

Original Article

## Relationship between biologic modifying agents and development of latent tuberculosis in pediatrics

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### Abstract

**Introduction:** Biologic modifying agents are associated with an increased risk for infection with mycobacteria. The aim of this study is to document patients who received different biologic modifying therapies in our pediatric rheumatology department and the possibility of development of tuberculosis (TB).

**Methodology:** This retrospective study was conducted in Ankara City Hospital. Pediatric patients who were treated with biologic modifying agents between 2010-2020 were documented. Development of TB and the risk factors were assessed in this patient group.

**Results:** There were 72 patients who were treated with different biologic modifying agents. Tuberculin skin test (TST) was positive in 7 (9.7%) patients during follow up. Three patients whose TST was positive had received canakinumab, 2 received etanercept, 1 received adalimumab and 1 received anakinra. Median duration of therapy was 43.5 (16.5-168) months for these patients and the duration was longer than patients who did not develop latent tuberculosis ( $p = 0.04$ ). Patients who developed latent TB under treatment were significantly older than the patients who did not ( $p = 0.01$ ).

**Conclusions:** According to our findings, 9.7% of pediatric patients who received biologic modifying agent therapy developed latent TB. Patients who developed latent TB were older, and the duration of treatment was longer than patients who did not develop latent TB. Although not statistically significant, canakinumab, which is known as an agent less likely to cause TST conversion, was in fact the most common agent that caused TST conversion.

**Key words:** biologic agent; tuberculosis; children; anti-tumour necrosis factor.

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### Introduction

Biologic modifying agents are drugs that interact with and modify a patient's immune system. They are produced by biological pathways rather than chemical synthesis, different from disease modifying anti-rheumatic drugs [1,2]. Biologic modifying agents are used to suppress the response in many autoinflammatory and autoimmune conditions like juvenile idiopathic arthritis, inflammatory bowel diseases, psoriasis, juvenile systemic lupus erythematosus (SLE) and vasculitis in pediatrics [1,3]. These agents are highly effective in controlling the signs and symptoms of underlying diseases but may lead to immunosuppression of the host, lasting weeks to months [4]. This immunosuppression may result in infectious complications, which have been the subject of many studies to date. Most of these drugs are associated with an increased risk for infection with

certain viral and bacterial (especially mycobacterial) pathogens, as well as some fungal and intracellular agents [5]. Therefore, screening for latent tuberculosis infection (LTBI) prior to treatment with many biologic modifying agents (especially tumor necrosis factor alpha inhibitors (TNFIs)) is routinely performed with the aim to detect patients at high risk of developing active tuberculosis infection and to treat the latent infection before it activates [6]. Most of the data on mycobacterial infection risk of biologic modifying agents are from adults, and findings for children are mostly extrapolated from these studies [1,2]. In countries with high prevalence of tuberculosis, activation of LTBI is an important problem during treatment with biologic modifying agents, especially anti-TNF treatment [5]. Thus, the aim of this study was to document patients who received different biologic modifying therapies in our pediatric rheumatology

department and who had the possibility of development of tuberculosis, since Turkey is an eastern Mediterranean country with moderate tuberculosis frequency (official incidence is 18/100 000) [7].

## Methodology

### *Study design*

This retrospective study was conducted in Ankara City Hospital which is a tertiary care children's hospital. Seventy-two pediatric patients who were followed up in Pediatric Rheumatology department and treated with biologic modifying agents between 2010-2020 were documented. The data of these patients was obtained from hospital records, which included the demographics of the patients, diagnosis requiring biologic modifying therapy, duration of primary disease, duration of TNFIs, previous corticosteroid treatment, prior and concomitant medication, history of tuberculosis (TB) contact, history of Bacillus Calmette-Guérin (BCG) vaccination and radiological examination reports including chest x-ray and/or computerized tomography evaluated by pediatric radiology department. Patients who had a history of TB infection or disease and patients who were switched between different biologic modifying agents were excluded from the scope of the study.

The frequently used biologic modifying agents in our center were: tocilizumab, abatacept, anakinra, etanercept, adalimumab, canakinumab and infliximab. In Turkey, the BCG vaccine is recommended and administered to all children, excluding children with primary or secondary immunosuppression, since 1952 and is regulated by the Ministry of Health.

