

Rates of latent and active tuberculosis in BCG vaccinated, immunosuppressed Crohn's disease patients from Bulgaria before and during anti-tumor necrosis factor therapy

A. GEORGIEVA^{1,2,3}, A. ATANASSOVA^{1,3,4}, M. MIRCHEV^{1,2,3}

¹Clinic of Gastroenterology, "St. Marina" University Hospital of Varna, Varna, Bulgaria

²Second Department of Internal Diseases, Clinic of Gastroenterology, "St. Marina" University Hospital of Varna, Medical University, Varna, Bulgaria

³Medical University, Varna, Bulgaria

⁴Department of Anatomy and Cell Biology, Clinic of Gastroenterology, "St. Marina" University Hospital of Varna, Medical University, Varna, Bulgaria

Abstract. – OBJECTIVE: Although the use of anti-tumor necrosis factor-alpha (anti-TNF- α) agents is highly effective in achieving and maintaining remission in patients with moderate-to-severe IBD, they place the patient at increased risk of developing opportunistic infections, including new cases of tuberculosis infection (TBI) and/or reactivation of latent tuberculosis infection (LTBI). Our study aims to determine the incidence of TBI [active tuberculosis (ATBI) and LTBI] among patients with Crohn's disease (CD) receiving anti-TNF- α therapy.

PATIENTS AND METHODS: We performed a retrospective analysis of consecutive CD patients undergoing anti-TNF- α (infliximab, adalimumab) treatment for a minimum of 6 months, in the period between June 2010 and December 2019, followed-up at a reference IBD center. All patients were HIV negative, and BCG vaccinated. In all patients, ATBI was excluded and all were tested for LTBI prior to initiating a biological treatment.

RESULTS: Before starting the biological treatment, we established LTBI in 11/109 (10.1%): 8/11 (72.7%) patients were TST positive, 2/11 (18.2%) were IGRA positive and TST negative, 1/11 (9.1%) were both IGRA and TST positive.

In patients undergoing biological therapy with previous negative screening test for tuberculosis, a total of 16/74 (21.6%) patients were newly diagnosed with LTBI. The median induration (not erythema) diameter of TST is 8 (IQR 5-17) mm.

Active pulmonary tuberculosis infection, developed in 3/74 (4.1%) patients. One patient developed ATBI on the background of chemoprophylaxis with INH for LTBI.

CONCLUSIONS: Specialists should thoroughly analyse all patient clinical data, chest X-ray results, epidemiological and BCG status, as well as perform a LTBI screening before initiating immunosuppressive and/or biological treatment. IBD patients have a higher risk of developing TBI in the first 12 months.

Key Words:

IBD, Crohn's disease, Anti-tumor necrosis factor-alpha, Tuberculosis infection, Incidence.

Introduction

Inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC) are chronic, recurrent, lifelong diseases of unknown etiology. Over the past 20 years, there has been great progress in their treatment with the implementation of biological drugs. Although the use of anti-tumor necrosis factor-alpha (anti-TNF- α) agents is highly effective in achieving and maintaining remission in patients with moderate-to-severe IBD, they place the patient at an increased risk of developing opportunistic infections, including new cases of tuberculosis infection (TBI) and/or reactivation of latent tuberculosis infection (LTBI)¹.

Anti-TNF- α agents are associated with a 5-fold increased risk of reactivation of TB in the first 52 weeks after the initiation of therapy².

Studies by Ali et al³, Winthrop⁴ and Wallis et al⁵ reported that the risk of developing TBI increases 1.6-25 times after the start of anti-TNF- α therapy depending on the drug used, a fact that is enhanced when tuberculosis incidence is very high.

The British Society for Rheumatology biologic register detected an incidence of TBI in 39 cases per 100,000 patients/year with entanercept, 103 cases per 100,000 with infliximab and 171 cases per 100,000 with adalimumab⁶.

On one hand, in 2019, the World Health Organization (WHO) reported a decline in the inci-

dence TBI by 20% worldwide, while on the other hand, the use of biologic drugs is still associated with an increased risk of developing TBI and/or LTBI reactivation. Among all European Union countries, Bulgaria is one of the leaders in the incidence of TBI – 20.6/100,000 inhabitants⁷.

Therefore, the assessment of TBI at the initiation and during the treatment course with biologics in IBD patients is an important part of the close monitoring of this vulnerable group since LTBI reactivation has been associated with increased mortality, rapid disease spread, and the risk of developing an active tuberculosis infection, which would lead to discontinuation of the initiated immunosuppressive and/or biological treatment. This leads to an increased risk of relapse of IBD, disease progression and deterioration of the quality of life.

Our study aims to determine the incidence of TBI [active tuberculosis (ATBI) and LTBI] among patients with CD receiving anti-TNF- α therapy.

