivity rates in QFT-Plus compared with other groups ($P < 0.01$). This result indicated that the positive rate of QFT-Plus was strongly associated with the immune response of lymphocyte subsets. In this study there was no significant difference between TB2 and TB1. With regard to the indeterminate rate, QFT-Plus had a significantly lower rate ($p = 0.015$) compared to QFT-3G of 0.65% (1/154) versus(5.2% (12/230). Igari's study demonstrates that QFT-Plus is an improved assay in patients who are immunocompromised but also demonstrate the need to screen individual for TB prior to immunosuppressive treatment.

3. QFT-Plus in the elderly

Since cumulative exposure to M. tuberculosis increases with aging of the subject, the IGRA positive rate of older subject increases With advanced age, the aging immune system may cause increased false negative results from current TB tests, including IGRAs.5), 6).

Table 2. Head-to-head comparison of sensitivity between QFT-3G and QFT-Plus in the elderly

		QFT-3G	**QFT-Plus**		
	No.	Positive	Positive		
			QFT-Plus	TB1	TB2
Age (y/o)		No. (%)	No. (%)	No. (%)	No. (%)
60-64	9	5 (55.6)	3 (33.3)	3 (33.3)	3 (33.3)
65-74	34	11 (32.4)	11 (32.4)	11 (32.4)	10 (29.4)
75-84	108	31 (28.7)	37 (34.3)	26 (24.1)	36 (33.3)
≧85	78	19 (24.4)	23 (29.5)	21 (26.9)	20 (25.6)

Data cited from 7)

Chien et al., compared the positive rates of QFT-3G and QFT-Plus in a head-to-head study among 229 elderly persons (median 80 years, 60 to 102 years old) staying in long-term elderly care facilities 7). The results showed that the positive rate of QFT-Plus in elderly aged 75 years and older was higher than that of QFT-3G, and the number of positive results from TB2 was more than TB1 (Table 2). In addition, in 66 subjects who were positive with both QFT-3G and QFT-Plus, after 2 weeks, they were re-measured with 2 QFTs. All QFT-Plus-positive subjects remained positive while 7 subjects of QFT-3G positive became negative, and the rate of each (0/66 vs. 7/66) was significantly (p= 0.029) different. The breakdown of the second measurement result of QFT-Plus was that 53 patients had TB1 and TB2 that were both positive. Nine subjects were positive only by TB2 only. Hence, the presence of 2 antigen tubes may have improved QFT-Plus's reproducibility.. In addition, the authors also defined the LTBI sensitivity of each assay based on test result reproducibility. Reproducible positive subjects determined by re-measurement were diagnosed as Definite-LTBI. QFT-Plus LTBI sensitivity was significantly higher than that of QFT-3G.

4. Utility of QFT-Plus in high risk group

The enhanced performance and clinical usefulness of the addition of CD8 T cells antigens in QFT-Plus in patients with decreased cellular immune function has been expected and the above articles show higher sensitivity of QFT-Plus compared to QFT-3G in HIV and TB co-infected patients, as well as in those with autoimmune disease and elderly patients with LTBI. Other comparison studies on the sensitivity in active TB between QFT-Plus and QFT-3G reported similar outcomes in younger age groups. For example, Yi et al.,8) (n = 162) used a cohort with a median age of 59 years old (39 to 70 years old), and Takasaki et al.9) (n = 99) used cohort with a median age of 42 years old (29-55 years old). The elderly were almost not included in these studies and results showed high sensitivity of QFT-Plus but without difference from QFT-3G. Although cellular immune function may be reduced by the condition of active TB, it would be expected to be less in younger cohorts and in those with less severe tuberculosis. Hence, enhanced performance from the addition of CD8 T cells antigens in QFT-Plus are less likely to be observed in younger cohorts with active TB and/or persons with minimal disease.

The growing number of studies on QFT-Plus consistently show equal to better sensitivity to QFT-GIT in active TB but with selective enhanced performance in both active TB and LTBI among individuals immunocompromised by HIV, immunosuppressive drugs and aging immune systems (1,3,7). The synergy of CD8 T cells and CD4 T cells antigens of QFT-Plus appears to be filling the sensitivity gap among those needing it most.

Mr. QFT

References

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QFT-Plus is an in vitro diagnostic aid for detection of Mycobacterium tuberculosis infection (including disease) and is intended for use in conjunction with risk assessment, radiography, and other medical and diagnostic evaluations. QFT-Plus results alone cannot distinguish active TB disease from latent infection. QFT-Plus Package Inserts, available in multiple languages, as well as up-to-date licensing information and product-specific disclaimers can be found at www.QuantiFERON.com.

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