Usefulness of interferon gamma release assay in the diagnosis of latent tuberculosis infection in patients with rheumatoid arthritis

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Usefulness of interferon gamma release assay in the diagnosis of latent tuberculosis infection in patients with rheumatoid arthritis

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ABSTRACT

Usefulness of interferon gamma release assay in the diagnosis of latent tuberculosis infection in patients with rheumatoid arthritis

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Use of anti-TNF-α agent increases the risk of reactivation of latent tuberculosis infection (LTBI) and detecting LTBI before using anti-TNF-α agent is mandatory. Tuberculin skin test (TST) is a traditional method for detecting LTBI, which is reported to be attenuated in patients with rheumatoid arthritis (RA). Interferon gamma release assay (IGRA), a novel T-cell based assay is reported to retain its sensitivity in the immunocompromised patients. The aim of this study was to determine whether IGRA shows superior performance than TST in patients with RA in South Korea. One hundred and twenty one patients with RA and 55 age- and sex- matched control patients who did both TST and Quantiferon TB gold-In-Tube (QFT-GIT) in Severance Hospital were retrospectively reviewed. TST was done by the Mantoux method using RT-23 2TU. Indurations

larger than 10 mm were considered as positive. QFT-GIT was performed according to the manufacturer's instructions. The rates of positive results in TST (33.3% vs. 43.4%) and QFT-GIT (35.9% vs. 41.5%) were not significantly different between RA and control group. However, the median induration size of the patients taking disease modifying anti-rheumatic drugs (DMARDs) was significantly smaller than those of the control group [1 (0~30) mm vs. 6 (0~24) mm, $p<0.05$] and the rate of positive result in TST showed a trend to be decreased as compared to that of the controls (27.6% vs. 39.6%, $p=0.078$), while the rate of positive results in QFT-GIT did not differ between the two groups. The agreement between TST and QFT-GIT in RA group was moderate ($\kappa=0.557$) and that of the controls was substantial ($\kappa=0.616$). The agreement between TST and QFT-GIT was poorer in the RA group taking DMARDs ($\kappa=0.396$) than in the DMARD naïve RA group ($\kappa=0.702$). Twelve patients underwent follow-up TST. Of the nine patients with negative TST result at baseline, four patients showed a positive conversion at follow-up and three of them had positive QFT-GIT results at baseline. Seven patients underwent follow-up QFT-GIT. The results of follow-up QFT-GIT in seven patients remained unchanged. These data suggest that QFT-GIT shows superior performance in patients with RA taking DMARDs. QFT-GIT may have a value in the diagnosis of LTBI in patients with RA.

Key words: rheumatoid arthritis, latent tuberculosis infection, tuberculin skin test, interferon gamma release assay, Quantiferon TB gold in tube

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I. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory polyarthritis. Although the use of disease modifying anti-rheumatic drugs (DMARDs) in RA has substantially improved the treatment outcome, there are still patients refractory to DMARDs. Anti-tumor necrosis factor (TNF)-α agent is a novel biologic agent which has proved to be effective in DMARD refractory patients with RA. TNF-α, which is a target molecule of anti-TNF-α agent, is a pro-inflammatory cytokine which plays an important role in the development of inflammation and autoimmunity [1]. It also plays a major role in the recruitment of immune cells against *Mycobacterium tuberculosis* (MTB) [2]. Hence, the use of anti-TNF-α agent is associated with reactivation of latent tuberculosis infection (LTBI) [3] and detecting and treating LTBI before using anti-TNF-α agent is mandatory.

Tuberculin skin test (TST) is a traditional method for detecting LTBI. It has been used world-wide and the sensitivity reaches 77% and the specificity for MTB ranges between 60 ~ 97% depending on the populations studied [4]. TST has some limitations such as cross reaction with non-tuberculosis mycobacterium (NTM) and bacillus Calmette-Guérin (BCG) and that it is attenuated in populations with immunocompromizing conditions such as HIV [5], ESRD [6], malnutrition [7] and organ transplantation [8]. In case of RA, tuberculin reaction has been reported to be attenuated compared to healthy controls probably due to the disease itself and the use of immunosuppressive drugs [9-10]. In this sense, determining the presence of LTBI in patients with RA based only on TST may have a risk of missing true LTBIs.

