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Risk factors for tuberculosis in inflammatory bowel disease: anti-tumor necrosis factor and hospitalization

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ABSTRACT

Aims: To determine risk factors for active tuberculosis in patients with inflammatory bowel diseases.

Methods: Retrospective, case-control study at 4 referral hospitals in Spain. Cases developed tuberculosis after a diagnosis of inflammatory bowel disease. Controls were inflammatory bowel disease patients who did not develop tuberculosis. For each case, we randomly selected 3 controls matched for sex, age (within 5 years) and time of inflammatory bowel disease diagnosis (within 3 years). Inflammatory bowel disease characteristics, candidate risk factors for tuberculosis and information about the tuberculosis episode were recorded. Multivariate analysis and a Chi-squared automatic interaction detector were used.

Results: Thirty-four cases and 102 controls were included. Nine of the 34 cases developed active tuberculosis between 1989 and 1999, and 25 became ill between 2000 and 2012. Multivariate regression showed an association between active tuberculosis and anti-TNF (tumor necrosis factor) therapy in the previous 12 months (OR 7.45; 95% CI, 2.39-23.12; p = 0.001); hospitalization in the previous 6 months (OR 4.38; 95% CI, 1.18-16.20; p = 0.027); and albumin levels (OR 0.88; 95% CI, 0.81-0.95; p = 0.001). The median time between the start of biologic therapy and the onset of active tuberculosis was 13 (interquartile range, 1-58) months. Tuberculosis developed after a year of anti-TNF therapy in 53%, and late reactivation occurred in at least 3 of 8 patients.

Conclusions: The main risks factors for developing tuberculosis were anti-TNF therapy and hospitalization. Over half the cases related to anti-TNF treatment occurred after a year.

Key words: Tuberculosis. Inflammatory bowel disease. Risk factors. Anti-TNF. Hospitalization.

INTRODUCTION

Patients with inflammatory bowel disease (IBD) are at higher risk of newly acquired or reactivated opportunistic infections, especially if they require hospitalization, are malnourished, or take immunosuppressants and biologics (1). In particular, patients on drugs that block tumor necrosis factor (anti-TNF agents) are at substantially greater risk for active tuberculosis (TB), mainly through reactivation of a latent TB infection (LTBI) (2). Screening for and treatment of LTBI before starting anti-TNF therapy has been reported to decrease the incidence of active TB by 80% (3), yet active TB continues to develop in these patients, attributable to primary infections (4), non-adherence to screening protocols (5) and the limitations of tests (low sensitivity in immunosuppressed patients) (6).

Little is known about risk in IBD patients who are not receiving anti-TNF therapy, although relevant risk factors (smoking and the use of corticosteroids) have been suggested (7). Moreover, IBD itself apparently confers risk. A recent study showed that the incidence of active TB was higher in patients with untreated Crohn's disease than in the general population, though risk increases further when patients are on corticosteroids or anti-TNF monotherapy, or their combinations (corticosteroids, immunomodulators, and/or anti-TNF agents) (8). In any case, it is clear that active TB continues to develop in IBD patients despite warnings of the need for vigilance and preventive measures.

We hypothesized that in the absence of information on risk from prospective studies in IBD patients, further retrospective exploration of risk for active TB would help raise physicians' awareness of the problem and encourage the design of large, systematic studies. Our main purpose in this multicenter retrospective study at 4 referral hospitals was to determine the factors associated with risk for active TB in our patients with IBD. We also sought

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to describe the characteristics of TB in IBD patients on anti-TNF treatment.

METHODS

Design and setting

This retrospective case-control study was based on 60 years of case records at 4 public hospitals (Hospital Universitario Central de Asturias [HUCA], Hospital de Cabueñes, Hospital San Agustín, and Complejo Asistencial Universitario de León) in 2 Spanish northern regions (Asturias and León) that provide care to a total population of 1,152,169 (December 2012). The study was approved by the ethics committee of HUCA on behalf of all the participating hospitals. All study participants provided informed written consent prior to study enrollment.

Patients

Cases were patients who developed active TB after a diagnosis of IBD. We located the records for patients with IBD diagnosed at all the centers between 1952 and December 2012. To avoid missing patients who had died or were lost to follow-up, we also searched the records of the microbiology and pathology departments; checked discharge codes at all hospitals and located records mentioning Crohn's disease, ulcerative colitis, and TB; IBD departmental records were cross-checked against registries for notifiable diseases to find cases unknown to us.

Controls were patients with IBD who did not develop active TB. For each case, we randomly selected 3 controls from the same hospital records. Controls were matched with cases for sex, age (within 5 years) and time of IBD diagnosis (within 3 years).

