Infliximab Does Not Suppress the Tuberculin Skin Test (Purified Protein Derivative)

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ABSTRACT. ***Objective.*** Tuberculin skin testing with purified protein derivative (PPD) is part of tuberculosis (TB) screening in patients receiving infliximab. We assessed whether infliximab, a strong inhibitor of inflammation, suppressed dermal induration, the outcome of this test. We also reassessed the booster phenomenon and the interobserver variability in tuberculin testing.

Methods. Forty-seven patients with various diagnoses, who had had a PPD test before infliximab use, were retested after infliximab treatment. The test was also assessed cross-sectionally among 31 patients with rheumatoid arthritis (RA) after 8.6 [± 4.1 standard deviation (SD)] months of infliximab use and in 82 patients with RA who had never used this agent. Booster phenomenon and the interobserver variability of reading the test were reassessed among 163 infliximab-naive patients with RA and Behçet's disease (BD) and 47 healthy controls.

Results. Among the 47 patients who received infliximab, and for whom sequential data were available, the mean skin induration was 5.9 ± 8.0 SD mm before and 6.1 ± 7.5 mm after 4.8 ± 3.7 months of treatment (p = 0.890). In the cross-sectional study the mean PPD induration was 7.8 ± 8.4 mm among infliximab-naive patients with RA, while it was 6.6 ± 2.1 mm in those receiving infliximab (p = 0.271). Booster phenomenon was observed in 14/49 (29%) of patients with RA, 7/31 (23%) of those with BD, and 1/10 of healthy controls. Interobserver variability of PPD reading was good (kappa = 0.92).

Conclusion. Infliximab use does not suppress the skin reaction to tuberculin. We confirm the booster phenomenon and that the PPD skin test has an acceptable interobserver reliability for an *in vivo* test. (First Release Feb 1 2007; J Rheumatol 2007; 34:474–80)

Key Indexing Terms:
TUBERCULOSIS RHEUMATOID ARTHRITIS PURIFIED PROTEIN DERIVATIVE
TUMOR NECROSIS FACTOR-ALPHA INHIBITOR INFLIXIMAB
TUBERCULIN SKIN TEST BEHÇET'S DISEASE

Tumor necrosis factor-α (TNF-α) inhibitors like infliximab act by suppressing TNF-α activity and decrease subsequent cytokine production, resulting in suppression of synovial inflammation and inhibition of joint damage. The use of TNF-α inhibitors has raised concern about an increased risk of infections, especially tuberculosis (TB)[1-3].

TB with TNF-α blocker use is a serious problem especially in endemic areas like Turkey where our study originates[1-3]. Current guidelines for TB prevention in patients using TNF-α inhibitors recommend screening patients for active and latent TB with the purified protein derivative (PPD) skin test and chest radiography when needed, before treatment is started[4,5]. Close monitoring is also recommended for screening these patients for new development of TB infection during TNF-α inhibitor use. It has been proposed that TNF is the key element that drives the delayed type hypersensitivity response by triggering or amplifying the chemokine release that is central to the PPD skin test[6,7]. However we had not come across clinical data on a possible effect of TNF-α inhibition on tuberculin testing. Such an effect, if it existed, would lessen the utility of this time-honored diagnostic skin test.

Another related issue is the so called booster phenomenon, an anamnestic response defined as an increase of at least 6 mm with a second PPD test administered 1-5 weeks after the first, in a PPD negative (< 10 mm) individual with the provision that the second PPD reading becomes positive (≥ 10 mm). In addition, before starting treatment with TNF-α inhibitors, testing for the booster phenomenon is recommended by some[4,8]. This is to avoid mislabeling the booster phenomenon as TB activation during sequential PPD testing. A further reason to repeat the test at a short interval is to detect patients with latent TB whose test is negative due to the immunosuppression caused by their disease or medications, or simply because of their increased age[9,10]. While widely

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referred to[11-17], the booster phenomenon had not been formally studied among patients with rheumatoid arthritis (RA). Repeated PPD testing is common among TNF-α inhibitor users and we felt that more data, especially among the diseased, were needed.