Patients and Methods

We performed a retrospective analysis of consecutive CD patients undergoing anti-TNF- α (infliximab, adalimumab) treatment for a minimum of 6 months, during the period between June 2010 and December 2019, followed up at a reference IBD center. All patients were HIV negative, and BCG vaccinated. In all patients, ATBI was excluded and all were tested for LTBI prior to initiating biological treatment.

According to the national and world health regulations, and ECCO consensus, the following were used to diagnose LTBI: tuberculin skin test (TST), interferon- γ release assay (IGRA) and chest radiography (Chest X-ray)/Chest-Computer tomography.

In all patients, the diagnosis of CD was made on the basis of clinical-laboratory, imaging, endoscopic and morphological criteria. Assessment of the extent and behavior of the disease was performed according to the Montreal classification, and of the disease activity – according to the Crohn's disease activity index (CDAI).

The patients' history of prior TB exposure, disease duration, IBD localization, CD behavior pattern, anti-TNF- α agent, treatment duration, concomitant immunosuppressive (IS) treatment, prophylactic isoniazid (INH) treatment (if any), screening for LTBI before anti-TNF- α , were analyzed.

According to the regulation of the Bulgarian

National Health Fund, IBD patients suitable for biological treatment are those who have moderate to high disease activity and no or partial response from previous IS treatment (absence of response or failure).

Patients who received azathioprine (AZA) (for at least 3 months) or systemic steroids (a daily dose equivalent to ≥ 20 mg of prednisolone for ≥ 2 weeks) during TBI screening before starting biologic therapy were considered to be within the group of patients who received IS therapy. In this group of patients, the diagnosis of LTBI is accepted on the basis of positive Mantoux induration (not erythema) ≥ 5 mm or/and IGRA positivity, in the absence of any chest radiography changes characteristic of previous tuberculosis infection (classic changes in the upper, middle and lower lung segments, enlarged hilar and mediastinal lymph nodes, the formation of cavitory lesions, the presence of fibrous openings with or without calcifications).

In patients not receiving IS therapy prior to initiating anti-TNF- α , LTBI was considered if TST induration (not erythema) was ≥ 10 mm and/or IGRA was positive, excluding any chest radiographic changes characteristic of preceding TBI.

Over the course of anti-TNF α therapy, patients were considered as having LTBI if TST was with induration (not erythema) ≥ 5 mm and/or if IGRA was positive, excluding any chest radiographic changes characteristic of ATBI.

Statistical Analysis

Statistical analysis was performed using SPSS software version 20.0 (SPSS Corp., Armonk, NY, USA). For data analysis, descriptive statistics, presented as numbers and percentage for categorical variables, and as mean \pm standard deviation or as medians and interquartile ranges for continuous variables, were used. Kappa statistics between TST and IGRA were used for the concordance analysis. The level of significance used for all analyzes was $p < 0.05$.

Results

During the period between June 2010 and December 2019, a total of 109 patients with Crohn's disease were screened before the start of biological treatment. Anti-TNF- α therapy was initiated by 97 patients, 74 of whom were retested for TBI during follow-up. Despite the screening, 12 of them did not reach treatment (one of them was diagnosed