Variables and data collection

Our data collection form included IBD characteristics and potential risk factors for active TB. For cases, we recorded information known at the time active TB developed. For controls, we recorded data at a matching time point after the IBD diagnosis. IBD variables were type (Crohn's disease, ulcerative colitis, unclassified colitis), phenotype (Montreal classification) (9), surgery, hospitalizations, and pharmacologic treatments (aminosalicylates, systemic corticosteroids, immunomodulators [thiopurines, methotrexate, ciclosporin], and anti-TNF agents [infliximab, adalimumab]). We checked for LTBI screening and whether adequate prophylaxis had been taken if indicated, according to the recommendations of the Spanish Working Group on Crohn's Disease and Ulcerative Colitis (GETECCU), which became available in 2003 (10). Information gathered on potential risk factors for active TB included history of smoking, nutrition (albumin serum level), history of relevant diseases or conditions (diabetes mellitus, chronic renal insufficiency, transplantation, cancer, immunodeficiency, silicosis, chronic obstructive pulmonary disease), risk professions (health care, work in closed institutions, mining), place of origin or residence in areas with a high incidence of active TB, close contact with a person with active TB, a chest radiograph suggestive of TB, or a positive tuberculin skin test (TST). Drugs taken for IBD and the need for surgery or hospitalization for any reason, in the 3, 6, and 12 months before the TB diagnosis, for cases and at corresponding time points for controls were listed. The data collection form also included information about the TB episode.

The regional reference laboratory for mycobacteriology at HUCA processed all biological samples. *Mycobacterium tuberculosis* complex isolates were identified with MPT64 antigen detection, and/or chemiluminescent DNA probes, or polymerase chain reaction (PCR) reverse hybridization line probe assays. Two molecular techniques were used for genotyping: spacer oligonucleotide typing (spoligotyping) (11) and restriction fragment length polymorphism (RFLP) of the IS6110 element (12). In Asturias, all genotypes identified since 2004 have been registered in a database. If the *M. tuberculosis* strain was known for a case, we investigated for evidence of strain clustering.

Statistical analysis

Symmetrically distributed variables were described by the mean ± SD and non-symmetrically distributed variables by the median and interquartile range. Student-Welch's *t* and Mann-Whitney tests were used to detect differences between means and medians, respectively. Categorical variables were described by absolute and relative frequencies. The Chi-squared test was used to check the independence of categorical variables. Odds ratios (ORs) were used to measure the effect sizes and 95% confidence intervals (CI) were calculated. The optimal multivariate model was estimated by a forward stepwise procedure, based on the likelihood ratio. In the multivariate model, an imputation procedure considering hemoglobin concentration, weight, and body mass index was used to compensate for missing information on albumin concentration. Finally, a decision tree based on the Chi-squared Automatic Interaction Detector (CHAID) algorithm was developed (13).

RESULTS

Among the 4,818 patients with IBD identified, 37 developed active TB. We excluded 2 cases for lack of information related to the TB episode and 1 case because the infection was caused by *Mycobacterium chelonae*. Table I shows clinical characteristics on diagnosis of TB for the remaining 34 cases and for 102 controls.

Active TB cases

Nine of the 34 cases developed active TB between 1989 and 1999, and 25 became ill between 2000 and 2012. Fifteen of these 25 were on anti-TNF therapy.

The most frequent symptoms at the time of diagnosis were fever (24/34, 71%), cough (17/34, 50%), malaise (10/34, 29%), chest pain (9/34, 26%), and dyspnea (9/34, 26%). Extrapulmonary presentation was more frequent in cases associated to anti-TNF therapy (11/15 [73%] *vs.* 6/19 [32%]; p: 0.03).

Table I. Patient characteristics

	Cases (active TB)	*Controls (matched patients without TB)*	*p value*
No. of patients	34	102	
Women, n (%)	17 (50)	51 (50)	---
Age at IBD diagnosis (y), mean ± SD	36.0 ± 16.0	35.8 ± 16.9	0.941
Type of disease, n (%)			0.422
CD	23 (68)	59 (58)	
UC	11 (32)	40 (39)	
Unclassified colitis	0 (0)	3 (3)	
Montreal classification for UC, n (%)			0.406
E1 (proctitis)	3(27)	5 (13)	
E2 (left-sided colitis)	2 (18)	13 (32)	
E3 (extensive)	6 (55)	22 (55)	
Montreal classification for CD, n (%)			
Age at diagnosis, years			0.754
≤ 16	1 (4)	2 (4)	
17-40	17 (74)	48 (81)	
> 40	5 (22)	9 (15)	
Disease location			0.461
Ileal	6 (26)	26 (44)	
Colonic	3 (13)	8 (14)	
Ileocolonic	11 (48)	20 (34)	
Upper gastrointestinal	3 (13)	5 (8)	
Disease behavior			0.014
Inflammatory	11 (49)	34 (58)	
Stricturing	2 (9)	16 (27)	
Penetrating	10 (43)	9 (15)	
Perianal disease	8 (35)	26 (44)	0.619
Smoking status, n (%)			0.018
Never	9 (26)	51 (50)	
Former or current	25 (74)	51 (50)	
Previous IBD hospitalizations, n (%)	22 (65)	59 (58)	0.614
Previous IBD surgery, n (%)	7 (21)	13 (13)	0.273
Previous IBD treatment, n (%)			
5-ASA	33 (97)	91 (89)	0.294
CS	23 (68)	68 (67)	> 0.999
IMM	18 (53)	29 (28)	0.012
Anti-TNF	16 (47)	11 (11)	0.001

5-ASA: 5-aminosalicylic acid; CD: Crohn's disease; CS: Corticosteroids; IBD: Inflammatory bowel disease; IMM: Immunomodulators; TB: Tuberculosis; TNF: Tumor necrosis factor; UC: Ulcerative colitis.

Twenty-five diagnoses (74%) were microbiologically confirmed. The main diagnostic methods to detect *M. tuberculosis* and their yield were as follows: culture, 80% (24/30); PCR, 56% (9/16), and smear examination, 52% (15/29).

