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SHORT COMMUNICATION - OBSERVATIONAL RESEARCH

Follow-up results of isoniazid chemoprophylaxis during biological therapy in Colombia

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Abstract The use of biological therapy has been linked with an increased risk of tuberculosis (TB) reactivation. The aim of this study was to present the follow-up results for isoniazid (INH) chemoprophylaxis in patients receiving different biological therapies. In this prospective observational study, patients with latent tuberculosis infection (LTBI) were given INH chemoprophylaxis between 2 and 9 months prior to the beginning of biological therapy. All patients were followed up monthly for any signs or symptoms of active TB or INH toxicity. A total of 221 patients, 122 females (55.2 %), with a mean age of 46.8 ± 11.3 years (16–74) were enrolled. LTBI was identified in 218 patients (98.7 %), all of whom received INH chemoprophylaxis. Seven patients (3.2 %) developed active tuberculosis, and 32 (17.2 %) patients developed intolerance or toxicity related to INH. Chemoprophylaxis with INH seems to be effective and safe for the prevention of most TB reactivation in individuals with LTBI, but toxicity must be monitored during follow-up.

Keywords Anti-TNF-α drugs · Tuberculosis · Colombia · Tuberculin test · Isoniazid

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Introduction

With increasing biological agents becoming available for clinical use, there are more and more concerns about the rates of infections secondary to the disturbance of physiological cytokine-mediated signaling by these agents [1]. Soon after the introduction of biological therapies, several studies have been reported on an increased risk of reactivation of tuberculosis (TB), especially within 3–6 months after initiating biological therapy use [2–5]. This increased TB risk was mainly due to reactivation of latent TB infections (LTBI), because most of these medications neutralize the essential role of tumor necrosis factor (TNF) in mycobacteria containment [6].

Although tuberculin skin test (TST) is a widely used diagnostic method for LTBI diagnosis, the presence of immune-mediated inflammatory diseases (IMID) and immunosuppressive therapy may lead to false-negative results [7]. Screening of these patients should include history of close contacts with infectious TB cases, TST and chest radiography, especially considering that the risk of reactivation is higher in developing countries, where the prevalence of active TB infection varies between 5 and 30 % [8]. Currently, multiple authorities recommend that all potential biological therapy users with LTBI must be treated with isoniazid (INH) for 9 months or rifampin for 4 months [9].

The prescribing patterns for the biological therapies in Colombia have been increasing over the past few years [10], and Colombia has an intermediate tuberculosis (TB) burden, with an annual incidence of TB of approximately 33 per 100,000 in the general population [11] where latent TB infection (LTBI) is expected to be present in about one-third of general population [12], and recently, the

introduction of biological therapies has been correlated with an increase in tuberculosis cases [13].

Objective

This study aims to present the follow-up results of 221 patients with chronic immune-mediated inflammatory diseases (IMID) who are now using different biological therapies in Medellín (Colombia), a region where TB is endemic, and highlights the effectiveness and safety of INH prophylaxis.

Materials and methods

Study design

Prospective observational study.

Setting

Infectious diseases outpatient consultation service of Fundación Antioqueña de Infectología (FAI), located in Medellín, Colombia.

Patient population

A total of 221 patients, who underwent biological therapy for their different immune-mediated inflammatory diseases, and who were suspicious of having latent tuberculosis infection (LTBI), were followed up from June 2010 to June 2014. The demographical and clinical characteristics of the patients were recorded.

Diagnosis of latent tuberculosis infection

A detailed medical history was gathered from all patients to include the type of primary disease and previous or concurrent use of immunosuppressive treatments. Relevant medical information along with demographics was recorded. A chest X-ray was taken from each patient followed by a tuberculin skin test (TST) using the intradermal *Mantoux* method applied to the volar surface of the forearm. Skin reactions were measured at 72 h, and a hardening of $\geq$5 mm (transverse diameter) was considered a positive result. In the event of an anergic reaction with the initial TST, the test was repeated a week later. A diagnosis of latent tuberculosis was based on either the presence of fibrotic changes on chest X-rays compatible with tuberculosis calcified granulomas or TST induration $\geq$5 mm. In all patients with fibrotic lesions on chest radiography, active tuberculosis was excluded with three consecutive negative sputum examinations for acid-fast bacilli and a TB culture.