Our study was designed to: (A) explore the effect of infliximab on the PPD skin test; and (B) reassess the booster phenomenon among patients with RA. The interobserver variability of the PPD skin test was also readdressed.

MATERIALS AND METHODS

Infliximab and the PPD skin test

Regular tuberculin skin testing began 11 months after the first use of infliximab in our clinic, after the risk of TB with TNF-α inhibitors, especially in an endemic area such as ours, had been determined and guidelines developed. Since the beginning of November 2001, patients attending our clinic who are prescribed TNF-α inhibitors have routinely had a PPD skin test. The usual dose for each infusion of infliximab has been 3-5 mg/kg. Infusions following the first infusion were given on the second and sixth week and every 8 weeks thereafter.

PPD test was administered with the Mantoux technique, using 5 international units (IU) of PPD solution (BB-NCIPD Ltd, Bulgaria, standardized to PPD-S), which is injected intradermally to the forearm by a nurse. Induration diameter was measured perpendicular to the long axis of the forearm at 48 hours.

All 112 patients (49 men, 63 women, mean age 38 ± 15.8 yrs) who had at least one infliximab infusion in the rheumatology outpatient clinic of Istanbul University, Cerrahpasa Medical School (a tertiary referral center) between January 2001 and March 2005 were initially surveyed (Figure 1). Thirty-eight patients were excluded from the survey because their treatment was discontinued before the third infusion (n = 25) or because they continued their treatment in other institutions due to national health authority directives to have their treatment with TNF-α inhibitors locally (n = 13). Five additional patients were excluded from this survey because they developed TB (subject of another report).

Among the remaining patients the effect of infliximab on PPD reaction was assessed in 2 groups: (1) the sequential study group (n = 47); (2) the cross-sectional group (n = 31).

The sequential study. This group was formed after the exclusion of 22 further patients who did not have an initial PPD test because their infusions had started before November 2001 (Figure 1). The remaining 47 patients were included in the sequential survey to assess the effect of infliximab on the PPD test (Figure 1). For this purpose the readings of the first PPD test, which was before the initial infliximab infusion, and the second PPD test, which was 4.8 ± 3.7 standard deviation (SD) months after the first, were assessed both in parametric and nonparametric analyses (Table 2). The 22 patients with RA from this group were also analyzed separately.

Initial PPD test results of 34 of the 47 patients in the sequential survey was sought from patient charts. The rest were recorded prospectively and included all postinfliximab readings.

The cross-sectional study. This analysis was conducted only among 31 patients with RA who had at least one postinfliximab PPD test. In this group 22 patients were also included in the sequential study group. To these were added 9 patients with RA who had been excluded from the sequential study because they did not have a preinfliximab PPD test.

The effect of infliximab on the PPD reaction was assessed by comparing the last PPD test in these 31 patients with RA to a convenience sample of patients with RA attending our outpatient clinic who had not received or needed infliximab (n = 82). These patients were included in the booster phenomenon study.