The risk factors for TB were defined as travel or residence in a high TB prevalence area, primary or secondary immune deficiencies, young age, and crowded or poor living conditions [8]. All patients were routinely screened for tuberculosis infection before biologic modifying agent implementation by tuberculin skin test (TST) and/or interferon gamma release assay (IGRA) (Quantiferon-TB Gold-in Tube® test, QTF-G; Cellestis, Carnegie, Australia) if possible. TST was performed according to the Mantoux method using 0.1 mL of purified protein derivative (PPD) RT 23 antigen equivalent to two tuberculin units, injected intradermally into the volar surface of the forearm, and the results were assessed by reference to the transverse diameter (in mm) of induration after 48-72 hours [7].

After initial assessment, patients were clinically re-evaluated every 3–6 months for tuberculosis infection. TST/IGRA were repeated once a year in the absence of signs or symptoms consistent with tuberculosis or

proven tuberculosis contact, and chest X-ray was repeated every 6 months, in accordance with the national guidelines [7].

The hallmark of LTBI is a positive TST or IGRA result. In this stage the child has no signs or symptoms of TB, a normal physical examination, and the chest radiograph is either normal or reveals only granuloma or calcifications in the lung parenchyma [8]. A positive TST was considered when there was  $\geq 5$  mm of transverse diameter during biologic modifying agent therapy.

When necessary, patients with any relevant symptoms, physical signs or examination findings were also evaluated with chest x-ray and other diagnostic tests immediately [7].

### *Ethical approval*

The Ankara Hematology Oncology Children's Training and Research Hospital Ethics Committee approved the study, with the reference number: 2018/193.

### *Statistical analyses*

Patients' data was collected from hospital records retrospectively. All statistical analyses were conducted using SPSS software (version 22, IBM, Chicago, IL, USA).

Continuous variables were presented as mean  $\pm$  standard deviation or median (range) according to the normality tests and compared using a two-sided Student's t-test or Mann-Whitney U-test, as appropriate. Categorical variables were compared using Chi square test. The statistical significance was set at  $p$  value  $< 0.05$ .

## Results

There were 72 patients included in the study. Among them, 28 (38.9%) were diagnosed with familial Mediterranean fever (FMF), 26 (36.1%) with oligoarticular juvenile idiopathic arthritis (JIA), 10 with polyarticular JIA, 4 (5.6%) with sacroiliitis, 1(1.4%) with psoriatic arthritis, 2 (2.8%) with polyarteritis nodosa and 1(1.4%) with adenosine de aminase -2 (ADA-2) deficiency.

41 (56.9%) of the patients were male, and 31 (43.1%) were female. The median age of the patient group was 13.2 years (IQR: 10.1-16.9).

All the patients were vaccinated with BCG vaccine and had a BCG scar.

All the patients were receiving a single biologic modifying agent. The biologic modifying agents used in treatment were: etanercept for 25 (34.2%),

canakinumab for 18 (25%), adalimumab for 12 (16.7%), anakinra for 11 (15.3%), tocilizumab for 4 (5.6%), abatacept for 1 (1.4%) and infliximab for 1 (1.4%) patient. The median duration of treatment was 30.5 months (IQR: 4-168).

The patients that were previously treated with corticosteroid/ disease-modifying antirheumatic drugs (DMARDs) were analyzed. In contrast to the existing literature, it was found that previous treatment with corticosteroid/DMARDs did not significantly affect TST conversion ( $p = 0.13$ ,  $p = 0.56$ ) (Table 1).

TST became positive in 7 (9.7%) patients during follow up. Of the 7 patients whose TST became positive, 3 were receiving canakinumab, 2 etanercept, 1 adalimumab and 1 anakinra. Development of LTBI did not differ according to treatment modality or diagnosis ( $p = 0.67$  and  $p = 0.94$ ). Median duration of therapy was

43.5 (16.5-168) months for these patients. This was longer than the therapy duration of patients who did not develop latent tuberculosis ( $p = 0.04$ ). Patients who developed latent tuberculosis under treatment were significantly older than patients who did not ( $p = 0.01$ ) (Table 1).

There were only 8 patients who were tested with IGRA because only TST was preferred for screening in many patients and IGRA was unavailable in our hospital. All of them were negative concomitant with PPD test.

