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Management of long-term therapy with biological drugs in psoriatic patients with latent tuberculosis infection in real life setting

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Abstract

Psoriatic patients with latent tuberculosis infection (LTBI) need a prophylaxis before starting a treatment with biological drugs. The aim of this study is to investigate the safety and efficacy of prophylaxis of LTBI in psoriatic patients receiving long-term biological drugs. The study included 56 patients (42 male and 14 female) affected by moderate-to-severe psoriasis (mean PASI: 12.8 ± 6.9 *SD*) treated with anti-TNF-α and/or anti IL 12, 23 and/or anti-CD11 drugs with a diagnosis of LTBI. LTBI diagnosis was based on tuberculin skin test and/or QuantiFERON TB Gold test positivity and chest X-ray suggestive, without clinical, or microbiological evidence of active disease. All patients received prophylactic therapy for 9 months with isoniazid (INH) 300 mg/day, starting 3 weeks before the beginning of biological treatment. Fifty-four patients completed prophylaxis with INH without any adverse events or intolerance; they continue the biological treatment without appearance of active tuberculosis. One patient developed tuberculosis pleurisy in course of treatment with etanercept. The infection has been treated and after a stable remission, treatment was restarted without tuberculosis reactivation. In this retrospective analysis, the prophylaxis of LTBI whit INH was effective and safe in longer follow-up period.

KEYWORDS

biological therapy, psoriasis, QuantiFERON, tuberculosis infection

1 | INTRODUCTION

Tumor necrosis factor-alpha (TNF-α) is a cytokine involved in many chronic inflammatory diseases such as Crohn's disease (CD), rheumatoid arthritis (RA), psoriatic arthritis (PsA), and psoriasis. TNF-α play an important role in the host immune response against *Mycobacterium tuberculosis* (MT) and it is essential for the cell-mediated immune response that leads to granuloma formation and inhibitions of infection (Kaplan & Freedman, 1996). Latent tuberculosis infection (LTBI) is a condition characterized by the presence of active bacteria contained in granulomas and by the absence of any clinical symptoms. LTBI is a risk to transform into active disease when subjects are immunosuppressed or exposed to an immunosuppressive therapy (Gardam et al., 2003; Keane & Bresnihan, 2008). The incidence of tuberculosis is estimated in seven new cases per 100,000 people per year in Italy (http://www.epicentro.iss.it/problemi/Tubercolosi/TubercolosiItalia.asp). The use of biologics, particularly TNF-α inhibitors (infliximab, etanercept, and adalimumab) in the treatment of chronic inflammatory diseases can increase five times the risk of developing active tuberculosis in these patients by the fragmentation of TNF-dependent granulomas (Amerio et al., 2013; Gardam et al., 2003; Hernandez, Cetner, Jordan, Puangsuvan, & Robinson, 2009; Keane & Bresnihan, 2008; National Psoriasis Foundation, 2008; World Health Organization, 2015). For this reason, to minimize the risk of reactivation, screening for LTBI is mandatory in all patients with moderate-to-severe psoriasis candidate to biological therapies (Gardam et al., 2003; Gisondi et al., 2015; Kaplan & Freedman, 1996; Keane & Bresnihan, 2008; Mutlu, Mutlu, Bellmeyer, & Rubinstein, 2006).

Before initiating biological treatment, a prophylactic therapy should be administered to all patients with evidence of LTBI (National Psoriasis Foundation, 2008; Smith et al., 2009). In literature there are data on incidence of tuberculosis infection in psoriatic patients, but

there are limited reports on efficacy of prophylaxis of LTBI in psoriatic patients treated for long-time with biological drugs (Gisondi et al., 2015; Gisondi, Pezzolo, Lo Cascio, & Girolomoni, 2014; Laffitte et al., 2009). The aim of our retrospective study is to evaluate in real life the safety and the efficacy of prophylaxis of LTBI in psoriatic patients who continued for long-term the treatment with biologics and the role of tests in identifying LTBI.

2 | MATERIALS AND METHODS

The study included a retrospective analysis of 56 adult patients (42 males and 14 female) with moderate-to-severe psoriasis according to the psoriasis area severity index (PASI), (mean PASI: 12.8 ± 6.9 *SD*), aged 61.9 ± 9.7 *SD* years, referring to three Italians Dermatologic Department (University of Modena and Reggio Emilia, University of Verona and University of Padua) from December 2004 to December 2012, treated with anti-TNF-α (infliximab, adalimumab, etanercept), anti-CD11 (efalizumab), and anti-IL 12, 23 (ustekinumab) drugs with diagnosis of LTBI based on tuberculin skin test (TST) and/or QuantiFERON TB Gold test positivity (QFT) and chest-X-ray negative for suspected MT infection (Puzenat et al., 2010). Demographic and clinical characteristics of the study population are reported in Table 1.

