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Tuberculosis in children and adolescents using biological agents: a nationwide cohort study from Turkey

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Abstract

Background The use of biological agents in various diseases in children has been increasing and the risk of tuberculosis (TB) increases with them. We aimed to investigate the role of biological agents in children diagnosed with TB in a moderate level of TB country where TB screening is mandatory before and during biological agent treatment.

Study design and methods This was a retrospective cohort study. All patients who were 0–18 years old and diagnosed with TB-related ICD-10 in the national health database system between 2018 and 2023 were included in the study. The number of patients, demographic characteristics, treatments used by the patients, underlying diseases, and organ involvement of TB were recorded. Children using and not using biological agents were compared.

Results A total of 4351 children were diagnosed with TB, and 1.9% of them were treated with biological agents. The age of diagnosis was older ($p=0.001$), and both pulmonary and extrapulmonary involvement was more frequent in children using biological agents ($p=0.001$). Pulmonary involvement was more frequent in rheumatological diseases ($p=0.001$), and naproxen usage was higher in children with pulmonary involvement ($p=0.014$). Naproxen was found to increase the risk of pulmonary TB in children using biological agents (OR:3.824, $p=0.033$).

Conclusions The low frequency of TB may be due to effective TB screening before and during the therapy. The age of diagnosis was older, pulmonary and extrapulmonary TB involvement was more common in children using biological agents, which may be related to the immunosuppressive effects. Children using biological agents who are also using naproxen should be closely followed up in terms of pulmonary TB.

Keywords Biological agents, Children, Naproxen, Tuberculosis

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Introduction

Biological agents, especially tumor necrosis factor-α (TNFα) blocking agents, have radically changed the therapeutic approach and disease courses, and nowadays they are used in various inflammatory and immune-mediated diseases [1, 2]. Biologic agents inhibit specific components of the immune system, such as cytokines, cytokine gene expression, and their complex interactions, which have revolutionized the treatment options in pediatric diseases such as juvenile idiopathic arthritis (JIA), familial Mediterranean fever (FMF), psoriasis, inflammatory bowel disease, etc [2, 3].,.

Despite the numerous benefits of biological agents, the development of active tuberculosis disease (TB) should be expected when using any biological agents, especially with anti-TNF activity. It is well known that the risk of developing TB was found to be 1.39–5.98 times higher in patients treated with biological agents than in those treated with other immunosuppressants or placebo [4, 5]. The risk of TB in patients may be associated with immunosuppression linked to the underlying disease, as well as due to the use of immunosuppressive medications, such as corticosteroids and biological agents [6]. There are many reports about the risk of TB in adults, however, studies in children are limited and with small groups of patients [5–8]. Children with many chronic diseases may also use anti-inflammatory drugs which may also affect the immune system. Naproxen is a non-selective cyclooxygenase (COX) inhibitor and catalyzes the conversion of arachidonic acid into prostaglandin [9]. There is limited data about the relation of nonsteroidal anti-inflammatory drugs with TB in children.

Turkey has a moderate level of TB. According to national TB surveillance data, the TB incidence was reported to have declined from 29.4 in 2005 to 10.6 (per 100,000 persons) in 2020. Although TB incidence rates have decreased, Turkey remains one of the 18 high-priority TB countries in the WHO European Region [10–12]. Children who need to use biological agents should be screened in terms of TB and latent TB infection (TBI) before initiating the treatment. Also during the treatment, they have to visit pediatric pulmonology and/or infectious disease every six months and annually have to be retested with a tuberculin skin test (TST) and/or interferon-gamma release assay (IGRA). Without the approval of pediatric pulmonology or infectious diseases, they cannot use the biological agents in our country. Although there are some reports about TB in children using biological agents in Turkey, the exact results across the whole country, are lacking.

In this study, we aimed to investigate the clinical features of children and adolescents using biological agents diagnosed with TB in Turkey, which is a moderate-level TB country.

Methods

This was a retrospective cohort study. The anonymized health records of all children and adolescents between 0 and 18 years with TB who were admitted to public, private, and university health institutions were collected via the e-health database of the Republic of Turkey Health Ministry. This study was conducted according to the Declaration of Helsinki and received approval from the Republic of Turkey Ministry of Health with a waiver for informed consent for retrospective data analysis and the health information privacy law (Date:11/21/2019, Number:95741342-020).

