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LETTER

Effect of biological therapies on TB treatment outcomes

Dear Editor,

Use of biological therapies (e.g., immune system modulators) is expanding due to their efficacy profiles and our improved understanding of immune regulation.[1] However, their use is associated with a higher risk of active TB due to increased susceptibility to infection, or to reactivation of latent infection.[2,3] The probability of developing TB is estimated to be 2–6 times higher when receiving biological therapies, especially anti-tumour necrosis factor-alpha (anti-TNF-α).[4–6]

We conducted a retrospective cohort study at Fundación Valle del Lili, Cali, Colombia, to analyse the outcomes of patients treated for TB following treatment with biological therapies. Patients aged ≥18 years with a first-time diagnosis of active TB from the Institutional Mycobacterial Registry between 2011 and 2018 were included. Patients diagnosed with a non-tuberculous mycobacterial infection or those lost to TB treatment follow-up were excluded. The main exposure was defined as treatment with biological therapies before TB diagnosis, and the main outcome was TB treatment outcome.[7] Patients were classified into a successful treatment group (cured or with treatment completed) and a deceased group. The Institutional Review Board of the Fundación Valle del Lili, Cali, Colombia, approved this study and patient informed consent was not required.

A descriptive analysis was performed. On bivariate analysis, we used cumulative incidences per outcome and risk ratios. Qualitative variables were compared using the χ^2 or Fisher's Exact test, and quantitative variables using the Mann-Whitney *U*-test. Variables with a $P < 0.100$ on bivariate analysis were included in multiple logistic regression. The fit of the model was evaluated using the Hosmer-Lemeshow test. We used the Kaplan–Meier method for survival analysis and assessed differences in survival using the log-rank test. We then built a multivariable Cox proportional hazard model.

A total of 104 patients were selected: 25 received treatment with biological therapies (according to the registry) and 79 untreated were selected using random sampling (strata per year of diagnosis). The Table shows the characteristics and treatment outcomes of the patients. Previous screening for TB infection was recorded in 14.4% of the patients. The proportion of those treated with biological therapies with a history of a positive tuberculin skin test was higher than those not treated (12%, $P = 0.015$); however, none received chemoprophylaxis. Pulmonary TB was the most frequent TB type in both groups (64.4%). Eleven patients had extrapulmonary TB: military ($n = 3$), gastrointestinal ($n = 2$), lymph node ($n = 2$), meningeal ($n = 1$), pericardial ($n = 1$), osteoarticular ($n = 1$) and pleural ($n = 1$). Treatment success was 87.5%, and 12.5% died. Of the 13 deaths, 9 (70%) were due to TB, and of these, 44% were on biological therapies. No significant differences were detected in the treatment group as regards treatment outcomes. Although the proportion of successful TB treatment in patients treated with biological therapies was significantly lower, there was no association between treatment outcome and treatment with biological therapies ($P = 0.544$), as there were no accumulated incidences in the treatment groups. Treatment variables related to the treatment results were sex (risk ratio [RR] 0.85, 95% confidence interval [CI] 0.73–0.99; $P = 0.032$), health insurance regime (RR 0.70, 95% CI 0.49–1.01; $P = 0.001$) and microbiological confirmation of TB (RR 0.77, 95% CI 0.53–1.11; $P = 0.033$). After adjustments, it was observed that being treated with biological therapies did not affect the treatment outcomes (adjusted OR [aOR] 0.41, 95% CI 0.09–1.75; $P = 0.232$). However, regardless of the type of primary treatment and the other covariates of the model, patients in the subsidised health insurance regime had 83% lower chance of having treatment success (aOR 0.17, 95% CI 0.04–0.71; $P = 0.015$). Sex and microbiological confirmation did not alter the response to treatment in the final model. The goodness-of-fit tests showed a good fit ($P = 0.900$). Overall survival was 90.3% (95% CI 82.72–94.66) at 30 days, 88.3% (95% CI 80.35–93.20) at 6 months and 87.0% (95% CI 78.61–92.27) at 1 year. At 1 year of follow-up, all deaths had already occurred. There were no differences in survival between exposed and unexposed groups ($P = 0.465$). The Cox-regression model, which included sex, health insurance regime and microbiological confirmation, showed that individuals insured by the subsidised regime had higher risk-adjusted mortality (hazard ratio 5.97, 95% CI 1.78–20.04; $P = 0.004$) (Supplementary Data).