Twenty-six cases (76%) were hospitalized for TB; 3 (9%) were admitted to the Intensive Care Unit. No TB-attributed deaths occurred. After the TB episode, 6 patients required anti-TNF therapy, which was started at a

median of 21 (5-204) months after the TB diagnosis. No reactivations occurred.

M. tuberculosis strain isolates were available for genotyping in 7 of the 25 microbiologically confirmed cases. In the remaining confirmed cases, isolates had not been frozen (12 from before 2004) or they had not been forwarded to the HUCA (6 cases). One strain was an orphan genotype. Six other strains were part of clusters of various sizes (in 3, 4, 6, 9, 12, and 121 patients according to spoligotyping, and in 3, 4, 6, 8, 11, and 46 patients according to IS6110-RFLP). In one patient we detected a nosocomial TB infection corresponding to a previously reported cluster (spoligotyping international type [SIT] 956) (14). Two patients were hospitalized at the same time as other individuals in their cluster.

Active TB associated with anti-TNF therapy

Of the 15 patients on anti-TNF agents who developed active TB (Table II), 12 cases presented after LTBI screening and management guidelines were published (10). The guidelines had not been followed in 7 of these 12 cases (58%). In 2 no LTBI screening was done. In 5, screening or management was incomplete: either a booster effect under immunosuppressant therapy was not tested for in 4 patients, or prophylactic antibiotics were not prescribed after a positive TST in one. Thus, the recommendations were followed strictly in only 5 cases (42%), 4 of whom were under immunosuppressant therapy when screened and had negative TST results. In our hospitals, adherence went from 0% before 2006 to 62.5% in the period between 2006 and 2012.

The median time between the start of biologic therapy and the onset of active TB was 13 (1-58) months. TB developed during the first year of anti-TNF therapy in only 7 (47%) of the 15 patients (Fig. 1). Active TB was a reactivation in at least 3 of the 8 patients whose disease developed after 1 year of biologic therapy. The patient infected with the SIT 956 strain developed active TB 30 months after contact with the cluster and 13 months after starting treatment with adalimumab. One patient with an abnormal chest radiograph who received no preventive treatment developed active TB 58 months after starting infliximab. A patient with a baseline positive TST, without preventive treatment, developed TB due to a non-circulating strain 33 months after starting infliximab treatment.

Risk factors for active TB

The results of univariate logistic regression of TB-associated factors are shown in table III. In the 6 months before an episode of TB, cases were hospitalized more often than controls (0.4 ± 0.7 *vs.* 0.1 ± 0.4 admissions, respectively; p = 0.015) and had longer hospital stays (4.8 ± 9.2 *vs.* 1.0 ± 4.9 days; $p = 0.028$). Multivariate regression confirmed an association between active TB and the following factors: using an anti-TNF agent in the previous 12 months (OR 7.45; 95% CI, 2.39-23.12; p = 0.001); hospitalization in the previous 6 months (OR 4.38; 95% CI, 1.18-16.20; p = 0.027); and albumin level (OR 0.88; 95% CI, 0.81-0.95; p = 0.001). The strongest factor of the 3, according to the CHAID-algorithm prediction model (Fig. 2), was anti-TNF treatment within the previous 12 months. Individuals in this category were at 3.7-fold higher relative risk (cases/controls, 0.625/0.170). The next most important factor was hospitalization in the last 6 months, which meant 2.2-fold higher relative risk (cases/controls 1.000/0.471). Among individuals who had not received anti-TNF treatment, a low albumin level conferred significant risk. Individuals with albumin levels of less than 3.5 g/dL had 4-fold greater relative risk (cases/controls, 0.417/0.103) for TB than individuals with albumin levels over that cut-off. The prediction model allows defining four groups of patients with different risk of active TB; those who have received anti-TNF treatment in the previous 12 months and needed hospitalization in the previous 6 months belong to the group of higher risk, against those who have not received anti-TNF nor hospitalization, and have albumin levels of more than 3.5 g/dL that would have the least risk of active TB.

Among IBD patients who developed active TB between 2000 and 2012, and had not been treated anti-TNF (n: 10), 50% had been hospitalized in the previous 6 months, 70% had received treatment with corticosteroids or immunosuppressive agents (30% ≥ 2 drugs), 80% were or had been smokers and 60% had other risk factors associated with the development of TB (diabetes mellitus, chronic renal failure, liver transplantation, health worker, chronic obstructive pulmonary disease, previously treated LTBI).

DISCUSSION

This study shows that two main factors put patients with IBD at risk for active TB in our setting: anti-TNF therapy and recent hospitalization. The incidence of active TB in our area is low (11 cases per 100,000 people in 2014) (15); however, the prevalence of LTBI in patients with IBD in our area is high, at 33.5% (16), in comparison with other Spanish regions (range, 4.5% to 12.5%) (4,6,17).

