Diagnosis and treatment of latent tuberculosis in patients who have chronic inflammatory diseases and use of TNF-α inhibitors*

Diagnóstico e tratamento da tuberculose latente em pacientes com doenças inflamatórias crônicas e uso de imunobiológicos inibidores do TNF-α

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Abstract

Objective: To determine the clinical and epidemiological profile of patients who are candidates for TNF-α inhibitor use and are classified as having latent tuberculosis (LTB), as well as to evaluate the outcomes of prophylactic treatment with isoniazid. **Methods:** A prospective descriptive analysis followed by an analytical, observational, cross-sectional study of the outcomes of prophylactic treatment in a group of 45 candidates for TNF-α inhibitor use. We evaluated the patients through anamnesis, clinical examination, chest X-ray, and tuberculin skin test (TST) using the Mantoux method. **Results:** The mean age was 45 years, and 56.0% of the patients were female. Chronic rheumatic diseases, chronic dermatological diseases, and Crohn's disease were present in 46.7%, 40.0%, and 13.3% of the patients, respectively. The mean TST induration was 14.6 mm (range: 5-30 mm). The majority (n = 30) of the 45 patients (66.7%) had an induration > 10 mm. In the 16 patients with BCG vaccination scars, the mean induration was 15.7 mm, and 14 of those patients had an induration > 10 mm. Chest X-ray results were considered normal, with minimal alterations, in 64.4% and 35.6% of the patients, respectively. The treatment with isoniazid was abandoned by 1 patient (2.2%) and completed by 41 (91.2%), whereas it was interrupted because of drug-induced hepatitis in 2 (4.4%), and 1 patient (2.2%) was transferred to another hospital. Of those who completed the treatment, 5 experienced mild side effects. **Conclusions:** Determining the profile of candidates for TNF-α inhibitor use is important for the management of LTB treatment and for the establishment of clinical protocols for the use and monitoring of the use of these medications.

Keywords: Tuberculosis; Latent tuberculosis; Tuberculin test; Isoniazid; Tumor necrosis factor-alpha.

Resumo

Objetivo: Traçar o perfil clínico-epidemiológico de pacientes candidatos ao uso de fármacos anti-TNF-α diagnosticados como portadores de tuberculose latente (TBL) e avaliar os desfechos do tratamento profilático com isoniazida. **Métodos:** Análise descritiva prospectiva seguida de um estudo analítico observacional transversal dos desfechos do tratamento profilático em um grupo de 45 candidatos ao uso de fármacos anti-TNF-α. A avaliação dos pacientes constou de anamnese, exame clínico, radiografia de tórax e teste tuberculínico (TT) por Mantoux. **Resultados:** A idade média dos pacientes foi 45 anos, e 56,0% dos pacientes eram mulheres. Doenças reumatológicas crônicas, doenças dermatológicas crônicas e doença de Crohn estavam presentes em 46,7%, 40,0% e 13,3% dos pacientes, respectivamente. A média de enduração do TT foi 14,6 mm (variação: 5-30 mm). A maioria dos pacientes (n = 30; 66,7%) apresentou enduração > 10 mm. Dos 16 pacientes com cicatriz vacinal BCG, a média de enduração foi de 15,7 mm, sendo que 14 tiveram enduração > 10 mm. Os resultados de radiografia de tórax foram considerados normais e com alterações mínimas em 64,4% e em 35,6%, respectivamente. Apenas 1 paciente (2,2%) abandonou o tratamento com isoniazida, 41 (91,2%) completaram o tratamento, 2 (4,4%) tiveram de interromper o tratamento por hepatite medicamentosa, e 1 (2,2%) foi transferido para outro hospital. Dos que completaram o tratamento, 5 apresentaram efeitos colaterais leves. **Conclusões:** A determinação do perfil dos candidatos ao uso de inibidores do TNF-α é importante para o manejo do tratamento da TBL, bem como para estabelecer protocolos clínicos de uso e acompanhamento do uso desses fármacos.