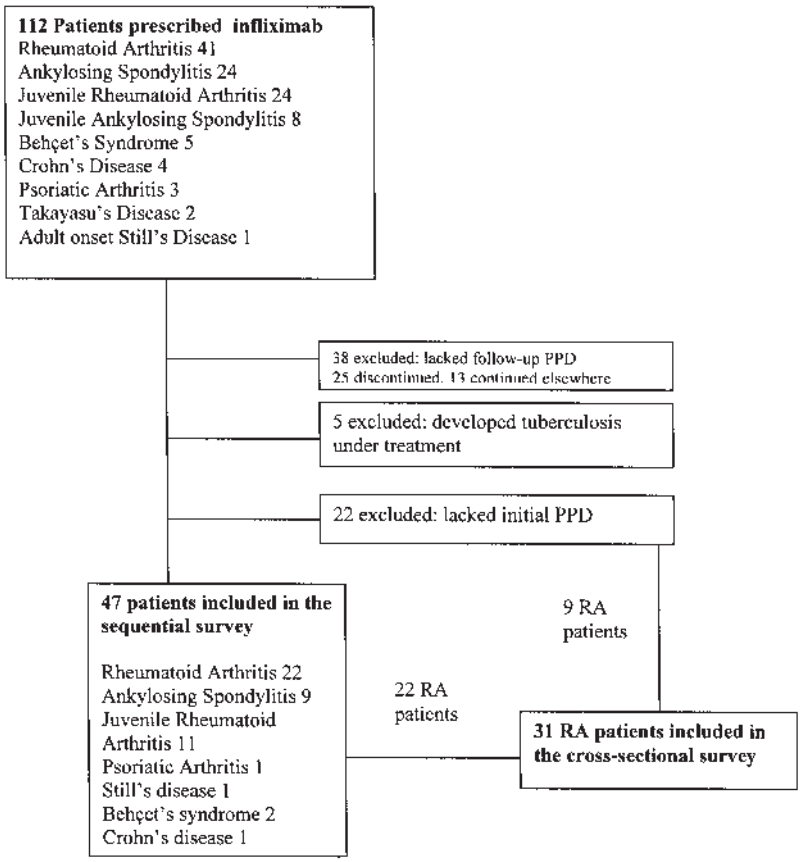

Figure 1. Patients prescribed infliximab between January 2001 and March 2005.

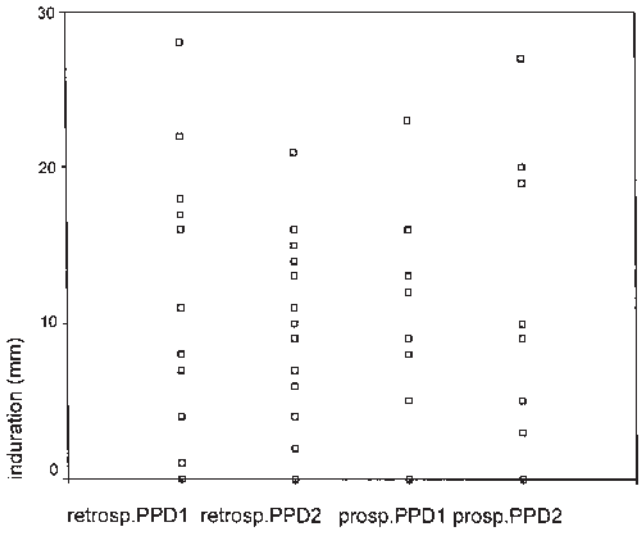

Figure 2. Initial (PPD1) and subsequent (PPD2) tuberculin skin tests of infliximab treated patients whose PPD1 reading was retrospective versus patients whose PPD1 reading was prospective.

Booster phenomenon

Eighty-two infliximab-naive patients with RA, 81 patients with Behçet's disease (BD), and 47 healthy controls (HC) were studied to assess the booster phenomenon and the interobserver variability in reading the PPD test.

Two PPD tests were administered one week apart, and the readings were made 48 hours after each injection by 2 physicians in a blinded manner. The physicians were blinded to both the diagnoses of the patients and to each other's measurement. Subjects put their arms through a curtain and their hands were covered to prevent physicians from recognizing the subject or any hand deformities revealing the diagnosis.

A booster effect was defined as an increase of at least 6 mm with a second PPD test administered 1-5 weeks after the first, in a PPD negative (< 10 mm) individual, with the provision that the second PPD reading becomes positive (≥ 10 mm). The frequency of a booster reaction and reversal was compared between patients treated with infliximab and infliximab-naive individuals who were included in the booster phenomenon study. Reversal was defined as a decrease in the induration with the second PPD test, where the first PPD test was positive (≥ 10 mm) and the second became negative (< 10 mm). The PPD booster reaction and reversal were also evaluated by defining the cutoff for a positive PPD as ≥ 5 mm.

Interobserver variability. To determine the interobserver variability, the readings in all PPD tests during the booster phenomenon study were compared between the 2 investigators.