Current corticosteroid use has been associated with higher risk for TB in the general population (18). Patients with IBD on corticosteroids have been reported to be at still higher risk (7,8). However, their risk is no greater than that of untreated IBD patients (8), consistent with our multivariate analysis finding that our patients who had taken corticosteroids in the last 12 months were not at higher risk. However, due to the retrospective design of the study, it was not possible to accurately collect the cumulative dose of corticosteroids, which is a limitation in assessing the possible role of these drugs as a risk factor for active TB. Current evidence sug-

Table II. Characteristics of patients with active TB and IBD on anti-TNF treatment

Case No.	*IBD type*	*Gender*	*Age at IBD diagnosis (y)*	*Age at TB diagnosis (y)*	*Year of TB diagnosis*	*Risk factors for TB*	*LTBI screening*	*Anti-TNF agent*	*Time from start of anti-TNF to TB diagnosis (mo)*	*TB presentation*
1	CD	F	26	53	2000	Hosp, contact, CS	No	IFX	3	Inguinal lymphadenopathy
2	CD	M	21	29	2000	Hosp, CS, IMM	No	IFX	9	Pulmonary and pleural
3	CD	F	13	22	2002	IMM	No	IFX	33	Pulmonary
4	CD	M	19	27	2003	Hosp, CS, IMM	Yes (TST on CS, no booster)	IFX	1	pleural
5	CD	F	44	50	2004	Hosp, contact, CS, IMM	Yes (TST on CS+ IMM, no booster)	IFX	9	Pulmonary, pleural, and mesenteric lymphadenopathy
6	CD	F	42	47	2005	IMM	No (abnormal chest X-ray, no ChP)	IFX	58	Osteoarticular (Pott disease)
7	CD	M	32	52	2005	Hosp, CS, IMM	Yes (TST+, no ChP)	IFX	33	Pulmonary, central nervous system, disseminated
8	UC	F	59	60	2007	CS, IMM	Yes (TST on CS+IMM, no booster)	IFX	14	Pulmonary
9	CD	F	19	30	2009	IMM	Yes (TST on IMM)	ADA	6	Pleural
10	UC	M	67	78	2010	Hosp, CS, IMM	Yes (TST on CS+ IMM, QFT-GIT)	IFX	2	Pulmonary and disseminated
11	UC	M	33	41	2010	CS, IMM	Yes (TST on CS, QFT-GIT)	ADA	1	Intrathoracic lymphadenopathy
12	CD	F	23	28	2011	Nosocomial transmission demonstrated	Yes (TST on CS)	ADA	13	Pulmonary and pericardial
13	CD	M	67	69	2011	IMM	Yes (TST on IMM, no booster)	IFX	15.7	Pulmonary
14	CD	M	27	45	2012	Hosp, IMM	No	IFX	41	Pleural
15	CD	F	28	34	2012	Hosp	Yes	ADA	32.3	Pulmonary

ADA: Adalimumab; CD: Crohn's disease; ChP: Chemoprophylaxis; CS: Corticosteroids; F: Female; Hosp: Hospitalization; IBD: Inflammatory bowel disease; IFX: Infliximab; IMM: Immunomodulators; IQR: Interquartile range (25^{th}-75^{th} percentile); LTBI: Latent TB infection; M: Male; QFT-GIT: QuantiFERON TB Gold-in-Tube; TB: Tuberculosis; TNF: Tumor necrosis factor; TST: Tuberculin skin test; UC: Ulcerative colitis.

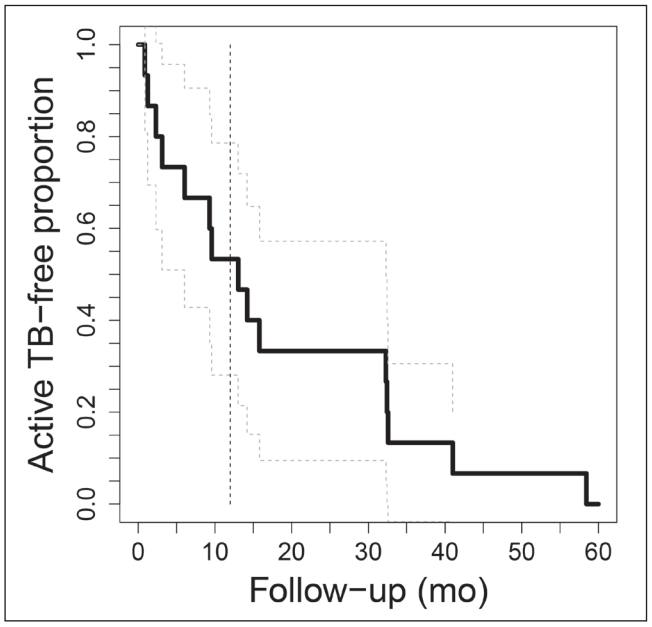

Fig. 1. Time until appearance of active tuberculosis (TB) in patients receiving anti-TNF treatment for inflammatory bowel disease.

gests that patients with IBD on immunomodulators are at greater risk of TB only if they are also taking corticosteroids and/or anti-TNF agents (8). Likewise, patients already on an anti-TNF agent who begin taking an immunomodulator increase their risk further (19,20).

Both the multivariate analysis and the CHAID algorithm showed that receiving treatment with an anti-TNF agent in the previous 12 months was the main risk factor for active TB. A meta-analysis of 22 trials failed to find significantly higher risk in patients on an anti-TNF agent in comparison with placebo (OR 2.52; 95% CI 0.62-10.21) (21), but the incidence of TB in randomized trials of these drugs in patients with IBD is very low, and the risk for active TB differs geographically in studies in clinical practice settings. In a Spanish series, risk continues to be high at 1.2% (4) or 1.7% (6), in contrast with 0% in a US series and 0.16% in a Belgian series (22,23). Likewise, regional differences in TB risk associated with anti-TNF therapy also emerged in a recent systematic review (20). Most of the cases occurred in countries where the incidence of active TB was high in the general population.