Descritores: Tuberculose; Tuberculose latente; Teste tuberculínico; Isoniazida; Fator de necrose tumoral alfa.

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Introduction

The discovery of TNF-α inhibitors revolutionized the clinical treatment of chronic inflammatory diseases, such as rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, and psoriasis. Since then, the use of such inhibitors has progressively become more widespread; however, this type of therapy has increased the risk of infectious diseases, such as tuberculosis.[1,2]

According to the World Health Organization, the number of new cases of tuberculosis worldwide was 9.4 million in 2008, which is equivalent to 139 cases per 100,000 population and is a cause for concern. Brazil currently ranks 18th in terms of tuberculosis incidence and is among the 22 countries that collectively account for 80% of all cases of tuberculosis worldwide.[3]

It is estimated that 50 million Brazilians are infected with *Mycobacterium tuberculosis*. Approximately 5% of all such individuals will develop active tuberculosis within the first two years after infection. The remaining 95% will avoid developing the disease, because their body mounts an effective cellular immune response, and will continue to have latent tuberculosis (LTB) for the rest of their lives unless they become immunocompromised, which increases the chance of developing the disease. The American Thoracic Society defines individuals with LTB as those who present with positive tuberculin skin test (TST) results, negative results on bacteriological analysis (if performed), and no clinical or radiological evidence of active tuberculosis.[4-6]

Regarding the detection of individuals infected with *M. tuberculosis* and of patients with LTB, the priority of the Brazilian National Tuberculosis Control Program was, until recently, to examine household contacts and treat infected individuals. This stance was recently reviewed in order to broaden the scope of detection of infected individuals and include other risk groups, such as those of patients who are candidates for the use of TNF inhibitors, corticosteroids, and other immunosuppressants used in chronic inflammatory diseases. To date, there have been few studies investigating such patients in Brazil.

The Brazilian National Health Surveillance Agency has approved the use of the biological agents infliximab, etanercept, and adalimumab, all of which are now commonly used for the treatment of patients who have chronic inflammatory diseases and do not respond to conventional therapies. In Brazil, those agents have been increasingly recommended and used. However, it is known that the use of TNF inhibitors in patients infected with *M. tuberculosis* increases the risk of progression to active tuberculosis.[7,8] In order to avoid that outcome, patients in this risk group have been referred for evaluation of the need to undergo prophylactic treatment with isoniazid. This has had an impact on the clientele of tuberculosis outpatient clinics; treating elderly patients, who, in addition to presenting with chronic diseases and comorbidities, use various other drugs, has also become a challenge. This population is completely different from that of patients who used to be selected for what was formerly known as "chemoprophylaxis". That population was principally composed of children and health professionals who had been in contact with infected individuals. We conducted the present study in order to gain a deeper understanding of this new population, establish the correct diagnosis of LTB, recommend preventive treatment, evaluate the response to preventive treatment, and devise follow-up strategies. The objective of the study was to provide guidance regarding the correct and safe management of patients who are candidates for TNF-α inhibitor use.

Methods

This was a prospective descriptive analysis of a group of patients who had chronic inflammatory diseases, were candidates for TNF-α inhibitor use, and were enrolled in the prophylactic LTB treatment program at the *Hospital Universitário Walter Cantídio da Universidade Federal do Ceará* (HUWC/UFC, Federal University of Ceará Walter Cantídio University Hospital), located in the city of Fortaleza, Brazil. The analysis was followed by an analytical, observational, cross-sectional study of the outcomes of the prophylactic treatment. The study was conducted between June of 2008 and December of 2009.