TB is a notifiable disease in Turkey. When a patient has an ICD-10 code related to TB detailed reports and diagnostic results must be entered into the system, and the diagnosis requires approval from a medical board. TB diagnosis was confirmed based on a combination of clinical, radiological, and microbiological findings in line with national TB surveillance guidelines. To minimize misclassification bias, cases were only included if they met the Ministry of Health's standardized TB diagnostic criteria. ICD-10 codes related to TB *(A15, A15.0, A15.1, A15.2, A15.3, A15.4, A15.5, A15.6, A15.7, A15.8, A15.9, A16, A16.0, A16.1, A16.2, A16.3, A16.4, A16.5, A16.6, A16.7, A16.8, A16.9, A17, A17.0, A17.1, A17.8, A17.9, A18, A18.0, A18.1, A18.2, A18.3, A18.4, A18.5, A18.6, A18.7, A18.8, A19, A19.0, A19.1, A19.2, A19.8, A19.9, A30.1, A30.2, J65, K23.0, K67.3, K93.0, M01.1, M01.10, M01.11, M01.12, M01.13, M01.14, M01.15, M01.16, M01.17, M01.18, M01.19, M49.0, M49.00, M49.01, M49.02, M49.03, M49.04, M49.05, M49.06, M49.07, M49.08, M49.09, M90.0, M90.00, M90.01, M90.02, M90.03, M90.04, M90.05, M90.06, M90.07, M90.08, M90.09, N33.0, N74.0, N74.1, P37.0)* were reviewed from the national health database system of the Republic of Turkey Health Ministry. Patients with incomplete clinical or diagnostic data were excluded from the study. Only cases with documented confirmation of TB diagnosis, treatment records, and follow-up data were included to reduce selection bias.

Existing data were obtained by querying the database for - the number of patients, age at diagnosis, current age, gender, organ involvement of TB, underlying diseases, drug treatments (biological agents and others) classified according to Anatomical Therapeutic Chemical (ATC) codes, and the number of deceased patients. Subgroup analyses were conducted to assess whether specific diseases were associated with a higher risk of TB.

Children using and not using biological agents were compared. Also, children using biological agents were compared in terms of pulmonary and extrapulmonary TB involvement.

Statistical analyses were performed using IBM SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA).

Table 1 Comparison of demographic and clinical data of children with TB using and not using biological agents

	Children with TB not using biological agents *n* = 4268 (%)	Children with TB using biological agents *n* = 83 (%)	*P*
Gender Female	2110 (50.4)	46 (55.4)	0.362
Male	2118 (49.6)	37 (44.6)	
Age of diagnosis (year)	10.2 ± 5.6	12.3 ± 4.1	0.001
Involvement			
Pulmonary	2593 (60.8)	48 (57.8)	0.001
Extrapulmonary	1580 (37.0)	25 (30.1)	
Pulmonary + Extrapulmonary	95 (2.2)	10 (12)	
Exitus	161 (3.8)	3 (3.6)	1.00

Table 2 Underlying diseases of children using biological agents

Underlying diseases	*n*	%
Juvenile idiopathic arthritis	38	45.7
Familial Mediterranean Fever	11	13.2
Crohn's Disease	9	10.8
Iridocyclitis	6	7.2
Ulcerative colitis	4	4.8
Anemia	3	3.6
Immunodeficiency	3	3.6
Renal transplantation	2	2.4
Psoriasis	2	2.4
Vasculopathy	1	1.2
Encephalitis	1	1.2
Lymphoma	1	1.2
Not specified	2	2.4

Table 3 List of biological agents used by the children with TB

Biological agent	*n*	%
Adalimumab	45	54.2
Etanercept	20	24.1
Infliximab	11	13.3
Tocilizumab	11	13.3
Canakunimab	7	8.4
Certolizumab	3	3.6
Abatacept	3	3.6
Rituximab	3	3.6
Eculizumab	2	2.4
Ustekinumab	1	1.2
Secukinumab	1	1.2
Ixekuzimab	1	1.2
Ranibizumab	1	1.2

In descriptive statistics, categorical variables were expressed as numbers and percentages, while continuous variables were presented as mean ± standard deviation. The Pearson chi-square test and Fisher's exact test were used for categorical variables. The Mann–Whitney U test was applied for non-normally distributed continuous variables, while the independent sample t-test was used for normally distributed data. To account for potential confounders, multivariate logistic regression analysis was performed, adjusting for variables such as age, gender, underlying diseases, and concurrent medication use. Multivariate logistic regression models were used to identify independent risk factors. Variables with a p-value < 0.200 in univariate analyses were included in the model, as this threshold allows for the consideration of potential confounders that may not reach traditional significance levels in univariate analysis. Multicollinearity was checked before finalizing the model, and the goodness-of-fit was assessed using the Hosmer-Lemeshow test. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for each included variable. A p-value of < 0.05 was considered statistically significant.