Non-adherence to LTBI screening recommendations prior to starting biologic treatment is one reason for high rates of active TB (5). In our series, the recommendations were rigorously followed in only 42% of the TB patients, and in another 42% adherence was only partial, the main error being failure to test for a booster effect in immunosuppressed patients. This failure is also the main component of non-adherence in patients with rheumatic diseases in Spain (5). Gastroenterologists' level of adherence to screening guidelines in IBD patients, at 65%, also clearly leaves room for improvement, although recent years have brought some progress as adherence has risen annually by 6.4% (24). It is important to emphasize the necessity to comply local LTBI screening recommendations before starting a biologic therapy, which will decrease the number of active TB.

Given the absence of response to TST in patients with IBD on immunosuppressants, false negatives occur (25). Eight of our 9 patients with negative TST results before developing TB were on immunosuppressants at the time of screening. The role of interferon gamma release assays (IGRAs) in this setting is still unclear. We recently showed that complementary use of TSPOT and QTF-GIT does not detect more LTBI cases than those already found by the TST in patients with IBD on 5-aminosalicylic acid or immunomodulator monotherapy. However, in patients on corticosteroid treatment, anti-TNF treatment or ≥ 2 immunosuppressants, the use of either the TSPOT or the QFT-GIT was useful, increasing diagnostic yield by 56% and 22%, respectively (16). Therefore, in IBD patients on immunosuppressants, additional IGRA screening might reduce the number of patients developing active TB during anti-TNF treatment. Recently, GETECCU recommends, before starting a biological therapy, a strategy of double screening (TST and IGRA) in patients with IBD who are immunosuppressed (26).

In patients with a history of LTBI, isoniazid therapy does not confer complete protection against active TB in anti-TNF-treated patients (6,20). Risk is very low, however, as shown by data from a Spanish registry of 1,154 rheumatic patients with LTBI who had taken anti-TB prophylaxis: only one of them developed TB while on anti-TNF therapy, whereas 2 of the 94 patients who received no prophylaxis did develop active disease (3).

LTBI reactivation is responsible for most active TB developing in patients on anti-TNF therapy, and most reactivations occur in the first 3 months of treatment (2). However, we saw that 53% of our cases developed after 12 months of anti-TNF therapy and that the median interval was 13 months. Such late appearance of active TB has been linked mainly to *de novo* infections (4), but at least 3 of our cases of late onset were in fact reactivations rather than *de novo* infections. This observation of a large number of late-appearing active TB cases supports recommendations to rescreen patients after starting biologic treatments, at least in our area. At present, the lack of official guidelines on whether or not to screen for TB during anti-TNF therapy may explain why only 33% of prescribers in the European Union undertake this screening (27). Given the local variability in TB incidence, future guidelines should probably be carefully adapted to the regions where they will be applied.

Health care systems are well aware of nosocomial transmission of *M. tuberculosis* (28). In developed countries, measures to prevent hospital infections have reduced the number of cases, yet TB outbreaks continue among both patients and staff (29). In our setting, where hospitalization in the last 6 months was the second most important risk factor for active TB after IBD patients started anti-TNF

Table III. Active TB risk factors

	Cases n = 34	*Controls n = 102*	*Univariate analysis OR (95% CI)*	*p value*
High-risk jobs[a], n (%)	4 (12)	10 (10)	1.22 (0.36-4.20)	0.749
High-risk diseases[b], n (%)	4 (12)	6 (6)	2.13 (0.56-8.06)	0.267
Close contact with TB, n (%)	7 (21)	5 (5)	5.03 (1.48-17.11)	0.011
Previous abnormal chest X-ray[c], n (%)	3 (12)	1 (2)	7.17 (0.71-72.63)	0.056
Previous positive TST[d], n (%)	2 (14)	1 (5)	0.33 (0.03-4.10)	0.561
Hemoglobin[e] (g/dL), mean ± SD	12.6 ± 1.7	13.7 ± 1.5	0.62 (0.46-0.85)	0.003
Serum albumin[f] (g/dL), mean ± SD	3.6 ± 0.7	4.2 ± 0.6	0.86 (0.80-0.93)	< 0.001
Hospitalization, all cause, n (%)				
12 months previous	11 (32)	19 (19)	2.09 (0.87-5.01)	0.101
6 months previous	10 (29)	7 (7)	5.66 (1.95-16.40)	0.002
3 months previous	9 (27)	4 (4)	8.82 (2.51-31.00)	0.001
IBD treatments, 12-months exposure, n (%)				
CS	14 (41)	17 (17)	3.50 (1.48-8.26)	0.004
IMM	19 (56)	23 (23)	4.35 (1.91-9.89)	< 0.001
Anti-TNF	15 (44)	9 (9)	8.16 (3.12-21.36)	< 0.001
≥ 2 drugs	16 (47)	13 (13)	6.08 (2.50-14.82)	< 0.001
IBD treatments, 6-months exposure, n (%)				
CS	12 (35)	14 (14)	3.43 (1.39-8.45)	0.007
IMM	18 (53)	22 (22)	4.09 (1.80-9.31)	0.001
Anti-TNF	14 (41)	9 (9)	7.23 (2.75-19.02)	< 0.001
≥ 2 drugs	14 (41)	12 (12)	5.25 (2.11-13.05)	< 0.001
IBD treatments, 3-months exposure, n (%)				
CS	10 (29)	11 (11)	3.45 (1.31-9.07)	0.012
IMM	17 (50)	22 (22)	3.64 (1.60-8.27)	0.002
Anti-TNF	13 (38)	9 (9)	6.40 (2.42-16.92)	< 0.001
≥ 2 drugs	12 (35)	9 (9)	5.64 (2.11-15.04)	< 0.001