Bacille Calmette-Guérin (BCG) vaccination. Checking the arms of individuals for BCG scars was not a part of the original design of the study. However, during the manuscript preparation we called back a convenience (mainly geographic) sample of the study subjects to assess for previous BCG vaccination.

Statistical analysis. Independent sample t test was used for comparing the initial and second PPD readings in the sequential study and to compare infliximab receiving and infliximab-naive patients with RA in the cross-sectional study. Kruskal-Wallis test was used to compare PPD postivity, boosting, and reversal (a positive skin test becoming negative, with no further restrictions such as a change in induration diameter like in the booster phenomenon) rates among groups. Sign test was used to compare the number of patients who had any increase and any decrease in PPD induration within groups. Magnitude of the change between 2 PPD tests was compared among patients who had any increase and those who had any decrease with Mann-Whitney U test.

First and second skin test results in the booster phenomenon study were compared with paired t test. PPD indurations among groups were compared using analysis of variance (ANOVA). The number of patients who had PPD positivity and those who had a booster reaction or reversal in each group was compared with Kruskal-Wallis test.

Kappa statistics was used to determine the interobserver variability in assessing skin induration, taking the cutoff at 5 mm and 10 mm, for each measurement.

RESULTS

Infliximab and the PPD test analyzed sequentially. Demographic data related to the 47 patients who were the subjects of the sequential survey are shown in Table 1. Since there was no significant difference between the retrospective and prospective readings of the mean PPD indurations (5.17 ± 7.31 SD mm and 7.77 ± 9.57 SD mm, respectively, p = 0.389) and that of the PPD positivity rates (12/34 and 4/13, respectively, p = 0.527), these readings were pooled for the purposes of our study.

In Table 2 the mean diameter of the first PPD as well as the

Table 1. Demographic features, previous and concurrent treatment of the 47 patients receiving infliximab treatment who had pre-infliximab and post-infliximab PPD tests.

N	47
Men	21
Women	26
Mean age ± SD (years)	37.9 ± 15.6
Previous treatment	
Prednisolone (< 15 mg/day)	35
Prednisolone (≥ 15 mg/day)	6
Methotrexate	36
Salazopyrine	24
Leflunomide	3
Hydroxychloroquine	12
Gold	1
Azathioprine	3
Cyclosporine	1
Concurrent treatment	
Prednisolone (< 15 mg/day)	36
Prednisolone (≥ 15 mg/day)	3
Methotrexate	38
Salazopyrine	2
Leflunomide	8
Hydroxychloroquine	4
Azathioprine	1
Cyclosporine	1

Table 2. Comparison of initial and second PPD tests of patients treated with infliximab.

	PPD1	PPD2	p
N	47	47	
Mean induration, mm	5.9 ± 8.0	6.1 ± 7.5	0.89*
PPD, no. (%)			
0 mm	26 (55)	22 (47)	0.54†
1–4 mm	2 (4)	5 (11)	0.44†
5–9 mm	5 (11)	5 (11)	1†
≥ 10 mm	14 (30)	15 (32)	0.83†

* Independent sample t test; † Fisher's exact test.

number of patients who had nonreactive skin tests, skin tests with indurations of 1-4 mm, 5-9 mm, and > 10 mm are compared with the second PPD test, which was 4.8 ± 3.7 SD months after the first. The median number of infliximab infusions before the second test was 3.

It is to be noted that there were no significant differences in the mean diameters of the PPD reactions in the initial and second readings. The same was true for the number of patients in the various subgroups of skin induration (Table 2).

The number of infliximab-treated patients with any increase was 17 and any decrease was 11 during the second test (p = 0.34, sign test). The delta differences between the initial and second readings in the magnitude of the reaction (data not given) in any direction was not significant (Mann-Whitney U, U = 88.5, p = 0.81).

Isoniazid was prescribed to 9 of the 14 patients who initially had a positive skin test. Among these 9 patients, skin induration increased in 2 patients and decreased in 7 patients, becoming negative in 4.