Results

During the study period, 4351 children and adolescents were diagnosed with TB, and 83 (1.9%) of them were using biological agents. All data about the children was complete and none of the children was excluded from the study. There was no difference in terms of gender between the children with TB using and not using biological agents; however, age at TB diagnosis was higher in children using biological agents ($p = 0.001$). Of all the children, 105 had disseminated TB; 95 children were in the not-using biological agent group, while 10 of them were in the using biological agent group. Moreover, both pulmonary and extrapulmonary involvement was more frequent in children using biological agents. A comparison of demographic and clinical data of children with TB using and not using biological agents is shown in Table 1.

The most common underlying diseases were JIA (47.5%) and FMF (13.2%). The list of underlying diseases of children using biological agents is shown in Table 2. The most common biological agents used by the children were TNF inhibitors (95.2%), and then IL-6 blockers (11%) and IL-1 blockers (11%); while 26 patients used two different biological agents during the study period. The list of biological agents used by children with TB is shown in Table 3. Most of the children with TB who were prescribed biological agents were also using other treatments such as steroids, NSAIDs, and

other immunosuppressants. The list of other drugs used by the children of TB using biological agents is shown in Table 4.

When we compared the other drugs between the children with TB using and not using biological agents, cortico-steroids, naproxen, colchicine, azathioprine, mesalazine, sulfasalazine, and cyclosporin use were higher in children with TB using biological agents ($p < 0.05$). The comparison of the treatments between the two groups is shown in Table 5.

In children using biological agents ($n = 83$), 58 (69.9%) of them had pulmonary involvement and 25 (30.1%) had extrapulmonary involvement. There were no differences in terms of gender and age between the two groups, however, children with pulmonary involvement had more frequent comorbid rheumatological diseases (72.4% vs. 32%; $p = 0.001$). The use of TNF inhibitors and other biological agents was similar in both groups ($p > 0.05$). However, among the other treatments, only naproxen usage was higher in children with pulmonary involvement (44.8% vs. 16%; $p = 0.014$). A comparison of demographic and clinical data of children with TB using biological agents in terms of pulmonary and extrapulmonary involvement is shown in Table 6.

In the logistic regression analysis, naproxen use was found to increase the risk of pulmonary TB in children using biological agents (OR:3.824, $p = 0.033$).

Table 4 List of other medications used by the children with TB using biological agents

Other drugs	*n*	%
Steroid	76	91.5
Naproxen	30	36.1
Diclofenac	19	22.1
Colchisin	17	20.5
Azathioprine	16	19.3
Mesalazin	14	16.9
Sulfasalazine	10	12
Cyclosporin	5 6	6
Methotrexate	1	1.2

Table 5 The comparison of the treatments between the children with TB using and not using biological agents

	Children with TB not using biological agents *n* = 4268 (%)	Children with TB using biological agents *n* = 83 (%)	*P*
Steroid	708 (16.6)	76 (91.5)	0.001
Naproxen	462 (10.8)	30 (36.1)	0.001
Diclofenac	675 (15.8)	19 (22.1)	0.094
Colchisin	63 (1.5)	17 (20.5)	0.001
Azathioprine	19 (0.4)	16 (19.3)	0.001
Mesalazin	16 (0.4)	14 (16.9)	0.001
Sulfasalazine	6 (0.1)	10 (12)	0.001
Cyclosporin	47 (1.1)	5 (6)	0.003
Methotrexate	0 (0)	1 (1.2)	-

Table 6 Comparison of demographic and clinical data of children with TB using biological agents in terms of pulmonary and extrapulmonary involvement