CS: Corticosteroids; IBD: Inflammatory bowel disease; IMM: Immunomodulators; OR: Odds ratio; TB: Tuberculosis; TNF: Tumor necrosis factor; TST: Tuberculin skin test. [a]High-risk jobs were those in prisons and other closed facilities, health-care settings, and mines. [b]High-risk diseases and conditions were diabetes, chronic obstructive pulmonary disease, silicosis, cancer, transplants, renal failure. [c]A previous chest X-ray was available for 26 cases and 56 controls. [d]A previous TST result was available for 14 cases and 19 controls. [e]Hemoglobin concentration available for 29 cases and 86 controls; normal values, 13-18 g/dL in males and 12-16 g/dL in females. [f]Albumin concentration available for 25 cases and 77 controls; normal serum values, 3.5-5.2 g/dL.

therapy, both the number and duration of hospitalizations were greater among cases than controls. We feel, therefore, that IBD patients on anti-TNF therapy should be monitored after discharge. We also emphasize that molecular epidemiology, specifically *M. tuberculosis* genotyping, can identify sources of infection. Unique strains are generally associated with the reactivation of old infections, whereas the emergence of a cluster of recent infections indicates that a strain is circulating. We demonstrated a clear nosocomial source for one of our cases (14), and we suspected hospital infection in 2 other patients. Immunosuppression is common in patients with IBD, making them more susceptible to contagion while hospitalized near patients with undiagnosed active disease. Patients may also incur risk when they come to the hospital for diagnostic tests (endoscopy, radiology), for day-hospital treatments, for scheduled visits, or for emergency care. In our setting, the risk for immunosuppressed individuals has probably been underestimated.

A limitation of our study was its retrospective design, which prevented us from gathering all the information for all patients. The small number of active TB cases may also have decreased the likelihood of finding statistically significant risk factors for subgroups. In addition, *M. tuberculosis* strains were only typed for a small number of the patients who developed active TB. Future studies should include systematic genotyping of all cases of TB in IBD patients, so that we can understand their risk. Finally, the risk factors we identified cannot be extrapolated to oth-