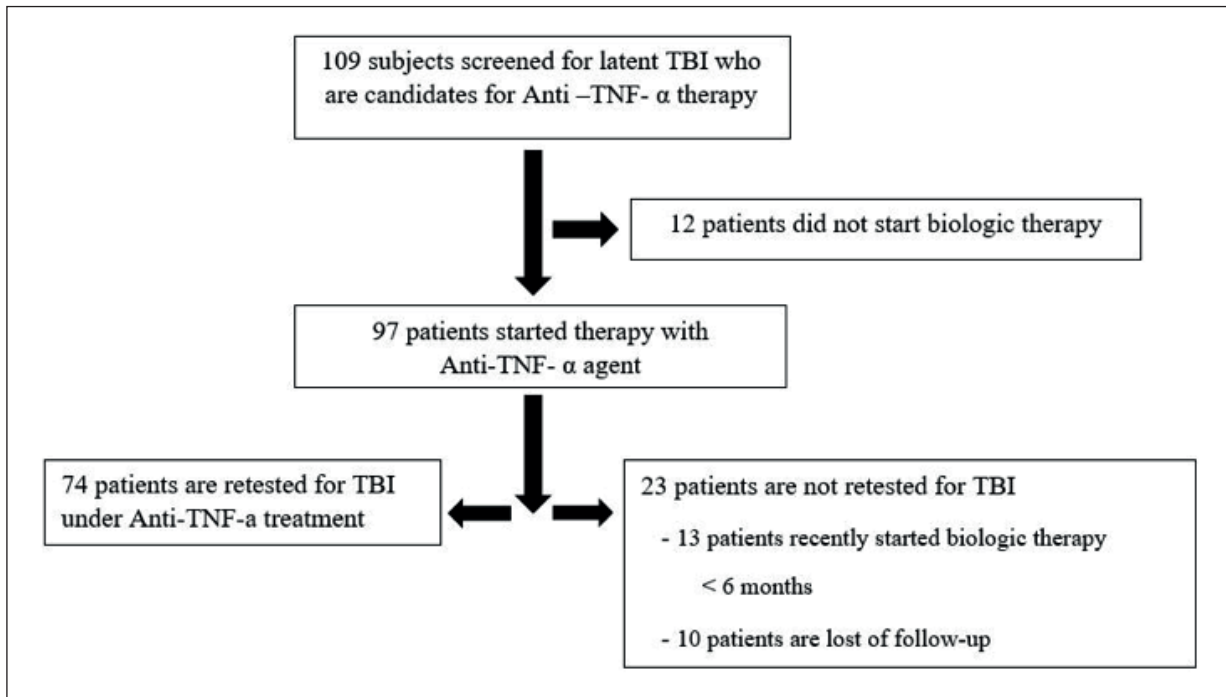


Figure 1. Chart of Crohn's disease patients included in the study. The median age at screening of the entire cohort of 109 CD patients was 37.00 (IQR 11 - 68) years, with 59/109 (54.1%) being men and 50/109 (45.9%) women (Table I). During screening, 99/109 (90.83%) patients received immunosuppressive therapy. Of them 68/109 (62.4%) received treatment with corticosteroids, and 30/109 (27.5%) received combination treatment with corticosteroid + AZA, respectively (Table II).

with latent tuberculosis, and the other 10 withdrew their consent to start treatment) (Figure 1).

The median age at screening of the entire cohort of 109 CD patients was 37.00 (IQR 11 - 68) years, with 59/109 (54.1%) being men and 50/109 (45.9%) women (Table I). During screening, 99/109 (90.83%) patients received IS therapy. Of them 68/109 (62.4%) received treatment with corticosteroids, and 30/109 (27.5%) received combination treatment with corticosteroid + AZA, respectively (Table II).

Latent Tuberculosis Screening Tests in Crohn's Disease Patients Before Anti-TNF-α Therapy

Before starting biological treatment, we established LTBI in 11/109 (10.1%): 8/11 (72.7%) patients were TST positive, 2/11 (18.2%) were IGRA positive and TST negative, 1/11 (9.1%) was both IGRA and TST positive (Table II). Chest X-ray abnormalities were not detected in all 11 patients. The median induration (not erythema) diameter of TST among this group of patients was 10 (IQR 7-23) mm.

After prophylaxis with isoniazid (INH) 300 mg/daily for 9 months, 9/11 (83.3%) patients

with LTBI reached treatment with an anti-TNF-α agent. Of this group 7/9 (77.8%) patients were monitored and retested for TBI: 6/7 (85.7%) in the follow-up TST and IGRA were negative, and one (14.3%) developed ATBI (Active pulmonary tuberculosis), despite chemoprophylaxis for LTBI with INH. Two patients were lost to follow-up.

Cohort of Crohn's Disease Patients Retested for TBI Under Anti-TNF-α Therapy

In the follow-up of patients under anti-TNF-α therapy, 74/97 (76.3%) patients were retested for TBI (Table III): 62/74 (83.8%) patients started treatment with adalimumab, 12/74 (16.2%) started with infliximab. Mean age at the start of biological therapy was 37.62 ± 12.69 (11-68), 42 (56.8%) of whom were male and 32 (43.2%) were female. Median Crohn's disease duration was 12 (IQR 1-180) months. The median duration of anti-TNF-α therapy was 24 (IQR 6-90) months.

In patients undergoing biological therapy with previous negative screening test for tuberculosis, a total of 16/74 (21.6%) patients were newly diagnosed with LTBI: 5/16 (31.3%) had TST conversion alone, 8/16 (50.0%) were TST positive

Table I. Baseline characteristics of all CD patients' candidates for biological treatment.

Characteristic	CD (n=109)
Age [median, (min-max)]	37.00 (11-68) years
Duration of the disease [median, (min-max)]	12.00 (1-204) months
Gender	Male, n [%]
	Female, n [%]
Localization	Terminal Ileum, n [%]
	Colon, n [%]
	Ileum and Colon, n [%]
	Ileum+Colon and Upper GI, n [%]
	Ileum and Upper GI, n [%]
Disease behavior	Non-stricturing
	non-penetrating, n [%]
	Stricturing, n [%]
	Penetrating, n [%]
Stricturing+ penetrating, n [%]	10 [9.2]
Perianal disease, n [%]	22 [20.2]
LTB positive, n [%]	11 [10.1]
IGRA +TST positive, n [%]	1 [0.92]
IGRA positive alone, n [%]	2 [1.83]
TST positive alone, n [%]	8 [7.34]

and IGRA negative, 1/16 (6.3%) were both TST + IGRA positive, 1/16 (6.3%) had IGRA conversion alone, 1/16 (6.3%) were TST negative and IGRA positive. The median induration (not erythema) diameter of TST is 8 (IQR 5-17) mm.