All patients who had chronic inflammatory diseases, were candidates for TNF-α inhibitor use, and were referred for evaluation at the HUWC/UFC tuberculosis outpatient clinic during the study period were considered eligible

for inclusion in the present study. A total of 68 patients were eligible. Of those, 45 were diagnosed with LTB. The diagnosis was based on anamnesis, clinical examination, chest X-ray, and TST using the Mantoux method. The TST was performed by a trained HUWC/UFC Clinical Analysis Laboratory technician and consisted of delivering PPD RT23 tuberculin intradermally in the middle third of the anterior face of the left forearm at a dose of 0.1 mL, which is equivalent to 2 tuberculin units. The TST was read 72-96 h after its application, and the result corresponded to the measurement (in mm) of the maximum transverse diameter of the area of palpable induration. Indurations > 5 mm were considered indicative of a positive response.[9,10]

Anteroposterior chest X-rays were taken at the Department of Radiology of the HUWC/UFC and examined by two independent technicians (a Department radiologist and a researcher who was one of the authors of the present study). Chest X-ray findings were classified as follows: normal; abnormal because of the presence of granuloma or a small calcified nodule; and abnormal because of the presence of other, minimal, residual changes (striae, nodular fibrosis, pleural thickening, or any combination of the three). We also evaluated the history of risk factors for developing tuberculosis, including respiratory symptoms, current or previous treatment for tuberculosis, and recent contact with patients with active tuberculosis.

All of the patients investigated in the present study underwent the TST and chest X-ray before starting the treatment with TNF-α inhibitors. A positive TST result and the absence of radiological evidence of active tuberculosis were considered indications for LTB treatment. The use of TNF-α inhibitors was allowed only one month after a six-month course of prophylactic treatment with isoniazid (300 mg/day p.o.), in accordance with the recommendations of the Brazilian National Ministry of Health and the Third Brazilian Thoracic Association Guidelines on Tuberculosis.[11]

All of the participants gave written informed consent. The study was approved by the HUWC/UFC Research Ethics Committee (Protocol no. 025.04.09).

Statistical analysis was performed with the aid of the Statistical Package for the Social Sciences, version 16.0 (SPSS Inc., Chicago, IL, USA). For the tests of significance of the associations, we used Pearson's chi-square test or Fisher's exact test for 2 × 2 tables when the values of the table cells were lower than 5. The level of statistical significance was set at $p < 0.05$.

Results

A total of 45 patients who were candidates for TNF-α inhibitor use were included in the present study. The patients were referred to the tuberculosis outpatient clinic from various other specialized HUWC/UFC outpatient clinics: 21 patients (46.7%) from the rheumatology outpatient clinic; 18 (40.0%) from the dermatology outpatient clinic; and 6 (13.3%) from the gastroenterology outpatient clinic. Among the underlying rheumatic diseases, the most common were rheumatoid arthritis and ankylosing spondylitis (22.3% each). Among the underlying dermatologic and gastrointestinal diseases, the most common were psoriasis (24.4%) and Crohn's disease (13.3%), respectively. The combined presence of more than one underlying disease was seen in 17.7% of the cases.

The mean age of the patients was 45 years, and approximately half of the patients (45.0%) were in the 40-49 year age bracket. Females predominated (56.0%; Table 1).

The clinical and epidemiological characteristics of the patients classified as having LTB are described in Table 1. The diagnostic evaluation consisted of the taking of a clinical history (of contact with infected individuals and diagnosis of or previous treatment for tuberculosis, as reported by the patients), clinical evaluation of respiratory symptoms, examination of BCG vaccination scars, analysis of the TST results, and analysis of the anteroposterior and lateral chest X-ray findings. Of the individuals under study, 9 (20.0%) reported having had contact with infected patients. Two patients reported having previously been treated for pulmonary tuberculosis. Most (88.9%) of the patients had no respiratory symptoms. Only 16 (35.6%) of the patients had been vaccinated with BCG, as confirmed by the presence of a vaccination scar on the right arm, whereas 6 (13.3%) had no BCG vaccination scars. When queried, 23 (51.1%) of the patients reported not knowing whether they had received BCG vaccination.