All patients were already enrolled in the Psocare project (www.psocare.it). None of patients had been previously vaccinated with bacillus Calmette–Guérin or had had previous active tuberculosis infection. None of the patients had taken immunosuppressive drugs such as cyclosporine, methotrexate, corticosteroids, or biologics at least 3 weeks prior screening. QFT was performed in In-Tube format (Cellestis, Inc./Qiagen, Carnagie, Australia). TST was administered intradermal with injection of five units of purified protein derivative on volar forearm. TST was defined positive with the appearance of an area of induration ≥ 5 mm after 72 hr (Rothel & Andersen, 2005). Thirty-one patients have been tested both with QFT and TST; 25 patients have been tested only with TST or QFT; 14 patients have been tested only with QFT because it was impossible to perform TST, since volar forearm was involved by psoriatic lesions. Eleven patients have been tested only with TST due to lack of QFT. All positive patients received prophylactic therapy for LTBI for 9 months with isoniazid (INH) 300 mg/day, starting 3 weeks before the beginning of biological treatment. Side effects and toxicity/intolerance to INH were evaluated by measuring the serum alanine aminotransferase (ALT) and aspartate aminotransaminase (AST) levels monthly for the first 3 months, successively every 2 or 3 months.

Statistical analysis: all data are presented as mean ± *SD*, and nominal variables as numbers with percentages.

3 | RESULTS

Results are reported in Tables 1 and 2. Nineteen patients had both TST and QFT positive, six patients were positive to TST and negative to QFT, six patients were positive to QFT and negative to TST. Fifty-four patients completed prophylaxis with INH without adverse events or intolerance; one patient interrupted the prophylaxis after 40 days due to a significant increase of ALT and AST, indicating a liver toxicity. The patient had therefore taken rifampicin (10 mg/kg/die) for 4 months.

One erythrodermic patient with both chest X-ray and QFT negative developed tuberculosis pleurisy in course of treatment with etanercept. He was receiving etanercept from 6 months. The infection has been treated effectively with rifampicin, ethambutol, and INH therapy for 26

TABLE 1 Demographic and clinical characteristics of the study population and results of screening for LTBI

Number of patients	56
Sex M/F	42/14
Age (years)	61.9 ± 9.7
Number of patients who completed prophylaxis with INH	54
PASI (baseline)	12.8 ± 6.9
PASI (last observation in treatment)	2.3 ± 2.4
Number of patients treated with one biologic drug (male/female)	39 (29/10)
Number of patients treated with two or more biologic drug (male/female)	17 (13/4)
Number of patients screened with TST and QFT	31
Number of patients with TST + and QFT +	19
Number of patients with TST − and QFT +	6
Number of patients with TST + and QFT −	6
Number of patients screened only with TST or QFT	25
Number of patients screened only with TST	11
Number of patients screened only with QFT	14

Note. Data are presented as mean ± standard deviation (*SD*). PASI = psoriasis area severity index; TST = tuberculin skin test; QFT = QuantiFERON TB gold test.

TABLE 2 Duration of treatment with biologics (months) after prophylaxis with INH

Treatment	No of cases (M/F)	Age (years)	Duration of treatment (months)
All biologics	56 (42/14)	61.9 ± 9.7	42.8 ± 23.9
ETA	19 (14/5)	55.9 ± 8.0	33.5 ± 21.6
ADA	3 (2/1)	57.3 ± 4.2	49.5 ± 8.5
IFX	15 (12/3)	64.1 ± 8.1	36.4 ± 22.5
UST	1 (0/1)	60.0	2.0
EFA	1 (1/0)	66.0	13.0
Switch from ETA to IFX	3 (2/1)	66.7 ± 11.9	64.7 ± 12.2
Switch from IFX to ADA	2 (2/0)	44.0 ± 3.0	58.0 ± 18.0
Switch from ETA to ADA to UST	2 (1/1)	58.0 ± 11.0	73.0 ± 11.0
Switch from ETA to ADA	6 (5/1)	63.3 ± 10.9	54.2 ± 18.9
Switch from EFA to ETA	2 (1/1)	61.5 ± 10.5	39.0 ± 33.0
Switch from EFA to ADA	1 (1/0)	60.0	48.0
Switch from IFX to ETA to ADA	1 (1/0)	65.0	52.0

Note. Data are presented as mean ± standard deviation (*SD*). ETA = etanercept; ADA = adalimumab; IFX = infliximab; UST = ustekinumab; EFA = efalizumab.

weeks (6 months). Etanercept treatment was restarted at the end of the therapy at dose regimens without any reactivation of symptoms of tuberculosis and with clinical benefits on psoriasis during 24 months of follow-up. In this particular case, it was impossible to perform TST because psoriatic lesions involved completely the volar forearm skin. After having completed the prophylaxis, all patients continued the biological treatment without appearance of clinical symptoms of reactivation of tuberculosis. Thirty-nine patients were treated with only one drug: 15 cases with infliximab, 19 with etanercept, 3 with adalimumab, 1 with ustekinumab, and 1 with efalizumab; others 17 patients discontinued the first biological therapy and received successively one or two biological drugs, in relation to clinical conditions and in relation to the clinical response obtained with each drug. Biological therapy was administered for a minimum of 2 months and a maximum of 84 months after the end of prophylaxis with INH. Overall, biological therapies showed highly effective, with a PASI reduction from 12.8 (± 6.9 *SD*) to 2.3 (± 2.4 *SD*).