Among the 47 patients of the sequential study group, 22 patients with RA (6 men, 16 women, mean age 47.7 ± 13.2 SD yrs) were separately analyzed. Again, no significant changes were observed in the mean diameters of PPD tests and in the number of patients with various degrees of skin test induration before and after infliximab (Table 3). Finally the number of infliximab-treated patients with any increase was 6 and any decrease was 4 during the second test (p = 0.75, sign test).

Infliximab and the PPD test analyzed cross-sectionally. The effect of infliximab on the PPD reaction was further assessed cross-sectionally among a group of patients with RA only. The last PPD test of 31 infliximab-treated patients with RA, 8.6 ± 4.1 SD months after the initial infusion, was compared to those among 82 infliximab-naive patients with RA also attending our clinic. The mean PPD induration among these 31 patients (6.6 mm ± 2.1 SD) was not significantly different from those of infliximab-naive patients with RA (7.8 ± 8.4 mm, p = 0.27).

Three of the 5 patients who developed active TB during infliximab treatment who are not reported here had nonreactive PPD tests both before infliximab was prescribed and when they were diagnosed as having TB. One patient had a positive test (10 mm) when he started infliximab, and the remaining patient did not have an initial test, but she was PPD positive (22 mm) when TB was diagnosed. Two of these patients had miliary, one had mediastinal, one had pulmonary, and one had abdominal and pelvic TB. TB bacilli were grown in 3/5 of the patients.

Table 3. Comparison of initial and second PPD tests of patients with RA treated with infliximab.

	PPD1	PPD2	p
N	22	22	
Mean induration, mm	5.3 ± 7.7	5.3 ± 7.4	0.98*
PPD, no. (%)			
0 mm	13 (59)	12 (55)	0.76†
1–4 mm	1 (5)	2 (9)	0.55†
5–9 mm	2 (9)	1 5)	0.55†
≥ 10 mm	6 (27)	7 (32)	0.74†

* Independent sample t test; † Fisher's exact test.

Booster phenomenon. As mentioned in Materials and Methods, all individuals in this group were infliximab-naive. Table 4 shows that the mean initial induration was significantly lower among patients with RA compared to patients with BD and HC (F_{2df} = 9.1, p < 0.001, ANOVA) and the magnitude of the mean increase in induration diameter was less among HC (F_{2df} = 2.87, p = 0.059, ANOVA).

In nonparametric analyses, the frequency of PPD positivity was significantly higher among HC when compared to patients with RA and BD (Kruskal-Wallis 19.1, p < 0.001).

In addition, Table 4 shows that the frequency of a booster reaction was not different among the 3 groups (Kruskal-Wallis 1.35, p = 0.25).

Finally a comparison was made between the frequencies of a booster effect in the formal booster study versus that in the sequential study. Table 5 shows that the booster rate was not significantly different among the groups both when the cutoff for positivity is taken as 10 mm and 5 mm, while the reversal rate was significantly higher among the infliximab-treated patients, when the cutoff for positivity was taken as either 10 mm or 5 mm (Kruskal-Wallis 16.47, p = 0.001 and Kruskal-Wallis 8.36, p = 0.039, respectively).

Interobserver variability. Interobserver variability was good, with a kappa coefficient of 0.86 when the cutoff for positivity was taken as ≥ 5 mm and 0.92 when taken as ≥ 10 mm. The mean difference between the readings of 2 observers was 2.9 ± 3.7 SD mm.

BCG vaccination. Twenty-eight of the 47 infliximab-treated patients, and 140 of the 210 individuals who were included in the booster study could be checked for BCG scars after the study was finished. At least one BCG scar was present in 22 of the 28 (79%) infliximab-treated patients and 104 of the 140 (74%) individuals included in the booster study (p = 0.416).

Among the individuals who entered the booster study, 12 of the 104 subjects who had BCG scars (12%), and 3 of the 33 subjects (9%) who did not have a BCG scar had a booster reaction (p = 0.428).