Interferon gamma release assay (IGRA) is a novel T cell-based assay for the diagnosis of LTBI. It measures the level of interferon-gamma released from circulating T cells sensitized to MTB after incubating patient's whole blood with MTB specific antigens. IGRA has shown superior performance even in the immunocompromised population including RA compared to TST [6, 11]. The studies supporting the usefulness of IGRA in RA, however, were done in either high [11] or low [12] tuberculosis (TB) burden areas and the comparison of TST and IGRA in populations with intermediate TB burden has rarely been studied.

The aim of this study was to determine whether Quantiferon TB gold in tube (QFT-GIT), an IGRA, shows better performance than TST in patients with RA living in South Korea, where the burden of TB is intermediate [13].

II. PATIENTS AND METHODS

1. Patients

One hundred twenty-one patients with RA fulfilling the 1987 American College of Rheumatology criteria and fifty-five patients with various non-inflammatory diseases who did both TST and QFT between 2005 and 2010 at Severance Hospital in Seoul, South Korea were retrospectively reviewed. Patients with any one of the followings were excluded from the study: 1) diseases related with immunosuppression (HIV infection, malignancy, diabetes mellitus, recipient in organ transplantation), 2) use of immunosuppressive medications (this criterion was applied only to the control group), 3) active TB, and 4) a history of hypersensitivity reaction to PPD. This study was approved by the local institutional review board.

2. Methods

The results of TST and QFT-GIT of each patient were obtained from the medical records. Information about BCG vaccination, history of close contact with active TB and prior history of active TB were acquired through telephone interview.

A. Tuberculin skin test

For TST, a purified protein derivative (PPD), RT 23, 2TU was injected by intradermal Mantoux method and the size of skin induration was measured after 48-72 hours. An induration larger than 10 mm in diameter was considered as positive.

B. Quantiferon TB Gold In Tube

QFT-GIT was performed at the Immunology laboratory in Severance Hospital according to the manufacturer's instructions (Cellestis Ltd, Carnegie, Australia). One milliliter blood was drawn from the patient directly into each of three evacuated tubes: 1) negative control tube containing only heparin 2) positive control tube containing phytohemagglutinin for T cell mitogen 3) TB antigen tube containing MTB specific antigens ESAT-6, CFP-10 and TB 7.7. The tubes mixed with patient's whole blood were incubated for 20 hours at 37℃ before plasma was harvested and were stored frozen at -20℃ until further analysis within 5 days. Using ELISA, the level of interferon gamma in each plasma sample was measured. Results were calculated using the software provided by the manufacturer.

C. Statistical analysis

With SPSS, version 15.0 (SPSS, Chicago, IL), student's *t*-test and Mann-Whitney U test were used to compare parametric and non-parametric continuous variables between RA and control group, respectively. Chi square test was used to compare the positive rates of TST and QFT-GIT between RA and control group. The agreement between TST and QFT-GIT was assessed by kappa statistic. Logistic regression analysis was used to determine the factors associated with TST and QFT-GIT results.

III. RESULTS

1. Patient characteristics

The mean age of the RA group was 50.7±11.3 years, and 72.6% were female, which were not different from those of the control group. History of pulmonary TB, close contact with active TB and BCG vaccination were not different between the two groups. For the RA group, median disease duration was 9 months and mean value of ESR and CRP were 56.5 mm/hr and 1.57 mg/dL respectively. About half (50.4%) of RA group were taking DMARDs at the time of the test and 66% of them were taking methotrexate (Table 1).

Table 1. Patient characteristics

	RA group (n=121)	Control group (n=55)	p
Age (mean±SD, years)	50.7±11.3	50.6±18	NS
Female (%)	72.6	62.3	NS
History of pulmonary TB (%)	6.8	11.3	NS
Close contact with active TB (%)	8.5	15.1	NS
BCG vaccination (%)	85.5	86.8	NS
Disease duration (median, months)	9 (1-203)		
ESR (mean±SD, mm/hr)	56.5±29		
CRP (mean±SD, mg/dL)	1.57±1.86		
DAS28 (mean±SD)	5.2±1.3		
Use of DMARD (%)	49.5		
Methotrexate (%)	66		
Low dose prednisolone (%)	80		

NS: not significant, TB: tuberculosis, BCG: bacillus Calmette-Guérin, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, DAS28: disease activity score 28, DMARD: disease modifying anti-rheumatic drug.