The mean TST induration was 14.6 mm (range: 5-30 mm). Of the 45 patients, 30 (66.7%) had an induration > 10 mm. In 15 of the patients, the induration was between 5 mm and 10 mm. Chest X-ray findings were considered normal in 29 (64.4%) of the patients, and 16 (35.6%) presented with radiological abnormalities that were considered minimal: 8 (17.8%) presented with calcified granulomas or nodules (calcified or otherwise); and 8 (17.8%) presented with small fibrous nodules, fibrotic bands, or pleural thickening confined to the apical region (Table 1).

Table 2 shows the correlation between the use of immunosuppressive drugs and the underlying diagnosis. Most of the patients who were referred to the tuberculosis outpatient clinic in order to be screened and treated for LTB had previously been treated or were still using immunosuppressive drugs in isolation or in combination: 36 patients (80.0%) were using methotrexate or other immunomodulators; and 20 (44.4%) were using prednisone.

Table 3 shows the influence of certain variables that could have modulated the TST response in the patients under study. However, none of those variables showed a statistically significant association with the TST results. Nevertheless, in the 16 patients with BCG vaccination scars, the mean TST induration was 15.7 mm, and 14 of those patients had an induration > 10 mm.

Table 4 shows that most of the individuals who constituted the initial group of patients (n = 41; 91.2%) completed the treatment. One patient (2.2%) was transferred to another hospital after having been followed at the HUWC/UFC for four months, and another abandoned the treatment (was lost to follow-up). In 2 (4.4%) of the patients, the treatment was discontinued because of drug intolerance.

In 2 (4.4%) of the 45 patients under study, the treatment was discontinued because of drug-induced hepatitis. Table 5 shows that 38 (88.4%) of the 43 patients completed the prophylactic treatment without any side effects, a significant difference in comparison with the group of patients who received no prophylactic treatment (p = 0.021). Mild side effects, such as gastric complaints, epigastric pain, heartburn, peripheral neuropathy, and urticaria, occurred in the remaining 5 patients (11.6%). We attempted to determine whether the side effects observed were associated with other factors. Of the 7 patients who experienced side effects, 4 (57.1%) presented with comorbidities (pathologies other than LTB or the underlying disease), the most common being arterial hypertension, diabetes, hypercholesterolemia, and osteoporosis. In addition, 5 (71.4%) of those 7 patients were using immunosuppressants to treat the underlying disease.

Table 1 - Clinical and epidemiological characteristics of the patients (n = 45) and results of the tests performed.

Characteristic	n	%
Gender		
Female	25	55.6
Male	20	44.4
Age, years		
< 40	11	24.4
40-49	20	44.5
≥ 50	14	31.1
Outpatient clinic of origin		
Dermatology	18	40.0
Gastroenterology	6	13.3
Rheumatology	21	46.7
BCG vaccination scar		
Present	16	35.6
Absent	6	13.3
Uncertain	23	51.1
Self-reported history of contact with tuberculosis		
Yes	9	20.0
No	15	33.3
Unknown	21	46.7
History of tuberculosis treatment		
Underwent treatment	2	4.4
Did not undergo treatment	43	95.6
Respiratory symptoms		
Cough, expectoration	5	11.1
No respiratory symptoms	40	88.9
Tuberculin skin test, induration		
5-10 mm	15	33.3
≥ 10 mm	30	66.7
Chest X-ray		
Normal	29	64.4
Abnormal	8	17.8
Other[a]	8	17.8

[a]Striae, nodular fibrosis, pleural thickening, or any combination of the three.

Table 2 - Relationship between the underlying disease and the use of immunosuppressive drugs or prednisone.