DISCUSSION

Our survey showed that, despite the proposed role of TNF on delayed hypersensitivity and the PPD skin test, TNF-α inhibition by infliximab does not suppress the PPD reaction. Our observations both in the sequential and the cross-sectional parts of our study support this contention. In fact when we analyzed for any degree of increase or decrease in induration, there was even a trend for stronger PPD reactions after infliximab.

Our observation of significantly more reversals of a pos-

Table 4. Booster phenomenon.

	RA (n = 82)		BD (n = 81)		HC (n = 47)	
	PPD1	PPD2	PPD1	PPD2	PPD1	PPD2
Mean induration, mm	7.84 ± 8.38	11.68 ± 10.44	11.5 ± 7.5	13.5 ± 8.9	13.74 ± 7.75	14.72 ± 7.83
p	< 0.001		< 0.009		0.247	
PPD, no. (%)						
0 mm	32/82 (39)	22/82 (27)	15/81 (19)	13/81 (16)	7/47 (15)	7/47 (15)
1–4 mm	4/82 (5)	3/82 (4)	4/81 (5)	3/81 (4)	1/47 (2)	0/47
5–9 mm	13/82 (16)	9/82 (11)	12/81 (15)	10/81 (12)	2/47 (4)	2/47 (4)
≥ 10 mm	33/82 (40)	48/82 (59)	50/81 (62)	55/81 (68)	37/47 (79)*	38/47 (81)
Booster phenomenon, no. (%)	14/49 (29)		7/31 (23)		1/10 (10)	

* PPD positivity was significantly more frequent among healthy controls (Kruskal-Wallis 19.1, p < 0.001); frequency of booster reaction was not different among the 3 groups (Kruskal-Wallis 1.62, p = 0.44). RA: rheumatoid arthritis; BD: Behçet's disease; HC: healthy controls.

Table 5. Booster and reversal rate in infliximab-treated patients compared to infliximab-naive individuals of the booster phenomenon study when the cut-off for positivity is taken as 10 mm and 5 mm. A booster effect is defined as an increase of at least 6 mm with a second PPD test, administered 1–5 weeks after the first, in a PPD negative individual with the provision that the second PPD reading becomes positive. Reversal is defined as a decrease in the induration with the second PPD test, where the first PPD test was positive and the second became negative.

	Infliximab, n = 47 (%)	RA (naive) n = 82 (%)	BD, n = 81 (%)	HC, n = 47 (%)	p*
Booster (10 mm)	5/33 (15)	14/49 (29)	7/31 (23)	1/10	0.398
Booster (5 mm)	5/28 (18)	11/37 (30)	6/20 (30)	2/8 (25)	0.707
Reversal (10 mm)	5/14 (36)	3/33 (9)	3/50 (6)	2/37 (5)	0.006
Reversal (5 mm)	4/19 (16)	0/45	2/61 (3)	1/39 (3)	0.001

* Kruskal-Wallis test, patients treated with infliximab have higher reversal rates than the other groups when the cut off for positivity is taken as either 10 mm or 5 mm.

itive PPD test to a negative one among the infliximab-treated patients when compared to patients with RA and BD and to HC in the booster study, at first sight, might be considered as evidence against our conclusion of no effect of infliximab on the PPD reaction. However: (1) When the reversals and the boosters in the sequential study were compared, there were no significant differences in the number of patients with a booster and with a reversal (Table 5). (2) The "reversals" observed in the booster study were based on a timeframe (one week between 2 tests) totally different from that involved in the sequential study. Moreover the infliximab-naive group had a higher mean PPD induration than the patients using infliximab. Thus, a small decrease in the magnitude of the reaction may cause a "reversal" based on its definition (see Materials and Methods) in the infliximab-treated group, but not in the infliximab-naive group. These considerations make us rather confident about the robustness of our findings.

In a recent report by Joven, *et al*, of 61 patients treated with infliximab, 1 of 13 patients who were initially PPD positive became PPD negative, and 4 of 48 initially PPD negative patients became PPD positive after 54 weeks of infliximab treatment[18]. The mean induration in PPD positive patients increased from 12 ± 7 mm to 16 ± 7 mm after treatment. The authors concluded, as we do, that infliximab did not suppress the PPD reaction.