During the follow-up, 3/74 (4.1%) patients are retested with IGRA alone, 34/74 (45.9%) were followed up with TST alone. In the remaining 37/74 (50.0%) a combination of the two methods was performed (TST + IGRA). Discordant results between IGRA and TST were found in 10/37 (27.03%). Among the discordant results, TST-positive and IGRA-negative (TST + / IGRA-) combinations prevailed 9/10. There is no correlation between TST and IGRA, with a poor coefficient of agreement (kappa: 0.181, $p > 0.05$) among our group of patients (Table IV).

During the follow-up, one patient remained TST positive. Due to LTBI data prior to initiating biologic treatment, despite prophylaxis with INH

300 mg/daily for 9 months, another patient developed infiltrative pneumonic pulmonary tuberculosis (both TST + IGRA conversion) in combination with Chest X-ray and CT abnormalities.

Active pulmonary tuberculosis infection, with present abnormalities in both Chest X-ray and CT, developed in 3/74 (4.1%) patients: two of them were IGRA positive alone, one both IGRA + TST positive. One patient developed ATBI on the background of chemoprophylaxis with INH for LTBI. In all three patients who developed ATBI during biologic therapy, anti-TNF- α treatment was immediately discontinued and anti-TB therapy was initiated.

Median duration after the first dose of biologic therapy to detection of TBI was 12 (IQR 6-60) months.

Data on the concomitant IS therapy with AZA in patients receiving biologic treatment was available for 60/74 (80.1%) of TBI re-tested patients.

Table II. TBI screening results according to concomitant immunosuppressive therapy, n = 109.

n=109	TST + IGRA		TST + IGRA		TST + IGRA		TST + IGRA	
	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
IS treatment before								
Anti- TNF α (n, %)								
Non-IS therapy n [%]	-	-	-	-	-	-	10 [9.17]	-
Steroids n [%]	5 [4.59]	-	1 [0.92]	-	2 [1.83]	-	61 [55.96]	-
AZA+ steroids n [%]	3 [2.75]	-	-	-	-	-	27 [24.77]	-

Immunosuppressive (IS), azathioprine (AZA), tuberculin skin test (TST), IGRA (interferon- γ release assay).

Table III. Follow-up of TST and IGRA in patients under ongoing anti-TNF- α therapy n = 74.

Before Anti- TNF α During Anti-TNF α	IGRA		TST	
	+	-	+	-
IGRA				
+	1	5		
-	-	34		
TST				
+			2	14
-			5	50

Of them, 15/60 (25.0%) received azathioprine. In the group of patients receiving combination therapy with anti-TNF- α + AZA, two developed TBI: one with LTBI (TST positive and IGRA negative) and one with ATBI (TST + IGRA positive). None of them received pre-biological chemoprophylaxis for LTBI.

Discussion

As the incidence of IBD increases worldwide, there is a change in the treatment strategy of these patients. In order to change the course of the disease and prevent future surgery, as well as achieving steroid-free remission, more and more often in the early stages of the disease treatment with anti-TNF- α drugs is started. This in turn puts patients at risk of reactivation of various opportunistic infections, including TBI^{8,9}. Therefore, it is necessary to introduce screening protocols for TBI among IBD patients, candidates for biological treatment.

The ideal screening should include TST, IGRA, chest radiography, the patient's epidemiological and BCG vaccination status in every patient prior to initiating any IS treatment and proactive monitoring at 3 months during the first year of biological treatment¹⁰.

Since 1951, BCG vaccination is mandatory in Bulgaria. The latter is applied within the first

24 hours after birth, achieving a high coverage rate. Nevertheless, Bulgaria is one of the leading countries in Europe in terms of tuberculosis incidence, unlike other countries on the continent where BCG vaccine has not been used for decades without an increase in morbidity¹¹.

Several authors^{9,12} point out that BCG vaccination affects the high incidence of false-positive TSTs among this group of patients.

In immunosuppressed IBD patients, TST and IGRA tests are often presented with false negative results¹²⁻¹⁴, so it is appropriate to perform these tests as early as the diagnosis of IBD, due to the fact that most patients undergo IS treatment long before the initiation of biological therapy, which increases the risk of developing TBI/LTBI among this group of patients¹⁵.

In the present study, prior to initiating biological treatment, we found LTBI data in 10% (n = 11/109) of patients among the screened CD patients. Despite the reduction in the incidence of TBI worldwide, as well as in our country, Bulgaria is among the countries in the European Union, which remains among the 18 high priority countries for combating TBI in the WHO European Region⁷.

In contrast, a team of Korean scientists¹⁶ reported a high number of patients with LTBI (n=255/702) before treatment with anti-TNF. Among them, 78 are IGRA and TST (+), 90 IGRA (+), TST (-), 87 are IGRA (-) and TST(+)¹⁶.