Chemoprophylaxis

Patients identified as having latent TB infection (LTBI) were treated with isoniazid (INH), 5 mg/kg per day with a maximum dose of 300 mg/day for 9 months, beginning with anti-TNF therapy between 2 and 9 months after initiation of chemoprophylaxis. If a patient had developed intolerance or toxicity related to INH, a second-line prophylaxis with rifampin would have been prescribed for 4 months.

Follow-up

Patients were followed up with physical examinations at monthly intervals to determine whether they would develop pulmonary or extrapulmonary tuberculosis symptoms, which in case of suggesting possible active tuberculosis, made it necessary to conduct appropriate diagnostic procedures according to clinical symptoms. Once on chemoprophylaxis, liver enzymes were monitored monthly and hepatotoxicity was accepted as the elevation of liver enzymes fivefold the upper limit of normal value.

Statistical analysis

Numerical values like age are reported as mean $\pm$ SD and range; categorical variables are shown as the number (*n*) and percent of cases.

Results

Patient characteristics

The demographical and clinical characteristics of patients are shown in Table 1.

Biological and immunosuppressive therapies

The most frequently used biological therapies were etanercept (37.1 %) and adalimumab (27.6 %). Overall, 68.3 % of patients were taking different kinds of immunosuppressive therapies at the time of initiation of treatment with the biological medication, mostly methotrexate alone, or in combination with some other drugs depending on clinical condition, as shown in Table 1.

Tuberculin skin test (TST) and chest X-rays

The TST was initially positive in 209 patients (94.6 %) and negative in 12 patients (5.4 %), but in those with an

Table 1 Characteristics of the study population

	Mean ± SD	Range
Age (years)	46.8 ± 11.3	(16–74)
Sex	*n*	%
Female	122	55.2
Primary disease		
Psoriasis	101	45.7
Rheumatoid arthritis	54	24.4
Ankylosing spondylitis	28	12.6
Ulcerative colitis	15	6.8
Crohn's disease	6	2.7
Uveitis	6	2.7
Sacroiliitis	5	2.2
Spondyloarthropathy typo ankylosing	5	2.2
Reactive arthritis	1	0.45
Immunosuppressive therapy[a]		
Yes	151	68.3
No	70	31.7
Biological therapy		
Etanercept	55	24.9
Adalimumab	38	17.2
Infliximab	20	9.0
Ustekinumab	12	5.4
Rituximab	6	2.7
Tocilizumab	4	1.8
Abatacept	3	1.3

[a] Immunosuppressive therapy used before biological therapy: methotrexate, hydroxychloroquine, leflunomide, azathioprine, prednisone, cyclosporine, sulfasalazine

Table 2 Chest X-rays, TST, INH chemoprophylaxis, INH toxicity and active TB development results

	n	%
Abnormal chest X-rays		
Yes	155	70.1
No	66	29.9
TST results		
<5 mm	3	1.3
≥5 mm	218	98.7
INH chemoprophylaxis		
Yes	186	84.2
No	35	15.8
INH toxicity		
Yes	32	17.2
No	154	82.8
Active TB development		
Yes	7	3.2
No	214	96.8

TST tuberculin skin test, *INH* isoniazid

initial anergic TST, it was repeated a week later looking for a booster effect, and nine additional positive patients were found. The average diameter of hardening among patients with a positive TST was 13.1 mm (min–max 5–45 mm). Chest X-rays on initial evaluation revealed the presence of fibrotic changes compatible with tuberculosis calcified granulomas in 70.1 % of patients, but only 1.8 % of patients gave a history of close contact with a patient with active tuberculosis (Table 2).

Chemoprophylaxis

From 218 TST-positive patients, 186 (84.2 %) completed 9 months of chemoprophylaxis with isoniazid (INH), nine patients did not accept to be treated, 16 never finished the 9-month treatment due to shortage of medication or not being able to attend follow-ups, and seven patients were switched to rifampin during 4 months. Overall, 17.2 % of the patients receiving INH developed intolerance or toxicity (allergic reaction, gastric intolerance and hepatotoxicity) (Table 2).