2. Results of TST and QFT-GIT

A. Comparison between RA group and control group

The median induration size [6(0-24) mm vs. 5(0-30) mm] and TST positive rate of both groups (33.3% vs. 43.4%) were not significantly different between the two groups. The positive rate of QFT-GIT (35.9% vs. 41.5%) was also not significantly different between the two groups either. The rate of indeterminate result was 3.4% in RA group and 3.8% in control group.

B. Comparison of RA subgroups with control group

RA group was divided into two groups according to the use of DMARDs. Sixty-one patients were taking DMARDs (RA on DMARDs) at the time of the test and 60 patients were not (DMARD naïve RA).

(A) DMARD naïve RA versus control

The induration size [7(0-29) mm vs. 6(0-24) mm], TST positive rate (34.4% vs. 39.6%) and QFT-GIT positive rate (37.9% vs. 41.5%) of DMARD naïve RA group and control group were not significantly different. The rate of indeterminate result was not different between the two groups (3.4% vs. 3.8%).

(B) RA on DMARDs versus control

The median induration size of the RA patients on DMARDs was significantly smaller than that of the control group [1(0-30) mm vs. 6(0-24) mm, p=0.04]. The

TST positive rate of the RA patients on DMARDs showed a trend of decrease without statistical significance (27.6% vs. 39.6%, p=0.078). However, the positive rates of QFT-GIT were comparable between the two groups (34.5% vs. 41.5%). The rate of indeterminate result was not different between the two groups (3.4% vs. 3.8%).

3. Agreement between TST and QFT

The agreement between TST and QFT-GIT in RA group in overall was moderate (80.3%, kappa=0.557) and that of the control group was substantial (81.1%, kappa=0.616) (Table 2). The agreement between TST and QFT-GIT differed according to the use of DMARDs in RA group. In RA patients taking DMARDs, the agreement was fair (74.5%, kappa=0.396) whereas the agreement in the DMARD naïve RA patients was substantial (86.2%, kappa=0.702) (Table 3).

Table 2. Agreement between TST and QFT in RA and control groups

	RA group (overall)			Control group		
	QFT-GIT +	QFT-GIT -	Total	QFT-GIT +	QFT-GIT -	Total
TST +	27	8	35	18	6	24
TST -	15	67	82	4	25	29
Total	42	75	117	22	31	53
Kappa		0.557			0.616	

RA: rheumatoid arthritis, QFT-GIT: Quantiferon TB gold in tube, TST: tuberculin skin Test.

Table 3. Agreement between TST and QFT-GIT according to the use of DMARDs

	RA on DMARDs			DMARD naïve RA		
	QFT-GIT +	QFT-GIT -	Total	QFT-GIT +	QFT-GIT -	Total
TST +	10	5	15	17	3	20
TST -	10	34	44	5	33	38
Total	20	39	59	22	36	58
Kappa		0.396			0.702	

RA: rheumatoid arthritis, DMARD: disease modifying anti-rheumatic drug, QFT-GIT: Quantiferon TB gold in tube, TST: tuberculin skin test.

4. Factors associated with positive results of TST and QFT-GIT

A. Factors associated with positive TST result

An univariate analysis of multiple clinical factors was performed, but no significant factors were associated with TST results in the RA group.

B. Factors associated with positive QFT-GIT result

Among the multiple clinical factors, increased age was significantly associated with QFT-GIT result in the univariate analysis. This association was still significant in the multivariate analysis (OR 1.047, 95% CI 1.004 – 1.092, p=0.03, Table 4).

Table 4. Multivariate analysis of factors associated with QFT-GIT

	B	Exp (B)	P
Age	0.046	1.047	0.03
Male sex	0.201	1.222	0.736
Contact with active TB	1.022	2.779	0.328
BCG vaccination	-0.397	0.672	0.538
DAS28	0.027	1.027	0.912
Use of methotrexate	1.170	3.222	0.418
Use of prednisolone	-1.593	0.203	0.251

TB: tuberculosis, BCG: bacillus Calmette-Guérin, DAS28: disease activity score 28.