Drug(s)	Use (dose)	Underlying disease						p*
		Rheumatic diseases		Dermatologic diseases		Crohn's disease		
		n	%	n	%	n	%	
Methotrexate or immunomodulators (or both)	No	6	28.6	3	16.7	0	0	0.274
	Yes	15	71.4	15	83.3	6	100.0	
Prednisone	No	9	42.9	14	77.8	2	33.3	0.008
	Yes (< 15 mg)	10	47.6	1	5.6	1	16.7	
	Yes (≥ 15 mg)	2	9.5	3	16.7	3	50.0	

*Pearson's chi-square test or Fisher's exact test.

Discussion

The rationale for the use of TNF inhibitors in the treatment of chronic inflammatory diseases is based on the fact that TNF-α is the principal cytokine signaling and regulating the remaining cytokines involved in the inflammatory process. However, TNF-α plays a fundamental role in the immune defense against *M. tuberculosis*, particularly in granuloma formation and maintenance. In animal models, it has been demonstrated that there is dissemination of tuberculosis infection after the administration of anti-TNF antibodies.[12-14]

Even if its metabolism is depressed, *M. tuberculosis* can grow intermittently inside the granuloma and subsequently reactivate the infection. It is the effectiveness of the immune

Table 3 - Relationship between the study variables and the tuberculin skin test induration.

Variable	TST, induration				p*
	> 10 mm		≤ 10 mm		
	n	%	n	%	
Age, years					0.460
11-39	8	26.7	3	20.0	
≥ 40	22	73.3	12	80.0	
Underlying disease					0.607
Rheumatic diseases	14	46.7	7	46.7	
Dermatologic diseases	11	36.6	7	46.7	
Crohn's disease	5	16.7	1	6.6	
Self-reported history of contact with tuberculosis					0.384
Yes	8	26.7	7	46.7	
No	7	23.3	2	13.3	
Unknown	15	50.0	6	40.0	
Chest X-ray					0.077
Normal	22	73.3	7	46.7	
Abnormal	8	26.7	8	53.3	
BCG vaccination scar					0.123
Absent or uncertain	16	53.3	13	86.6	
Present	14	46.6	2	13.3	
Use of methotrexate or immunomodulators (or both)					0.661
Yes	24	80.0	12	80.0	
No	6	20.0	3	20.0	
Use of prednisone					0.772
No	16	53.3	9	60.0	
Yes (< 15 mg)	9	30.0	3	20.0	
Yes (≥ 15 mg)	5	16.7	3	20.0	

TST: tuberculin skin test. *Pearson's chi-square test or Fisher's exact test.

Table 4 - Adherence to the prophylactic treatment and the occurrence of side effects in the patients under study (n = 45).

Treatment variable	n	%
Adherence		
Completed the treatment	41	91.2
Abandoned the treatment	1	2.2
Was transferred	1	2.2
Discontinued because of intolerance	2	4.4
Side effects		
No	38	84.4
Yes	7	15.6

system of an individual—defined by genetic encoding (natural resistance) and previous tuberculosis infections (acquired resistance); by certain diseases or immunosuppressive conditions (advanced age, malnutrition, smoking, diabetes, sarcoidosis, silicosis, cancer, and HIV infection); or by the use of immunosuppressive drugs—that will influence the balance of the process, determining whether the infection will remain under control or will progress, causing disease. If the infection is controlled, the granuloma might calcify, hindering its subsequent reactivation. However, even if the infection is controlled, any future impairment of the immune system can reactivate the latent focus and cause tuberculosis (endogenous reactivation). Therefore, TNF-α plays a critical role in maintaining tuberculosis in its latent form, maintaining the integrity of the granuloma. The use of TNF inhibitors upsets this balance and favors the progression to active tuberculosis.[12,15,16]

Important data related to the management of chronic inflammatory diseases include the types of drugs that are routinely used by patients and how often they use such drugs, as well as the risk of developing infectious diseases, such as tuberculosis. Cases of tuberculosis in association with TNF-α inhibitor use are reported far more often than are cases of tuberculosis associated with other opportunistic infections and tend to occur after a median of 12 weeks of treatment, principally when infliximab is used. In this condition, tuberculosis most often manifests in its extrapulmonary form—especially as disseminated tuberculosis—and is often atypical in presentation, making it difficult to diagnose.[6,7,17]