## Discussion

This study is significant as it examines the relationship between biologic modifying agents and development of LTBI. In contrast to many other existing studies, this study evaluates different types of

**Table 1.** Patient characteristics and tuberculosis infection.

	Total (n = 72)	No latent tuberculosis in follow up (n = 65)	Latent tuberculosis in follow up (n = 7)	<i>P</i>
<b>Age (months)</b> (median (min-max)) **	13.2 (4-22.3)	12.8 (4-22.3)	18.1 (9.8-21.5)	0.01
<b>Gender*</b>				
Male	31 (43.1%)	28 (90.4%)	3 (9.6%)	0.12
Female	41 (56.9%)	37 (90.3%)	4 (9.7%)	
<b>Diagnosis*</b>				
FMF	28 (38.9%)	23 (35.4%)	5 (71.4%)	0.67
JIA oligoarticular	26 (36.1%)	25 (38.5%)	1 (14.3%)	
JIA polyarticular	10 (13.9%)	9 (13.8%)	1 (14.3%)	
Sacroileitis	4 (5.6%)	4 (6.2%)	0	
Psoriatic arthritis	1 (1.4%)	1 (1.5%)	0	
PAN	2 (2.8%)	2 (3.1%)	0	
ADA-2 deficiency	1 (1.4%)	1 (1.5%)	0	
<b>History of contact with a TB case *</b>				
Yes	2 (2.8%)	1 (1.5%)	1 (14.3%)	0.18
No	70 (97.2%)	64 (98.5%)	6 (85.7%)	
<b>Glucocorticoid treatment*</b>				
Yes	3 (4.2%)	3 (4.6%)	0	0.56
No	69 (95.8%)	62 (95.4%)	72 (100%)	
<b>Synthetic DMARD*</b>				
Yes	40 (55.5%)	27 (41.5%)	5 (71.4%)	0.13
No	32 (44.5%)	38 (58.5%)	2 (28.6%)	
<b>Biologic agent*</b>				
Etanercept	25 (34.2%)	23 (35.4%)	2 (28.6%)	0.94
Canakinumab	18 (25.0%)	15 (23.2%)	3 (42.8%)	
Adalimumab	12 (16.7%)	11 (16.9%)	1 (14.3%)	
Anakinra	11 (15.3%)	10 (15.4%)	1 (14.3%)	
Tocilizumab	4 (5.6%)	4 (6.1%)	0	
Abatacept	1 (1.4%)	1 (1.5%)	0	
Infliximab	1 (1.4%)	1 (1.5%)	0	
<b>Duration of treatment with the biologic agent (months) **</b>	30.5 (4-168)	27.5 (4-114.5)	43.5 (16.5-168)	
<b>TST before treatment</b>				
0-4 mm	59 (81.9%)	54 (83.1%)	5 (71.4%)	0.12
5-9 mm	4 (5.6%)	4 (6.1%)	0 (0)	
10-15 mm	5 (6.9%)	4 (6.1%)	1 (14.2%)	
≥ 15 mm	4 (5.6%)	3 (4.7%)	1 (14.2%)	

\*Chi-square test was performed; \*\*Mann Whitney U test was performed. FMF: familial Mediterranean fever; JIA: juvenile idiopathic arthritis; PAN: polyarteritis nodosa; ADA: adenosine deaminase; TB: tuberculosis; DMARD: disease-modifying antirheumatic drugs; TST: tuberculin skin test.

biologic modifying agents in pediatrics, rather than only TNFIs. According to our results, 9.7% of pediatric patients receiving biologic modifying agent therapy developed LTBI. Patients who developed LTBI were older and had longer duration of therapy than patients who did not. The patients who developed LTBI were mostly receiving canakinumab and etanercept, not TNFIs.

It is clearly established that biologic modifying agent therapy increases the risk of LTBI, especially in adults. However, pediatric data on this is limited, and the real incidence is not known [9]. Mostly, TNFIs are blamed for TB, but biologic modifying agents other than TNFIs may also be responsible for the development of TB [10].

A study by Brunelli *et al.* demonstrated that 4% of JIA patients required primary prophylaxis for positive screening test during biologic modifying agent [11]. In the Cochrane review by Singh *et al.*, the overall odds ratio (OR) of tuberculosis reactivation was 4.7 (95% CI: 1.2–18.6) among patients receiving biologic modifying agents compared with those receiving placebo, with the absolute risk measured at 20 cases per 10,000 compared with 4 per 10,000 patients receiving placebo [12]. There are few studies on TST conversion in children using anti-TNF in Turkey. In the study of Acar *et al.*, 21.9% of patients receiving anti TNF therapy had TST conversion during follow-up [13]. In another pediatric report, the prevalence of LTBI during biological modifying agent therapy was 23.4% [14]. According to our study, 9.7% (n = 7) of pediatric patients receiving biologic modifying agent therapy needed prophylaxis for tuberculosis. The rate of LTBI was found to be higher in our study compared to international literature. The reason for this is possibly that the incidence of TB is higher in Turkey compared to those countries and the lower incidence compared to reports from Turkey may be due to the region and characteristics of the study population.