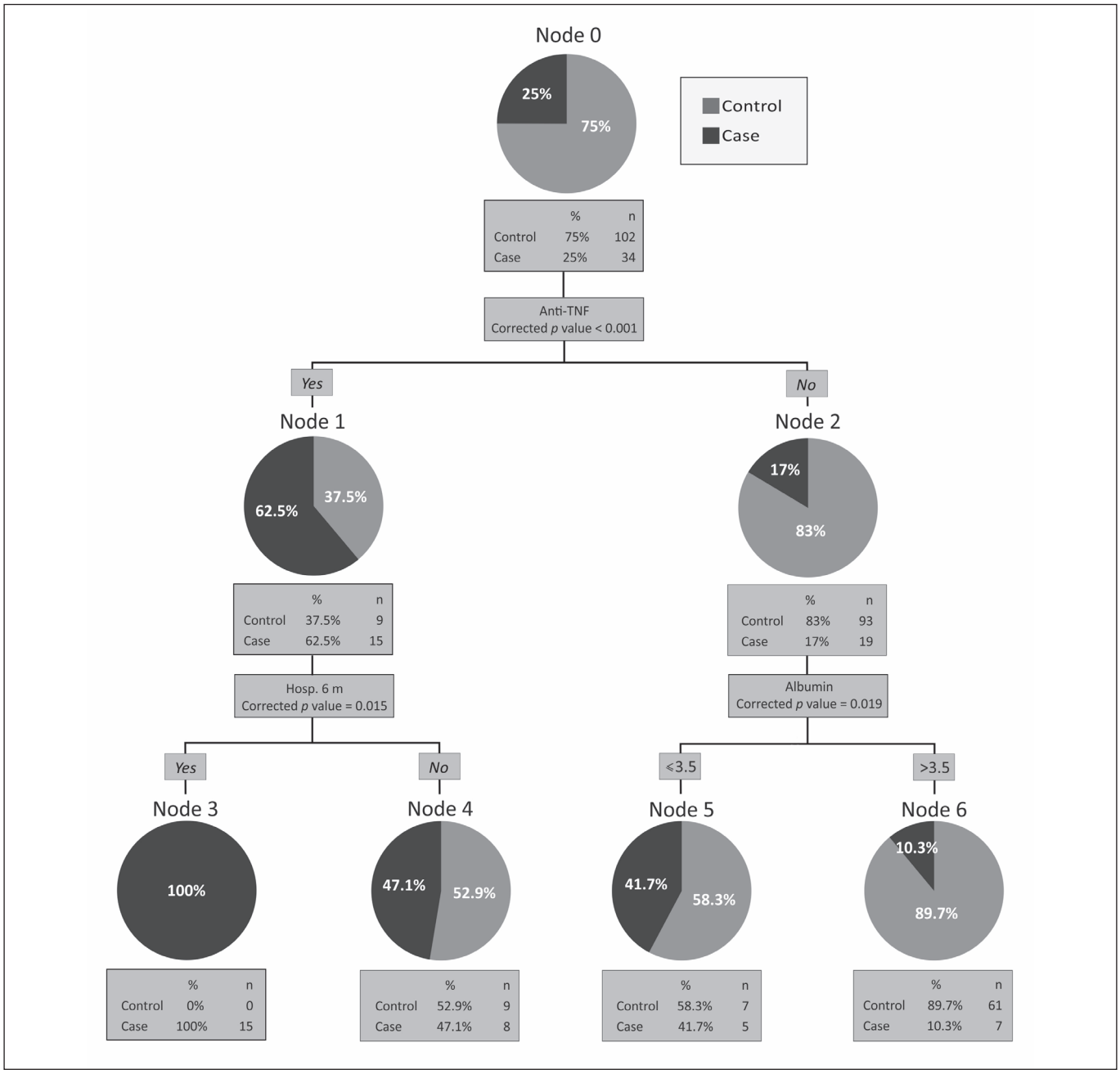

Fig. 2. Prediction tree model of risk for active tuberculosis in patients with inflammatory bowel disease (Chi-squared Automatic Interaction Detector Algorithm). The risk factors included had been identified by multivariate analysis.

er geographic areas with different incidence rates of TB infection. Local studies should be done.

In conclusion, the results presented herein indicate that in patients with IBD in our area the main risk of developing active TB is the use of anti-TNF therapy in the previous 12 months. Hospitalization confers risk for 6 months. We draw attention to the fact that over half the cases of anti-TNF-associated active TB in our series occurred after a year of treatment and that late reactivations were common. Future studies should assess whether LTBI screening while patients are on biologic treatments could lower the number of new cases.

CONFLICT OF INTEREST

Riestra S has worked as a consultant for the following companies: MSD and AbbVie. He has also provided expert testimony for Shire, Tillots, Hospira, and Ferring and has received support for attending meetings from AbbVie,

Ferring, Tillots, and MSD. De Francisco R has provided expert testimony for Shire, Ferring, and Tillots. She has received funding to attend meetings from Abbott, Ferring, and MSD. Palacios JJ has received funding to attend meetings from Werfen Group and ALERE Healthcare. Saro C has worked as a consultant for MSD, AbbVie. She has also provided expert testimony for Shire and Ferring and has received support for attending meetings from AbbVie and MSD. García-Alvarado M and Duque JM have received support for attending meetings from AbbVie and MSD. Muñoz F has worked as a consultant for MSD and AbbVie. He has also received support for attending meetings from AbbVie, Ferring, and MSD. Pérez-Martínez I has provided expert testimony for AbbVie and has received support for attending meetings from AbbVie, Ferring, and MSD. The other authors have no conflicts of interest to disclose.