Table IV. Patients with CD followed up simultaneously with TST and IGRA, n = 37.

	IGRA				Total	
	Positive		Negative		n	%
	n	%	n	%		
TST						
Positive > 5 mm	2	66.7	9	26.5	11	29.7
Negative	1	33.3	25	73.5	26	70.3
Total	3	100.0	34	100.0	37	100.0

A Portuguese team¹⁷ reported a 32% incidence of LTBI during screening period, 51% of patients are TST (+), 40% IGRA (+), 31 % have a history of contact with a TB-infected person. The prevalence of LTBI was 32% (n = 37/117) - TST (+) in 18 patients (51%); IGRA (+) in 14 patients (40%) and undetermined in 7 (6%); history of contact in 11 patients (31%)¹⁷.

In the present study, a low correlation between TST and IGRA tests was observed ($\kappa = 0.18$). Similar data for the discrepancy between these two tests is described by other authors^{17,18}.

The small number of reported data on the incidence of LTBI before starting biological therapy, as well as the different combination of screening tests, make the data difficult to compare.

Data from this study shows a 21.6% incidence of LTBI among the group of CD patients under anti-TNF- α therapy, with a median period of 12 (IQR 6-60) months between the first dose of biological therapy and tuberculosis detection.

Kang et al¹⁸ reported an 11.4% incidence of LTBI among IBD patients treated with anti-TNF drugs. Among those, 49 (58.3%) showed negative TST and positive IGRA results, whereas 18 (21.4%) showed positive results for both TST and IGRA, 16 (19.0%) showed a positive TST and a negative or indeterminate IGRA result, and 1 patient (1.2%) presented chest X-ray findings suggestive of spontaneously healed tuberculosis, with no history of tuberculosis treatment.

Due to the high incidence of TBI, it is appropriate to have a proactive monitoring of IBD patients under anti-TNF- α therapy, including an IGRA test at 3 months from the start of the biological treatment, for early detection of LTBI. Several studies¹⁹⁻²¹ have found that LTBI reactivation is observed within 3 to 6 months of initiation of anti-TNF- α therapy.

A meta-analysis of 128 studies²²⁻²⁴ in countries with low, medium and high incidence of TBI, revealed that 73% of IBD patients treated with anti-TNF agents, despite negative screening results, developed ATBI.

In the present study, active pulmonary tuberculosis infection was found in 3/74 (4.1%) IBD patients on the background of biological treatment: two of them were only IGRA positive, one IGRA + TST positive. One patient developed ATBI on the background of chemoprophylaxis with INH for LTBI. In all three patients who developed ATBI during biologic therapy, anti-TNF- α treatment was immediately discontinued and anti-TB therapy was initiated.

A similar study among IBD patients in Turkey²⁵ found an infiltrative pneumonic pulmonary tuberculosis developed in three patients (4.1%) during biological treatment, two of whom had not previously received chemoprophylaxis for LTBI. This may be attributed to false negative TST/IGRA due to the initiation of IS treatment (azathioprine and/or steroids) at screening.

Mañosa et al²⁶ reported an incidence of 1.2% (4/330) active tuberculosis in IBD patients under anti-TNF- α therapy in Spain. Lee et al²⁷ showed an incidence of active tuberculosis of 1.4% (9/661) in patients with CD who were treated with anti-TNF α in Korea. However, studies in Brazil and Latin America on the development of active TB in IBD patients under treatment are scarce²⁸.

One of our CD patients with disease onset in childhood developed active pulmonary tuberculosis 18 months after the initiation of anti-TNF- α therapy irrespective of the performed chemoprophylaxis due to the presence of LTBI. It is known that chemoprophylaxis for latent tuberculosis before starting IS treatment significantly reduces the chance of developing active tuberculosis up to 78%²⁹⁻³³. The risk of developing ATBI in IBD patients under biological therapy is due to either reactivation of undiagnosed LTBI^{22,34} or *de novo* infection^{35,36}.

The main limiting factors in most studies on the incidence of TBI/LTBI among IBD patients are: design (retrospective analysis), the small number of cases, the combination of different screening tests for LTBI, and the use of BCG vaccine among the general population.

Therefore, results from different geographical regions cannot be directly compared, and local studies should be performed.

Our study is limited by a small sample size patient. However, it instructs the clinician to be specifically vigilant when initiating anti-TNF- α therapy in IBD patients, because the reactivation of tuberculosis infection is a life-threatening complication in immunosuppressed patients. Current TB screening protocols need to be revised to use more specific and sensitive tests to diagnose latent TB infection, especially in countries where BCG vaccination is part of a routine vaccination schedule, as well as for countries with a high incidence of TBI.

All IBD patients should be monitored and evaluated regularly for LTBI reactivation, as there is no gold standard for diagnosing LTBI and none of the screening tests are 100% sensitive. Even IGRA tests sometimes give false negative results in the course of IS treatment.