This study explored the relationship between treatment with biological therapies and TB treatment outcomes. It was found that 84% of those treated had successful treatment as an outcome, with no differences from the untreated group (i.e., the use of

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Table Sociodemographic and clinical characteristics and treatment outcomes of the included patients ($n = 104$)

	Use of biological therapies				
	Yes ($n = 25$)		No ($n = 79$)		
Characteristics	*n*	%	*n*	%	*P* value
Age, years, median [IQR]	58 [46–63]		56 [39–67]		0.849
Male sex	13	52	40	50.6	0.905
Race/ethnicity					0.544
Mestizo	21	84	70	88.6	
Other	4	16	9	11.4	
Origin					
Urban	25	100	74	93.7	—
Rural	—	—	5	6.3	—
Health insurance regime					0.195
Contributive	23	92	64	81	
Subsidised	2	8	15	19	
Comorbidities					
Rheumatological	18	72	3	3.8	<0.001
Haematological	7	28	5	6.3	0.003
Diabetes	4	16	16	20.3	0.638
HIV	1	4	5	6.3	0.663
History					
Smoker	4	16	20	25.3	0.335
Healthcare worker	3	12	9	11.4	0.930
Close contact	1	4	3	3.8	0.960
TST-positive	3	12	1	1.3	0.015
Signs and symptoms					
Fever	19	76	39	49.4	0.019
Weight loss	11	44	39	49.4	0.640
Cough	11	44	42	53.2	0.424
Microbiologically confirmed TB	22	88	69	87.3	0.931
Pulmonary localisation	14	56	53	67.1	0.516
Standard treatment regime	7	28	39	49.4	0.061
Use of steroids	13	52	7	8.9	<0.001
Treatment outcomes					
Cured	10	40	25	31.6	0.441
Completed	11	44	45	57	0.257
Death	4	16	9	11.4	0.544

TST = tuberculin skin test.

biological therapies did not affect TB treatment results). A South African study also found no differences due to biological drugs on outcomes such as mortality and recovery.[8] In a Brazilian study that included TB patients using anti-TNF drugs, mortality was not significant and 10-year survival was 95.7%, which may reflect successful treatments in these patients.[9] Although several studies have indicated that exposure to these drugs increases the incidence of TB,[4–6] their use does not seem to affect the outcomes. A statistically significant difference was not found in our population ($P = 0.544$). The sample size was perhaps insufficient to demonstrate the hypothesis, and our study may also have included a possible selection bias.

TB preventive treatment (TPT) should be mandatory in this population, and previous studies have demonstrated it to be effective and well-tolerated in reducing the risk of TB in rheumatic patients requiring biological therapy. Also, coexisting host-related risk factors, such as comorbidities, are crucial to identify those at higher risk of TB.[10] The ESCMID (European Society of Clinical Microbiology and Infectious Diseases) Study Group for Infections in Compromised Hosts consensus document on the safety of targeted and biological therapies recommends the implementation of prevention measures to reduce the risk of TB among individuals receiving anti-TNF-α therapy.[11] In our study, a subsidised health insurance regime was the only factor that significantly decreased the probability of successful treatment. This is relevant because these patients tend to belong to underprivileged social and economic sectors, with problems of access to health care services.[12] This is a modifiable social determinant. On the other hand, given that rheumatological and haematological diseases are often managed using various types of immune regulation, it is common to find patients being administered immunosuppressants concomitant to biological drugs. It has been shown that biological therapies with added immunosuppressants have a risk of TB reactivation that is 13–24 times higher than patients who only receive biological therapy.[13] Consequently, it has been recommended to screen for TB infection periodically to offer adequate prophylaxis to patients being treated.[8,14]

In conclusion, TB treatment outcomes in patients treated with biological therapies were not different from untreated patients. Beyond the biology of the infection, it is the health insurance regime (a proxy for the social and economic status of patients) that determined an unfavourable outcome. This is important as it is a modifiable factor, and this population should be targeted for TPT.

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