The overall meantime exposure to biologic treatment was 42.8 months (± 23.9 *SD*) and a maximum period was 7 years in a patient treated with infliximab. In the group of patients who underwent therapeutic switch from one biologic drug to another, this period was longer and it reaches 64.9 months (± 20.25 *SD*)

We observed discordance between two screening methods in 12 cases. In six cases TST was positive and QFT negative; in six cases TST was negative and QFT positive.

4 | DISCUSSION

Screening for tuberculosis is recommended in patient candidate to biological therapies to detect cases of LTBI (Amerio et al., 2013; National Psoriasis Foundation, 2008). However, there is not a gold-standard test for detecting LTBI and the screening is based on TST and/or interferon-γ release assays (IGRA) results, depending on the different guidelines considered (National Institute for Health and Care Excellence, 2011; National Psoriasis Foundation, 2008; Pathirana et al., 2010; Rangaka et al., 2012). The sensitivity of QFT in psoriatic patients is generally considered higher than that of TST. We observed discordance between TST and QFT results with higher positivity for TST than QFT. This can represent a problem of interpretation in respect to the necessity to perform a prophylaxis. Moreover, in psoriatic patients TST can be difficult to evaluate; some authors assert that TST positivity seems to be overestimated probably due to Koebner phenomenon (Tsiuori et al., 2009). Therefore QFT may be more helpful in severe psoriatic patients with skin lesions involving largely the volar forearm, which is the standard testing site (Keystone, Papp, & Wobeser, 2011; Tsiuori et al., 2009). Recently, some studies confirmed that IGRA such as QFT are more sensitive and specific than TST to diagnose LTBI because it does not cross-react with others nontuberculous mycobacteria; the patients with TST positive and QFT negative can be considered a false positive LTBI (Diel, Loddenkemper, Meywald-Walter, Gottschalk, & Nienhaus, 2009; Mariette et al., 2012; Saraceno et al., 2014; Tsiuori et al., 2009). In our experience, many patients started biological therapies before the introduction of principal guidelines; for this reason, 11 patients were screened only with TST due to lack of QFT and we treated with INH patients with TST positive and QFT negative.

Despite guidelines and recommendations, new cases of active tuberculosis were observed in patents treated with biologics (Dobler, 2016; Liao, Zhong, Liu, & Zou, 2017); this seems particularly related to a low compliance to prophylaxis treatment (Volmink & Garner, 2007). Epidemiological studies showed that if prophylaxis is completed for 9 months can prevent the developing of an active disease in 90% of

patients, if it is protracted only for 6 months can prevent the developing of an active disease in 60–80% (Vernon, 2013). Literature data reported a probability of reactivation of tuberculosis seven times higher when the patient did not take the medicine according to the prescribed dose (Gomez-Reino, Carmona, & Descalzo, 2007). In addition, biological therapies, necessarily prolonged in time, represent a risk factor for immunosuppression in patients, especially with regard to tuberculosis. In rheumatic patients with LTBI treated with biologics, the INH prophylaxis showed intolerance or toxicity ranging between 8.9 and 17.2% and high levels of efficacy (Catano & Morales, 2015; Hanta, Ozbek, Kukeci, Sert, & Kocabas, 2007; Nobre et al., 2012).

In a retrospective analysis of 52 patients affected by immunological diseases and with LTBI treated with different biologics, no cases of active tuberculosis has been observed during a 4 years follow-up period (Ramos et al., 2015). In our series the prophylaxis of LTBI with INH for 9 months showed a great effectiveness and safety in longer follow-up period, even in patients who switched from treatment with a biologic agent to another. Despite the long-term therapy with biological drugs for many months or years after the interruption of the prophylaxis with INH, we did not observe any reactivation of tuberculosis during the follow-up period. One patient developed active tuberculosis. Our study had several limitations: it has a retrospective in design with a relatively low number of patients including a heterogeneous population. The cases were enrolled progressively over time and following different methods of screening of LTBI depending on the types of tests available gradually. However, our study examines accurately the approach in daily clinical practice in screening, treatment, and management of LTBI in patients with psoriasis treated with biologics. Certainly, more information is needed and be obtained through prospective trial or by analysis of data collected in the registers of psoriatic disease.

CONFLICT OF INTEREST

The authors have no conflicts of interest relevant to this article to disclose.

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