Conclusions

Specialists should thoroughly analyze all patient clinical data, chest X-ray results, epidemiological and BCG status, as well as LTBI screening before initiating IS and/or biological treatment. IBD patients have a higher risk of developing TBI in the first 12 months. It is necessary to discuss and inform the patient about the potential risk of developing tuberculosis during all periods of anti-TNF- α therapy as part of the personalized approach to the treatment of IBD. Active tuberculosis can develop even in patients who have received anti-tuberculosis treatment for previous active tuberculosis and those who have received chemoprophylaxis for LTBI.

Authors' Contribution

Avgustina Georgieva: concept and design of the study, drafted the manuscript, statistical analysis.

Antonia Atanassova: analysed the data and interpreted the results.

Milko Mirchev: analysed the data and interpreted the results, bibliography (other published reviews/articles, online materials).

Conflicts of Interest

The authors declare that they have no conflict of interest.

References

- 1) Global Tuberculosis Control. WHO Report 2019. World Health Organization; 2019. www.who.int/tb.
- 2) Solovic I, Sester M, Gomes-Reino JJ, Rieder HL, Ehlers S, Milburn HJ, Kampmann B, Hellmich B, Groves R, Schreiber S, Wallis RS, Sotgiu G, Schölvinck EH, Goletti D, Zellweger JP, Diel R, Carmona L, Bartalesi F, Ravn P, Bossink A, Duarte R, Erkens C, Clark J, Migliori GB, Lange C. The risk of tuberculosis related to tumour necrosis factor antagonist therapies: a TBNET consensus statement. *Eur Respir J* 2010; 36: 1185-1206.
- 3) Ali T, Kaitha S, Mahmood S, Ftesi A, Stone J, Bronze MS. Clinical use of anti-TNF therapy and increased risk of infections. *Drug Healthc Patient Saf* 2013; 5: 79-99.
- 4) Winthrop KL. Risk and prevention of tuberculosis and other serious opportunistic infections associated with the inhibition of tumor necrosis factor. *Nat Clin Pract Rheumatol* 2006; 2: 602-610.
- 5) Wallis RS, Broder M, Wong J, Beenhouwer D. Granulomatous infections due to tumor necrosis factor blockade: Correction. *Clin Infect Dis* 2004; 39: 1254-12255.
- 6) Mir Viladrich I, Daudén Tello E, Solano-López G, López Longo FJ, Taxonera Samsó C, Sánchez Martínez P, Martínez Lacasa X, García Gasalla M, Dorca Sargatal J, Arias-Guillén M, García García JM. Consensus Document on Prevention and Treatment of Tuberculosis in Patients for Biological Treatment. *Arch Bronconeumol* 2016; 52: 36-45.
- 7) Tuberculosis surveillance and monitoring in Europe, 2019, Surveillance report, Mar 2019, www.ecdc.europa.eu/en/publications-data/tuberculosis-surveillance-and-monitoring-europe-2019.
- 8) Chebli JM, Gaburri PD, Chebli LA, da Rocha Ribeiro TC, Pinto AL, Ambrogini Júnior O, Damião AO. A guide to prepare patients with inflammatory bowel diseases for anti-TNF- α therapy. *Med Sci Monit* 2014; 20: 487-498.
- 9) Rahier JF, Magro F, Abreu C, Armuzzi A, Ben-Horin S, Chowers Y, Cottone M, de Ridder L, Doherty G, Ehehalt R, Esteve M, Katsanos K, Lees CW, Macmahon E, Moreels T, Reinisch W, Tilg H, Tremblay L, Veereman-Wauters G, Vigeat N, Yazdanpanah Y, Eliakim R, Colombel JF; European Crohn's and Colitis Organisation (ECCO). Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis* 2014; 8: 443-468.
- 10) Kucharzik T, Ellul P, Greuter T, Rahier JF, Verstockt B, Abreu C, Albuquerque A, Allocca M, Esteve M, Farraye FA, Gordon H, Karmiris K, Kopylov U, Kirchgessner J, MacMahon E, Magro F, Maaser C, de Ridder L, Taxonera C, Toruner M, Tremblay L, Scharl M, Vigeat N, Zabana Y, Vavricka S. ECCO Guidelines on the Prevention, Diagnosis, and Management of Infections in Inflammatory Bowel Disease. *J Crohns Colitis* 2021; 15: 879-913.
- 11) Dara M, Acosta CD, Rusovich V, Zellweger JP, Centis R, Migliori GB. WHO EURO Childhood Task Force members. Bacille Calmette-Guérin vaccination: the current situation in Europe. *Eur Respir J* 2014; 43: 24-35.
- 12) Kurti Z, Lovasz BD, Gecse KB, Balint A, Farkas K, Morocza-Szabo A, Gyurcsanyi A, Kristof K, Vegh Z, Gonczi L, Kiss LS, Golovics PA, Lakatos L, Molnar T, Lakatos PL. Tuberculin Skin Test and Quantiferon in BCG Vaccinated, Immunosuppressed Patients with Moderate-to-Severe Inflammatory Bowel Disease. *J Gastrointest Liver Dis* 2015; 24: 467-472.
- 13) Hsia EC, Schluger N, Cush JJ, Chaisson RE, Matteson EL, Xu S, Beutler A, Doyle MK, Hsu B, Rahman MU. Interferon-gamma release assay versus tuberculin skin test prior to treatment with golimumab, a human anti-tumor necrosis factor antibody, in patients with rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis. *Arthritis Rheum.* 2012; 64: 2068-2077.
- 14) Ponce de Leon D, Acevedo-Vasquez E, Alvizuri S, Gutierrez C, Cucho M, Alfaro J, Perich R, Sanchez-Torres A, Pastor C, Sanchez-Schwartz C, Medina M, Gamboa R, Ugarte M. Comparison of an interferon-gamma assay with tuberculin skin testing for detection of tuberculosis (TB) infection in patients with rheumatoid arthritis in a TB-endemic population. *J Rheumatol* 2008; 35: 776-781.