5. Results of follow-up test

A. Follow-up TST

Twelve patients with RA underwent follow-up TST. The median duration between baseline and follow-up was 11 (4-30) months. All patients received DMARDs and 3 patients received anti-TNF-α agent during the follow-up period. Nine patients had negative TST results at baseline. Among them, 4 patients (44.4%) showed a positive conversion at follow-up. Of the 4 patients who showed positive conversions, 3 had positive QFT-GIT result at baseline. The results of follow-up TST in 3 patients who had positive TST results at baseline did not change.

B. Follow-up QFT-GIT

Seven patients underwent follow-up QFT-GIT. Median duration between baseline and follow-up was 9.5 (4-11) months. All patients received DMARDs and 2 patients received anti-TNF-α agent during the period. Five patients had positive QFT-GIT result and 2 patients had negative result at baseline. None of the 7 patients showed a change in the results of follow-up QFT-GIT.

IV. DISCUSSION

Attenuated tuberculin reaction in patients with RA has been shown by several studies [14-17]. IGRA including QFT-GIT is currently in the spotlight as a novel diagnostic method for LTBI in general population. However, the performance of QFT-GIT in immunocompromized populations such as RA has been evaluated only by small numbers of studies[18-19]. Moreover, they have rarely been compared in regions with intermediate TB burden and high BCG vaccination coverage. Also, there are reports of HLA-associated inability to respond to ESAT-6 and CFP-10[20], which suggests an ethnic difference in the rate of response to QFT-GIT. In this sense, our study has a value in that it was done in patients with "RA" living in "South Korea", where the burden of TB is intermediate and BCG vaccination is routine.

TST in DMARD naïve RA group were comparable to those of the control group whereas the DMARD taking RA group showed a reduced tuberculin reaction. In a study by Maria et al[21], negative PPD and PPD anergy were associated with the use of glucocorticoid and methotrexate. Similar results were reported by Murakami et al[22]. The RA patients taking DMARDs in this study were receiving methotrexate in 66% and prednisolone in 80%. Although the attenuated tuberculin reaction in RA has been attributed to the disease itself, the tuberculin reaction in DMARD naïve RA has rarely been studied. In this study, I found that TST in DMARD naïve RA patients were comparable to those of the control group.

The results of QFT-GIT were comparable to those of control group in RA group

irrespective of the use of DMARDs. Similar findings have been reported by several studies [11, 19, 23], although discordant results are also reported [12]. The comparable performance of QFT-GIT between RA and control group irrespective of the use of DMARDs supports that QFT-GIT is not influenced by external factors. Indeterminate results were found in 3.4% of RA group which were similar to control group. Some studies have reported that indeterminate results are more common in patients with RA, which raises a concern about the use of IGRA. However, the reported rate of indeterminate results in patients with RA varied among studies[12, 22-24]. A recent study reported that the delay in the incubation increases the rate of indeterminate results in QFT-GIT [25]. The interpretation of indeterminate result is a difficult problem. Indeterminate results may come from the attenuated immunity of the host [26] and may mask true LTBI. Indeterminate result may turn into positive when the mixture of patient's whole blood and the antigen is incubated for a longer duration. The agreement between TST and QFT was moderate to substantial in this study. The agreement in patients taking DMARDs, however, was poorer than that of DMARD naïve RA group. This is mainly due to the discrepant results where QFT-GIT is positive and TST negative. The use of DMARD might have attenuated the results of TST. In this study, 23 of 117 RA patients had discrepant results. 15 had QFT-GIT +/ TST- and 8 had QFT-GIT-/TST+. In a study by Chen et al [27], active TB developed after treatment with adalimumab in 2 out of 35 patients who had negative TST at baseline. Two patients who developed active TB had positive QFT-GIT result in the follow-up and 1 had positive conversion in

TST. In this sense, TST-/QFT-GIT+ should be interpreted as LTBI in RA. The interpretation of TST+/QFT-GIT- discrepancy should also be done with caution. The sensitivity of QFT reaches only 77% [4]. Negative QFT result does not exclude the presence of LTBI. Although TST+/QFT-GIT- discrepancy may indicate false positive TST due to BCG vaccination, the effect of BCG on TST result wanes with time and disappears in several years when it is performed during the neonatal period [28].