One study reported that the relative risk of developing tuberculosis, in comparison with that observed for the general population, is 19 times higher in individuals using TNF inhibitors than in the general population, whereas it is only 4 times higher in individuals using conventional immunosuppressants.[18] That study also reported that the risk of developing tuberculosis is 3 times higher in individuals using infliximab than in those using etanercept.[18]

In our study we found that most of the patients were using corticosteroids and other immunosuppressants concomitantly, which suggests a potential additive or synergistic effect of TNF-α inhibitor use. In various studies, the principal variable for the diagnosis of LTB has been the TST results. In our study, one of our initial questions was whether the immunosuppressive drugs used in order to treat the underlying disease had any influence on skin reactivity to the PPD used in the TST.

It is known that a positive TST result in isolation is only an indication of infection and is not sufficient to establish a diagnosis of active tuberculosis. The TST results should be

Table 5 - Relationship between side effects and comorbidities, as well as between side effects and adherence to the prophylactic treatment (n = 45).

Characteristic	Side effects				p*
	Yes		No		
	n	%	n	%	
Comorbidities					
Yes	4	57.1	17	44.7	0.422
No	3	42.9	21	55.3	
Adherence to the treatment					
Yes	5	71.4	38	100	0.021
No	2	28.6	0	0.0	

*Pearson's chi-square test or Fisher's exact test.

interpreted with caution in individuals having received BCG vaccination within the last 3 years, as well as in those presenting with other situations that can interfere with the results, such as infection with atypical mycobacteria, immunosuppressive diseases, and treatment with corticosteroids or immunosuppressants.[19,20]

The increasing use of TNF-α inhibitors can increase the probability that individuals with LTB will develop active tuberculosis if care is not taken when selecting candidates for TNF-α inhibitor use, especially in Brazil, where tuberculosis remains a public health problem. Therefore, LTB should always be investigated, which can be difficult in Brazil because BCG vaccination is mandatory for all neonates. The immunity conferred by BCG vaccination depends on memory T lymphocytes and can last 10-15 years, thus making it difficult to interpret the TST results. Another factor that can influence TST reactivity is the use of immunosuppressants and corticosteroids, such as prednisone.[11] We therefore attempted to evaluate the influence of certain variables that might be involved in changes in the immune response, and consequently in the response to the TST. However, none of the variables studied showed a statistically significant association with the TST response. An interesting and surprising finding was the high mean TST induration in this group of patients. A plausible explanation for that is that a high proportion of the patients had a history of contact with a tuberculosis patient. In our study sample, indurations ranged from 8 mm to 30 mm (mean, 15 mm). One patient who had previously been treated for and cured of tuberculosis had an induration of 22 mm. The mean TST induration in patients who had a BCG vaccination scar was slightly higher than was that in those who did not (15.7 mm vs. 14.0 mm).

The major challenge when interpreting the TST results in this risk group lies in determining the induration cut-off point for the diagnosis of tuberculosis and that for preventive treatment for LTB. The issue remains controversial. Some authors advocate that patients who are immunocompromised at the time of the TST should undergo LTB treatment before starting the treatment with TNF inhibitors, even if the TST result is negative.[14]

A study conducted in Spain and involving patients undergoing treatment with TNF inhibitors reported that, among patients with a TST induration ≥ 5 mm and chest X-ray findings suggestive of previous tuberculosis, those who had not been treated for LTB were 7 times more likely to develop tuberculosis than were those who had received such treatment.[7] The British Thoracic Society has estimated that the annual risk of developing tuberculosis is 5 times higher when TNF inhibitors are used than when any of various other epidemiological factors are present.[21]