- 15) Aberra FN, Stettler N, Brensinger C, Lichtenstein GR, Lewis JD. Risk for active tuberculosis in inflammatory bowel disease patients. *Clin Gastroenterol Hepatol* 2007; 5: 1070-1075.
- 16) Lee EH, Kang YA, Leem AY, Park MS, Kim YS, Kim SK, Chang J, Kim SY. Active Tuberculosis Incidence and Characteristics in Patients Treated with Tumor Necrosis Factor Antagonists According to Latent Tuberculosis Infection. *Sci Rep* 2017; 7: 6473.
- 17) Sousa M, Ladeira I, Ponte A, Fernandes C, Rodrigues A, Silva AP, Silva J, Gomes C, Afeto E, Carvalho J. Screening for latent tuberculosis in patients with inflammatory bowel disease under antitumor necrosis factor: data from a Portuguese center. *Eur J Gastroenterol Hepatol* 2019; 31: 1099-1102.
- 18) Kang J, Jeong DH, Han M, Yang SK, Byeon JS, Ye BD, Park SH, Hwang SW, Shim TS, Jo KW. Incidence of Active Tuberculosis within One Year after Tumor Necrosis Factor Inhibitor Treatment according to Latent Tuberculosis Infection Status in Patients with Inflammatory Bowel Disease. *J Korean Med Sci* 2018; 33: e292.
- 19) Jauregui-Amezaga A, Turon F, Ordás I, Gallego M, Feu F, Ricart E, Panés J. Risk of developing tuberculosis under anti-TNF treatment despite latent infection screening. *J Crohns Colitis* 2013 Apr; 7: 208-212.
- 20) Lee JW, Choi CH, Park JH, Kim JW, Kang SB, Koo JS, Kim YH, Kim YS, Joo YE, Chang SK. Clinical features of active tuberculosis that developed during anti-tumor necrosis factor therapy in patients with inflammatory bowel disease. *Intest Res* 2016; 14: 146-151.
- 21) Kim ES, Song GA, Cho KB, Park KS, Kim KO, Jang BI, Kim EY, Jeon SW, Lee HS, Yang CH, Lee YK, Lee DW, Kim SK, Kim TO, Lee J, Kim HW, Jee SR, Park SJ, Kim HJ. Significant risk and associated factors of active tuberculosis infection in Korean patients with inflammatory bowel disease using anti-TNF agents. *World J Gastroenterol* 2015; 21: 3308-3316.
- 22) Abitbol Y, Laharie D, Cosnes J, Allez M, Nancey S, Amiot A, Aubourg A, Fumery M, Altwegg R, Michetti P, Chanteloup E, Seksik P, Baudry C, Flamant M, Bouguen G, Stefanescu C, Bourrier A, Bommelaer G, Dib N, Bigard MA, Viennot S, Hébuterne X, Gornet JM, Marteau P, Bouhnik Y, Abitbol V, Nahon S. Negative screening does not rule out the risk of tuberculosis in patients with inflammatory bowel disease undergoing anti-TNF treatment: a descriptive study on the GETAID cohort. *J Crohns Colitis*. 2016; 10: 1179-1185.
- 23) Kedia S, Mouli VP, Kamat N, Sankar J, Ananthakrishnan A, Makharia G, Ahuja V. Risk of tuberculosis in patients with inflammatory bowel disease on infliximab or adalimumab is dependent on the local disease burden of tuberculosis: a systematic review and meta-analysis. *Am J Gastroenterol* 2020; 115: 340-349.
- 24) Lingna Ye, Thomas P. Chapman, Zhenzhen Wen, Lang Lin, Yun Qiu, Zhanju Liu, Jiaming Qian, Kaichun Wu, Xiang Gao, Pinjin Hu, Minhu Chen, Simon P. L. Travis, Qian Cao, Targeted versus universal tuberculosis chemoprophylaxis in 1968 patients with inflammatory bowel disease receiving anti-TNF therapy in a tuberculosis endemic region. *Aliment Pharmacol Ther* 2021; 53: 390-399.
- 25) Çekiç C, Aslan F, Vatanserver S, Topal F, Yüksel ES, Alper E, Dalli A, Ünsal B. Latent tuberculosis screening tests and active tuberculosis infection rates in Turkish inflammatory bowel disease patients under anti-tumor necrosis factor therapy. *Ann Gastroenterol* 2015; 28: 241-246.
- 26) 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: e499-e500.
- 27) Lee CK, Wong SHV, Lui G, Tang W, Tam LS, Ip M, Hung E, Chen M, Wu JC, Ng SC. A Prospective Study to Monitor for Tuberculosis During Anti-tumour Necrosis Factor Therapy in Patients With Inflammatory Bowel Disease and Immune-mediated Inflammatory Diseases. *J Crohns Colitis* 2018; 12: 954-962.
- 28) Cury DB, Moss AC, Oliveira RA. Rate of de novo TB Infection in an IBD Population Treated With Adalimumab in Brazil. *Gastroenterology* 2015; 148: 238.
- 29) Sichletidis L, Settas L, Spyrtos D, Chloros D, Patakas D. Tuberculosis in patients receiving anti-TNF agents despite chemoprophylaxis. *Int J Tuberc Lung Dis* 2006; 10: 1127-1132.
- 30) Agarwal A, Kedia S, Jain S, Gupta V, Bopanna S, Yadav DP, Goyal S, Mouli VP, Dhingra R, Makharia G, Ahuja V. High risk of tuberculosis during infliximab therapy despite tuberculosis screening in inflammatory bowel disease patients in India. *Intest Res* 2018; 16: 588-598.
- 31) Park DI, Hisamatsu T, Chen M, Ng SC, Ooi CJ, Wei SC, Banerjee R, Hilmi IN, Jeon YT, Han DS, Kim HJ, Ran Z, Wu K, Qian J, Hu PJ, Matsuoka K, Andoh A, Suzuki Y, Sugano K, Watanabe M, Hibi T, Puri AS, Yang SK. Asian Organization for Crohn's and Colitis and Asia Pacific Association of Gastroenterology consensus on tuberculosis infection in patients with inflammatory bowel disease receiving anti-tumor necrosis factor treatment. Part 2: management. *Intest Res* 2018; 16: 17-25.
- 32) Carmona L, Gómez-Reino JJ, Rodríguez-Valverde V, Montero D, Pascual-Gómez E, Mola EM, Carreño L, Figueroa M; BIOBADASER Group. Effectiveness of recommendations to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists. *Arthritis Rheum* 2005; 52: 1766-1772.
- 33) Lee J, Kim E, Jang EJ, Lee CH, Lee EY, Im JP, Han SK, Yim JJ. Efficacy of treatment for latent tuberculosis in patients undergoing treatment with a tumor necrosis factor antagonist. *Ann Am Thorac Soc* 2017; 14: 690-697.
- 34) Carpio D, Jauregui-Amezaga A, de Francisco R, de Castro L, Barreiro-de Acosta M, Mendoza JL, Mañosa M, Ollero V, Castro B, González-Conde B, Hervías D, Sierra Ausin M, Sancho Del Val L, Bo-