Tuberculosis cases

During the follow-up period, seven patients (3.2 %) developed active tuberculosis, being pulmonary tuberculosis the most common clinical presentation. Development time of TB varied widely from 2 to 12 months after beginning biological therapy (not from time after start INH prophylaxis). Five patients with active TB who received prophylaxis with INH were treated with moxifloxacin plus rifampin–ethambutol and pirazinamide for 2 months followed by seven additional months of moxifloxacin and rifampin according to a susceptibility test. Those two patients who never received INH prophylaxis were treated with 9 months of regular tetraconjugate according to local guidelines and a susceptibility test. The demographical and clinical characteristics of the patients who developed active tuberculosis are shown in Table 3.

Discussion

Latent tuberculosis infection (LTBI) is diagnosed in patients who are free from symptoms of tuberculosis active disease, but who have a chest X-ray with fibrotic changes suggestive of a previous tuberculosis infection, or ≥5 mm hardening on TST [7, 14, 15]. On this case definition, the rate of LTBI in our patient population was higher (98.7 %) than in similar published studies [16, 17], a difference which could be attributed to the higher incidence of active tuberculosis in Colombia, with the possibility of being infected while on immunosuppressive treatment before

Table 3 Characteristics of cases that developed active tuberculosis

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age (years)	37	52	28	54	55	30	47
Sex	Female	Female	Female	Male	Male	Male	Male
Primary disease	Psoriasis	Rheumatoid arthritis	Psoriasis	Rheumatoid arthritis	Psoriasis	Crohn's	Ankylosing spondylitis
Biological therapy	Etanercept	Etanercept	Etanercept	Infliximab	Adalimumab	Infliximab	Adalimumab
TST (mm)	10	8	12	11	6	0	14
INH Chemoprophylaxis (months)	9	9	9	9	No	No	9
Time to TB development (months)[a]	2	7	6	10	8	3	12
Site of TB	Pulmonary	Disseminated (pulmonary and lymph nodes)	Pulmonary	Pulmonary	Peritoneal	Pulmonary	Lymph nodes
Diagnostic method	Sputum examination	BAL[b] and lymph node biopsy	BAL[b]	Pulmonary biopsy	Peritoneal Bx[c]	Sputum examination	Lymph node Bx[c]
Fibrotic lesion on chest X-rays	Yes	Yes	Yes	Yes	No	Yes	No
Previous immunosuppressive therapy	Yes	Yes	Yes	Yes	Yes	Yes	Yes

[a] Time to TB development after start biological treatment

[b] *BAL* Bronchoalveolar lavage

[c] *Bx* Biopsy

starting biological therapy, but mostly because the study population was sent to our consultation service because the primary care physician had a big clinical suspicion of LTBI.

We found TST to be more sensitive than chest X-ray for diagnosis of LTBI (94.6 vs. 70.1 %), and surprisingly, only 1.8 % of patients remembered ever having a close contact with a patient with active tuberculosis, something that was not previously reported. Overall, 84.2 % of the patients with LTBI who were on biological therapy received INH chemoprophylaxis for 9 months and were followed monthly for any symptoms suggesting active tuberculosis or INH toxicity. From them, 32 patients (17.2 %) were found to have developed gastrointestinal intolerance or toxicity, which is much lower than similar reported studies [18], where 39 % of patients discontinued INH because of adverse events.

Despite screening and chemoprophylaxis, seven patients (3.2 %) developed active tuberculosis during the study period, mostly pulmonary tuberculosis, which is higher than in previously reported studies [19, 20], where rates of tuberculosis reactivation while on biological therapy range from 0.85 to 1.9 %, being extrapulmonary and disseminated forms of tuberculosis the most common clinical presentation, but in this study only three of our patients developed extrapulmonary tuberculosis during follow-up.

One of the main limitations of our study was that TST was preferred over interferon gamma release assays (IGRA) for the diagnosis of LTBI, mainly due to the cost, but IGRA is a good alternative diagnostic method that can be useful in immunosuppressive patients with LTBI, when the cost can be afforded.

Conclusion

In conclusion, diagnostic accuracy of TST for detecting latent tuberculosis infection is high among patients with immune-mediated inflammatory diseases, even in the setting of immunosuppression. If proper chemoprophylaxis regimen is adhered, the incidence of active tuberculosis remains within the acceptable limits even in an intermediate tuberculosis incidence country like Colombia, but INH hepatotoxicity is an adverse event that should be screened frequently during follow-up.

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Conflict of interest The authors declare that there is no actual or potential conflict of interest in relation to this article.

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