The booster phenomenon is an anamnestic response, resulting from the recall of waned cell-mediated immunity[11]. It is associated with remote TB infection, BCG vaccination[19], exposure to nontuberculous mycobacteria, and old age[9,20]. Its frequency is reported between 2.1% and 43% in different diseased and healthy populations. Testing for booster phenomenon is recommended for patients who will undergo serial tuberculin testing to avoid misinterpretation of the boosting reaction as a new infection. It should be mentioned that in the clinical setting only PPD negative individuals would be tested for booster phenomenon. We retested all individuals for study purposes.

It is thought that variations in administration and reading of the PPD will result in a standard deviation of less than 3 mm. This is the reason for utilizing, as we did, the increase of 6 mm (2 SD) to distinguish real boosting from increases due to random variation[20].

We confirmed the booster phenomenon in our patients with RA and diseased and HC, in a population with high background rates of exposure to TB. In our study, PPD positivity (≥ 10 mm) rate was 40% among patients with RA, 62% among patients with BD, and 79% among HC. These values are similar to those in a study involving 2835 Turkish subjects, where the reported mean induration among the positives was 11.95 ± 6.74 mm, and the rate of PPD positivity was 67.3%[21].

In the booster study those patients with RA were significantly less PPD positive at baseline when compared to patients with BD and HC. It is well known that the delayed hypersensitivity is depressed in RA[22]. What is more interesting, we believe, is the fact that the percentage of patients with a boost was 29% among patients with RA, 23% among those with BD, and 10% among HC ($p = 0.444$). These differences were not statistically significant, but this is perhaps a Type II error due to the small number of HC. The magnitude of the increase in the induration diameter with the second test was also less among our HC ($p = 0.059$). While this might be related to the significantly higher baseline PPD positivity among HC, we also propose that it might also be related to the contention that it required a boosting to restore the impaired delayed hypersensitivity among the diseased, due to the nature of the disease, drugs used, or both, especially in RA.

BCG vaccination is regularly performed in Turkey. Studies in different Turkish populations report the frequency of having at least one BCG scar from 20% (among the elderly) to 92.7% (among young adults). Unfortunately, we initially had not looked for BCG scars during our study. We called the patients back after the study ended and were able to check for BCG scars in 60% of infliximab-treated patients and 67% of the individuals who entered the booster phenomenon study. Overall 75% of the subjects had at least one scar. Frequency of having a scar was not different among those who received infliximab and those who did not. The rate of boosting also did not seem to be related to BCG vaccination.

Another drawback of this survey was that its design was not totally prospective when it addressed the effect of infliximab on the skin test in the sequential survey. Most of the patients had their initial tests before this study started. However, the fact that the cross-sectional part also supported the finding that infliximab did not suppress the dermal reaction makes us more confident in our observations.

A further limitation was that 54% of our patients treated with infliximab were not included in the sequential part of the study because they either did not have an initial PPD or because they had to continue their treatment elsewhere. This was due to a change in the regulations of the ministry of health during the survey period whereby patients receiving TNF-α antagonists could also be followed at nonacademic hospitals.

Finally, we did not formally assess the response of these patients to treatment with infliximab. This might be important since inadequate TNF blockade may go with a lack of effect of infliximab on PPD reaction.

Our main aim was to assess whether a potent and widely used inhibitor of the inflammatory-immune reaction, infliximab, suppressed and thus impaired the clinical usefulness of a commonly used diagnostic test, the tuberculin test. Our results indicate that this was not so. The more involved issue of whether infliximab therapy restores the impaired delayed hypersensitivity response needs to be further addressed by studies specifically designed to address this possibility.