Increased age was significantly associated with positive results QFT-GIT result in multivariate analysis while other conventional risk factors for LTBI were not associated with either TST or QFT-GIT. Similar association was reported in a study by Martin et al [29]. One possible explanation for this association may be that as the subject ages, the chance to have a close contact with active TB may increase. This would be an indirect evidence of the superiority of QFT-GIT compared to TST.

In the analysis of follow-up TST and QFT-GIT, among the nine patients who had negative TST results at baseline, 4 (44.4%) patients showed a positive conversion while the results of QFT-GIT did not change. Interestingly, three of the four patients with positive conversion of TST had positive QFT-GIT result at baseline. These four patients were treated with DMARDs including biological agent and did not contact with active TB patient during the period from baseline and follow-up.

V. CONCLUSION

In this study, QFT-GIT showed better performance in Korean patients with RA on DMARDs compared to TST. QFT-GIT may have a value in the diagnosis of LTBI in patients with RA.

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ABSTRACT (IN KOREAN)

류마티스 관절염 환자의 잠복 결핵 진단에 있어 interferon gamma release assay의 유용성

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이 광 훈

항 TNF-α 제제의 사용은 잠복 결핵의 재활성화의 위험을 증가시키며 약제의 사용 전 잠복 결핵을 진단하는 일은 필수적이다. 투베르쿨린 피부 반응 검사 (tuberculin skin test, TST)는 잠복 결핵을 진단하는 전통적인 방법으로 류마티스 관절염 환자에서 반응이 떨어지는 것으로 알려져 있다. Interferon gamma release assay (IGRA)는 새로운 T 세포 기반 진단 기법으로서 면역력이 저하된 환자에서도 민감도를 유지하는 것으로 알려져 있다. 본 연구에서는 국내 류마티스 관절염 환자에서 IGRA가 TST보다 우월한 성과를 보이는지 알아보고자 하였다. 세브란스 병원에 내원한 121명의 류마티스 관절염 환자와 나이, 성별을 맞춘 55명의 대조군 환자를 후향적으로 조사하였으며 모든 환자들은 TST와 Quantiferon Tb gold In tube (QFT-GIT)를 시행하였다. TST는 RT-23, 2 tuberculin unit (TU)를 Mantoux 방법을 이용해 시행하였고 10 ㎜ 이상의 피부 경결을 양성으로 판정하였다. QFT-GIT는 제조회사의 안내서에 따라 시행하였다. TST의 양성률 (33.3% vs. 43.4%)과

QFT-GIT의 양성률(35.9% vs. 41.5%)은 류마티스 관절염군과 대조군간 차이가 없었다. 반면, Disease modifying anti-rheumatic drug (DMARD)를 복용하는 류마티스 관절염 환자군의 평균 피부 경결 크기는 대조군에 비해 의미있게 작았으며 [1 (0~30) mm vs. 6 (0~24) mm, p<0.05], TST의 양성률은 더 낮은 경향을 보였다 (27.6% vs. 39.6%, p=0.078). 반면 QFT의 양성률은 양군간 차이가 없었다. TST와 QFT-GIT의 일치율은 류마티스 관절염 군에서 moderate (κ=0.557) 였고 대조군에서 substantial (κ=0.616) 하였다. DMARD를 복용하는 류마티스 관절염군에서의 일치율(κ=0.396)은 복용하지 않는 군(κ=0.702)에 비해 더 불량하였다. 12명의 환자는 추가적으로 TST를 시행하였다. 기저 시점에서 음성의 TST 결과를 보인 9명의 환자 중 4명(44.4%)의 환자에서 양성으로 전환되는 것이 관찰되었고 이 4명 중 3명은 기저 시점에서 이미 QFT-GIT는 양성이었다. 7명의 환자에서 시행된 추가적인 QFT-GIT 검사에서는 결과의 변화는 관찰되지 않았다. 이러한 결과들은 QFT-GIT가 DMARD를 복용하는 류마티스 관절염 환자에서 더 우월한 성과를 보임을 시사한다. QFT-GIT는 류마티스 관절염 환자의 잠복 결핵 진단에서 가치가 있을 것이다.

핵심되는 말 : 류마티스 관절염, 잠복 결핵, 투베르쿨린 피부 반응검사, interferon gamma release assay, Quantiferon TB gold In Tube