- tella-Mateu B, Martínez-Cadilla J, Calvo M, Chaparro M, Ginard D, Guerra I, Maroto N, Calvet X, Fernández-Salgado E, Gordillo J, Rojas Fera M; GETECCU. Tuberculosis in anti-tumour necrosis factor treated inflammatory bowel disease patients after the implementation of preventive measures: Compliance with recommendations and safety of retreatment. *J Crohns Colitis*. 2016; 10: 1186-1193.
- 35) Riestra S, de Francisco R, Arias-Guillén M, Saro C, García-Alvarado M, Duque JM, Palacios JJ, Muñoz F, Blanco L, Castaño O, Pérez-Martínez I, Pablo Martínez-Cambor P, Pérez-Hernández D and Suárez A. Risk factors for tuberculosis in inflammatory bowel disease: anti-tumor necrosis factor and hospitalization. *Rev Esp Enferm Dig* 2016; 108: 541-549.
- 36) Gagnière C, Bourrier A, Seksik P, Gornet JM, De Wit O, Nancey S, Altwegg R, Abitbol V, Laharie D, Reenaers C, Buisson A, Pariente B, Viennot S, Vuitton L, Stefanescu C, Marteau P, Bouguen G, Cosnes J, Amiot. A risk of serious infection in healthcare workers with inflammatory bowel disease: a case-control study of the Groupe d'Etude Thérapeutique des Affections Inflammatoires du tube Digestif (GETAID). *Aliment Pharmacol Ther* 2018; 48: 713-722.