In Brazil, where the incidence of tuberculosis is considered alarmingly high, certain questions remain unanswered. Should we maintain a TST induration cut-off point of 5 mm? Should the treatment of LTB be extended to all candidates for TNF-α inhibitor use, regardless of the TST results? According to one group of authors,[22] patients with LTB should receive prophylactic treatment for active disease before the use of TNF-α inhibitors, because false-negative TST results can be obtained for immunocompromised patients. In a study conducted in Spain,[23] another group of authors addressed the issue of conducting prophylaxis before the use of TNF-α inhibitors, regardless of the TST results or the diagnosis of LTB. More than 1,000 patients were treated prophylactically, and only 1% presented with a significant increase in hepatic enzyme levels. In that study sample, there were no deaths or hospitalizations.

In the present study, we observed that all of the LTB patients being treated at the tuberculosis outpatient clinic of the HUWC/UFC received isoniazid for 6 months, as recommended by the Brazilian National Ministry of Health. Despite the underlying disease, the presence of comorbidities, and the use of various other drugs, 91.0% of the patients completed the treatment. Only 1 patient (2.2%) abandoned the treatment, which is in disagreement with the abandonment rates reported in other studies evaluating chemoprophylaxis in other situations, such as in the contacts of tuberculosis patients. Studies conducted in Brazil and analyzing factors related to treatment abandonment in a 5-year historical series involving 395 individuals receiving chemoprophylaxis with isoniazid in the city of Vitória, Brazil, reported that the rates of

chemoprophylaxis abandonment ranged from 21.9% to 37.1%.[24]

Of the 43 patients who completed the prophylactic treatment in the present study, 38 (88.4%) experienced no side effects, which was a significant difference in comparison with the group of patients who received no prophylactic treatment (p = 0.021). In 2 (4.4%) of the 45 patients studied, the treatment with isoniazid was discontinued because of drug-induced hepatitis. Mild side effects occurred in 5 (11.6%) of the 43 patients who completed the treatment. Although that proportion is considered high, drug-induced hepatitis has been shown to be a possible side effect in patients over 35 years of age. It should be highlighted that side effects occurred principally in patients who presented with comorbidities.

In conclusion, we found that determining the profile of patients who have chronic inflammatory diseases and are candidates for TNF inhibitor use can contribute to the standardization of the procedures for LTB screening, as well as to the establishment of clinical protocols for the recommendation and monitoring of preventive treatment with isoniazid. The Third Brazilian Thoracic Association Guidelines on Tuberculosis[11] and the Brazilian National Ministry of Health recommend that LTB be investigated in high-risk groups, emphasis being given to the following: history of contact with infected patients; previous BCG vaccination; clinical examination; use of immunosuppressive drugs; chest X-ray; and TST. The risk of developing tuberculosis by endogenous reactivation during treatment with TNF-α inhibitors should be emphasized because it constitutes an ongoing problem. Screening and the prophylactic use of isoniazid reduce that risk but do not eliminate it, TST reactivity being important in the evaluation. However, until new tests for a confident diagnosis of LTB and active tuberculosis are validated, we should take into consideration the clinical and epidemiological conditions, principally for immunocompromised patients, in order to determine the most appropriate TST induration cut-off point.

In the present study, the treatment outcomes were considered good: 91.0% of the patients completed the treatment; and 88.4% of those who completed the treatment reported no isoniazid-related side effects. In our study sample, despite the high mean age, the presence of comorbidities, and the use of other drugs in association with isoniazid, the rate of treatment abandonment was low (2.2%), which is in disagreement with the high treatment abandonment rates reported in other studies conducted in Brazil and evaluating chemoprophylaxis outcomes in the contacts of tuberculosis patients.

We believe that one of the factors related to the good treatment adherence observed in our study was the awareness of patients regarding the importance of preventing tuberculosis during treatment with immunobiological drugs. Finally, we emphasize the fact that, in patients with chronic inflammatory diseases using TNF-α inhibitors, disease surveillance should extend beyond the completion of isoniazid therapy.

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