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REFERENCES

1. Rahier JF, Magro F, Abreu C, et al. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. J Crohns Colitis 2014;8:443-68. DOI: 10.1016/j.crohns.2013.12.013
2. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor α-neutralizing agent. N Engl J Med 2001;345:1098-104. DOI: 10.1056/NEJMoa011110
3. Carmona L, Gómez-Reino JJ, Rodríguez-Valverde V, et al. Effectiveness of recommendations to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists. Arthritis Rheum 2005;52:1766-72. DOI: 10.1002/art.21043
4. Mañosa M, Domènech E, Cabré E. Current incidence of active tuberculosis in IBD patients treated with anti-TNF agents: Still room for improvement. J Crohns Colitis 2013;7:499-500. DOI: 10.1016/j.crohns.2013.04.021
5. Gómez-Reino JJ, Carmona L, Ángel Descalzo M, et al. Risk of tuberculosis in patients treated with tumor necrosis factor antagonists due to incomplete prevention of reactivation of latent infection. Arthritis Rheum 2007;57:756-61. DOI: 10.1002/art.22768
6. Jáuregui-Amezaga A, Turon F, Ordás I, et al. Risk of developing tuberculosis under antiTNF treatment despite latent infection screening. J Crohns Colitis 2013;7:208-12. DOI: 10.1016/j.crohns.2012.05.012
7. Aberra FN, Stettler N, Brensinger C, et al. Risk for active tuberculosis in inflammatory bowel disease patients. Clin Gastroenterol Hepatol 2007;5:1070-5. DOI: 10.1016/j.cgh.2007.04.007
8. Marehbian J, Arrighi HM, Hass S, et al. Adverse events associated with common therapy regimens for moderate-to-severe Crohn's disease. Am J Gastroenterol 2009;104:2524-33. DOI: 10.1038/ajg.2009.322
9. Satsangi J, Silverberg MS, Vermeire S, et al. The Montreal classification of inflammatory bowel disease: Controversies, consensus, and implications. Gut 2006;55:749-53. DOI:10.1136/ gut.2005.082909
10. Obrador A, López San Román A, Muñoz P, et al. Guía de consenso sobre tuberculosis y tratamiento de la enfermedad inflamatoria intestinal con infliximab. Grupo Español de Trabajo de Enfermedad de Crohn y Colitis Ulcerosa (GETECCU). Gastroenterol Hepatol 2003;26:29-33. DOI: 10.1016/S0210-5705(03)70338-0
11. Kamerbeek J, Schouls L, Kolk A, et al. Simultaneous detection and strain differentiation of Mycobacterium tuberculosis for diagnosis and epidemiology. J Clin Microbiol 1997;35:907-14.
12. Van Embden JD, Cave MD, Crawford JT, et al. Strain identification of Mycobacterium tuberculosis by DNA fingerprinting: Recommendations for a standardized methodology. J Clin Microbiol 1993;31:406-9.
13. Kass G. An exploratory technique for investigating large quantities of categorical data. Applied Statistics 1980;29:119-27. DOI:10.2307/2986296
14. Casas-Fischer R, Penedo-Pallarés A, Palacios-Gutiérrez JJ, et al. Outbreak or coincidental cases of tuberculosis? Genotyping provides the clue. Am J Infect Control 2012;40:9-10. DOI: 10.1016/j.ajic.2011.03.003
15. Centro Nacional de Epidemiología. Instituto de Salud Carlos III. Informe epidemiológico sobre la situación de la tuberculosis en España. 2014. Madrid, 2015. Available from: URL: http://www.isciii.es/ISCIII/ es/ contenidos/fd-servicios-cientifico-tecnicos/fd-vigilancias-alertas/fd-enfermedades/pdf_2015/TB_Informe_2014.pdf
16. Arias-Guillén M, Riestra S, De Francisco R, et al. T-cell profiling and the immunodiagnosis of latent tuberculosis infection in patients with inflammatory bowel disease. Inflamm Bowel Dis 2014;20:329-38. DOI: 10.1097/01.MIB.0000438429. 38423.62
17. Zabana Y, Domènech E, San Román AL, et al. Tuberculous chemoprophylaxis requirements and safety in inflammatory bowel disease patients prior to anti-TNF therapy. Inflamm Bowel Dis 2008;14:1387-91. DOI:10.1002/ibd.20496
18. Jick SS, Lieberman ES, Rahman MU, et al. Glucocorticoid use, other associated factors, and the risk of tuberculosis. Arthritis Rheum 2006;55:19-26. DOI: 10.1002/art.21705
19. Deepak P, Stobaugh DJ, Ehrenpreis ED. Infectious complications of TNF-inhibitor monotherapy versus combination therapy with immunomodulators in inflammatory bowel disease: Analysis of the Food and Drug Administration Adverse Event Reporting System. J Gastrointestin Liver Dis 2013;22:269-76.
20. Lorenzetti R, Zullo A, Ridola L, et al. Higher risk of tuberculosis reactivation when anti-TNF is combined with immunosuppressive agents: A systematic review of randomized controlled trials. Ann Med 2014;46:547-54. DOI:10.3109/07853890.2014.941919
21. Ford AC, Peyrin-Biroulet L Opportunistic infections with anti-tumor necrosis factor-α therapy in inflammatory bowel disease: Meta-analysis of randomized controlled trials. Am J Gastroenterol 2013;108:1268-76. DOI: 10.1038/ajg.2013.138
22. Colombel JF, Loftus Jr EV, Tremaine WJ, et al. The safety profile of infliximab in patients with Crohn's disease: The Mayo Clinic experience in 500 patients. Gastroenterology 2004;126:19-31. DOI: 10.1053/j.gastro. 2003.10.047
23. Fidder H, Schnitzler F, Ferrante M, et al. Long-term safety of infliximab for the treatment of inflammatory bowel disease: A single-centre cohort study. Gut 2009;58:501-8. DOI: 10.1136/ gut.2008.163642
24. Vaughn BP, Doherty GA, Gautam S, et al. Screening for tuberculosis and hepatitis B prior to the initiation of anti-tumor necrosis therapy. Inflamm Bowel Dis 2012;18:1057-63. DOI: 10.1002/ibd.21824
25. Mow WS, Abreu-Martin MT, Papadakis KA, et al. High incidence of anergy in inflammatory bowel disease patients limits the usefulness of PPD screening before infliximab therapy. Clin Gastroenterol Hepatol 2004;2:309-13. DOI: 10.1016/S1542-3565(04)00060-6
26. Riestra S, Taxonera C, Carpio D, et al., en representación de GETECCU. Recomendaciones del Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa (GETECCU) sobre el cribado y tratamiento de la tuberculosis latente en pacientes con enfermedad inflamatoria intestinal Enferm Inflam Intest Día 2015;14:109-19. DOI: 10.1016/j.eii.2015.09.001
27. Smith MY, Attig B, McNamee L, et al. Tuberculosis screening in prescribers of anti-tumor necrosis factor therapy in the European Union. Int J Tuberc Lung Dis 2012;16:1168-73. DOI: 10.5588/ijtld.12.0029
28. Pearson ML, Jereb JA, Frieden TR, et al. Nosocomial transmission of multidrug-resistant Mycobacterium tuberculosis. A risk to patients and health care workers. Ann Intern Med 1992;117:191-6. DOI: 10.7326/0003-4819-117-3-191
29. Harris TG, Sullivan Meissner J, Proops D. Delay in diagnosis leading to nosocomial transmission of tuberculosis at a New York City health care facility. Am J Infect Control 2013;41:155-60. DOI:10.1016/j.ajic.2012.02.015.