According to our findings, patients who had latent TB were older than who did not. In a study on adults, Xie *et al.* concluded that older age was significantly related to the occurrence of TB, since the immune system weakens with age [15]. There is not much data about the risk posed by age in pediatric literature. This finding may be related with the longer duration of using DMARDs or other previously used immunosuppressants that affect the immune system and it may also be that the risk of encountering tuberculosis bacillus increases with age. Nevertheless, the finding that the risk of TB disease increases with older age is striking and should be supported by new studies.

Longer duration of treatment is known as a risk factor for LTBI during biologic modifying therapy [14,16]. Similar to the literature, our study showed that the duration of biologic treatment was longer in patients with LTBI than patients who did not develop LTBI.

As is well-known, co-administration of DMARD or corticosteroid therapy increases TST conversion because of immune suppression [10]. In our study group, none of the patients were simultaneously treated with DMARDs/corticosteroid and biologic modifying agents. Besides, receiving previous corticosteroid therapy did not significantly induce development of LTBI in this study.

According to the current literature, the most common biologic modifying agents that are related to tuberculosis disease are TNFIs. The risk is higher with anti-TNF antibodies (like infliximab and adalimumab), whereas it is lower with soluble TNF receptors (etanercept) and monoclonal antibodies [17].

Gulez *et al.* reported that 24.1% of patients who were treated with canakinumab therapy developed LTBI [18]. In another study from Turkey, the rate was 25% for canakinumab therapy [14]. According to our findings 4 (57.1%) of the LTBI patients were treated with monoclonal antibodies (not TNFIs). 42.8% of the patients whose TST converted were receiving canakinumab and 16.6% of patients who were receiving canakinumab had TST conversion during treatment. Due to the low number of patients using tocilizumab, abatacept or infliximab, it cannot be speculated that these agents do not predispose to tuberculosis. However, the finding that the majority of the patients who developed tuberculosis were receiving canakinumab is an original and remarkable finding as there is scant evidence on this in the current literature. As the result was not statistically significant, it is not possible to indicate that LTBI is more prevalent with canakinumab. Nevertheless, this is a new and striking finding, which should be further examined by prospectively designed future studies.

Another important finding of our study was that the second most common TST conversion group comprised patients who were receiving etanercept (28.6%). A previous cohort study identified rates of 6 to 39 cases of tuberculosis for etanercept, compared with 71 to 100 cases for infliximab and adalimumab per 100,000 patient-years [19]. Another report by Dixon *et al.* stated that the rates of tuberculosis were higher in patients receiving either of the monoclonal antibodies than in those taking etanercept [20]. Lovell *et al.* suggested that the acceptable safety profile of etanercept therapy was

maintained for up to 8 years in the population of JIA patients [21].

The low use of IGRA in this study group was noteworthy. Some studies show that IGRA is more effective than TST in detecting latent tuberculosis as it is not affected by BCG vaccination [22,23]. In 90.6% of patients, TST was negative despite BCG vaccination and, therefore, IGRA was not used in these patients.

Limitations of our study are the retrospective design and the small size of our study group which makes it difficult to generalize the results. Prospective future studies with large cohorts will clearly enlighten the possible effects of biologic modifying therapies other than anti-TNFs. In addition, IGRA was used in limited numbers. The fact that TSTs carry the risk of cross-reactivity with BCG, *Mycobacterium avium* intracellulare and non-tuberculous mycobacteria, and have the potential of boosting with serial testing, as well as the variability in test interpretation, might affect the positivity of the test.

## Conclusions

Our results show that 9.7% of the pediatric patients receiving biologic modifying agent therapy developed latent tuberculosis. Patients who developed latent tuberculosis were older than patients who did not. Another important point was that the longer the duration of therapy, the greater the risk of TB. TNFIs are known to be the leading reasons for TST conversion and tuberculosis. Similarly, etanercept was one of the most frequent agents that caused LTBI in our study and although not statistically significant, canakinumab, which is an agent that is supposed to have a lower effect on TST conversion, was the agent that most commonly caused TST conversion in our study. This is a new finding in pediatric literature and should be supported by future studies.

## Authors' contributions

All authors significantly contributed to the work reported in this article. TBD, GTD, BS and FA were responsible for collecting data and writing the initial and final manuscript. TBD and AOP assisted with technical aspects, reviewing, and editing the final article.

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