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REFERENCES

1. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med 2001;345:1098-104.
2. Gomez-Reino JJ, Carmona L, Valverde VR, Mola EM, Montero MD, BIOBADASER Group. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. Arthritis Rheum 2003;48:2122-7.
3. Long R, Gardam M. Tumour necrosis factor-alpha inhibitors and the reactivation of latent tuberculosis infection. CMAJ 2003;168:1153-6.
4. Furst DE, Cush J, Kaufmann S, Siegel J, Kurth R. Preliminary guidelines for diagnosing and treating tuberculosis in patients with rheumatoid arthritis in immunosuppressive trials or being treated with biological agents. Ann Rheum Dis 2002;61 Suppl 2:ii62-3.
5. Mariette X, Salmon D. French guidelines for diagnosis and treating latent and active tuberculosis in patients with rheumatoid arthritis treated with TNF blockers. Ann Rheum Dis 2003;62:791.
6. Orme IM, Cooper AM. Cytokine/chemokine cascades in immunity to tuberculosis. Immunol Today 1999;20:307-12.
7. Long R, Gardam M. Tumor necrosis factor-alpha inhibitors and the reactivation of latent tuberculosis infection. CMAJ 2003;168:1153-6.
8. Keser G, Direskeneli H, Akkoc N, et al. TNF-a Engelleyici Ilaç Kullanan Olgularin Tedavi Öncesinde Tüberküloz Açısından Degerlendirilmesi ve Alınması Gerekli Önlemler. RAED II. Uzlasi Toplantısı Raporu. 2005 May.
9. Slutkin G, Perez-Stable EJ, Hopewell PC. Time course and boosting of tuberculin reactions in nursing home residents. Am Rev Respir Dis 1986;134:1048-51.
10. American Thoracic Society, Centers for Disease Control. Targeted tuberculin testing and treatment of latent tuberculosis infection. Am J Respir Crit Care Med 2000;161:S221-47.
11. Thompson NJ, Glassroth JL, Snider DE Jr, Farer LS. The booster phenomenon in serial tuberculin testing. Am Rev Respir Dis 1979;119:587-97.
12. Wauters A, Peetermans WE, Van den Brande P, et al. The value of tuberculin skin testing in haemodialysis patients. Nephrol Dial Transplant 2004;19:433-8.
13. Hoft DF, Tennant JM. Persistence and boosting of bacille Calmette-Guerin-induced delayed-type hypersensitivity. Ann Intern Med 1999;131:32-6.
14. Sepkowitz KA, Feldman J, Louther J, Rivera P, Villa N, DeHovitz J. Benefit of two-step PPD testing of new employees at a New York City hospital. Am J Infect Control 1997;25:283-6.
15. Menzies R, Vissandjee B, Rocher I, St Germain Y. The booster effect in two-step tuberculin testing among young adults in Montreal. Ann Intern Med 1994;120:190-8.
16. Rosenberg T, Manfreda J, Hershfield ES. Two-step tuberculin testing in staff and residents of a nursing home. Am Rev Respir Dis 1993;148:1537-40.
17. Slutkin G, Perez-Stable EJ, Hopewell PC. Time course and boosting of tuberculin reactions in nursing home residents. Am Rev Respir Dis 1986;134:1048-51.
18. Joven BE, Almodovar R, Galindo M, Mateo I, Pablos JL. Does anti-tumor necrosis factor alpha treatment modify the tuberculin PPD response. Ann Rheum Dis 2006;65:699.

19. Moreno S, Blazquez R, Novoa A, et al. The effect of BCG vaccination on tuberculin reactivity and the booster effect among hospital employees. Arch Intern Med 2001;161:1760-5.
20. Menzies D. Interpretation of repeated tuberculin tests. Boosting, conversion, and reversion. Am J Respir Crit Care Med 1999;159:15-21.
21. Ucan ES, Sevinc C, Abadoglu O, Arpaz S, Ellidokuz H. Tüberkülin Testi Sonuçlarının Yorumlanması Ülkemiz Standartları ve Yeni Gereksinimler. Toraks Dergisi 2000;1:25-30.
22. Helliwell MG, Panayi GS, Unger A. Delayed cutaneous hypersensitivity in rheumatoid arthritis: the influence of nutrition and drug therapy. Clin Rheumatol 1984;3:39-45.