	Pulmonary involvement *n* = 58 (%)	Extrapulmonary involvement *n* = 25 (%)	*P*
Gender Female	32 (50.4)	14 (55.4)	0.945
Male	26 (49.6)	11 (44.6)	
Age of diagnosis (year)	12.4 ± 4.1	12.2 ± 4.4	0.908
Underlying disease			
Rheumatological (FMF, JIA,.)	42 (72.4)	8 (32)	0.001
Others (Crohn's, ulcerative colitis,…)	16 (27.6)	17 (68)	
Use of TNF inhibitor	45 (77.6)	19 (76)	0.542
Use of naproxen	26 (44.8)	4 (16)	0.014

FMF: Familial mediterranean fever, JIA: Juvenile idiopathic arthritis; TNF: Tumor necrosis factor

Discussion

Tuberculosis is a prominent concern in children using biological agents. We found that children with TB using biological agents are older, and both pulmonary and extrapulmonary involvement are more common in these children. Moreover, naproxen which is usually used by children with many inflammatory diseases, seems to increase the risk of pulmonary TB in children using biological agents.

Many studies in adults have shown that TB incidence increases in the population treated with biological agents in various countries [13]. The risk of active TB was found to increase by approximately 1.6–25.1 times in adults with TNF antagonist therapy [14]. An integrative review of 37 studies between 2010 and 2021, in children and adolescents aged 0–19 years with rheumatologic diseases using biological drugs, showed that 26 cases had pulmonary TB and 4 cases had extrapulmonary TB [6]. The lower rate of TB in children using biological agents was found to be associated with the screening and appropriate treatment of TBI cases before initiating the use of a biological drug [6]. Similarly, mandatory TB screening before and during the biological agent treatment may have lowered the incidence of TB in our study.

The largest study about TB in children using biological agents was published in 2020. It was conducted in 32 European countries and 66 centers. Only 19 patients with TB were reported during 3 years of follow-up. The low number of TB cases was found to be the result of several factors, such as lower incidence of TBI in children compared with adults, low background TB prevalence in countries where anti–TNF-α agents are commonly used (which applies to all Northern, Western, and Southern European countries), and successful implementation of TBI screening before commencing anti–TNF alpha

therapy in the pediatric setting [15]. The higher number of TB cases in our study may be related to the longer duration of the study period (5 yrs), the higher incidence of TB in Turkey, compared to the European countries, and strict TB follow-up before and during the biological agent treatment.

In our study, the age of children with TB using biological agents was higher, than those who were not using biological agents. It is known that adolescents have increased susceptibility to TB [16]. Although the reasons are not completely understood, sex hormones, changing social contact patterns, and immunological changes are thought to have a role [16, 17]. Due to these factors, the older age of children with TB using biological agents may contribute to TB susceptibility.

Both pulmonary and extrapulmonary TB involvement was detected more frequently in children using biological agents in our study. In the European 'PTBNET' study, all children using biological agents had severe TB and most of them had disseminated TB [15]. It is well known that *M. tuberculosis* can migrate from the primary infection site i.e. lungs, via the lymphatic system and bloodstream to the whole body. Although the detailed mechanisms of bacterial dissemination remain unclear, there are several risk factors for it [18]. Both host and bacterial factors such as HIV infection, race/ethnicity, gender, age, and bacterial genes may have a role in the dissemination of TB. Host genetic factors and immune state may also contribute to dissemination. The innate immune response to *M. tuberculosis* is primarily through macrophages and many intracellular signaling pathways. Bacterial antigen pattern recognition receptors, such as Toll-like receptors 2, recognize *M. tuberculosis* and initiate the innate immune response to infection [19]. Many cytokines also have a role in these pathways where TNF alpha plays the main role in the inflammatory process in TB [13, 18]. It was shown that biological agents cause disseminated TB in previous studies [18, 20, 21] and blocking the cytokines, especially TNF alpha and other cytokines in the immunopathogenesis of TB may facilitate the dissemination. Also, it should be kept in mind that underlying diseases and other anti-inflammatory and/or immunosuppressive medications used by these children may also contribute to both the development of TB and dissemination.

Previous studies showed that HIV infection, female gender, end-stage renal disease, excessive alcohol use, geographical origin, and age < 15 years were the risk factors for extrapulmonary TB [22–24]. Although there are limited studies about extrapulmonary TB in children, two recent studies had a larger cohort of children with extrapulmonary TB in China and the Czech Republic [25, 26]. The ratio of pulmonary TB to extrapulmonary TB was 79.8/20.2 in the 35-year cohort Chezc Republic and, the most common organ involvement was lymph nodes [25]. The other study showed that pulmonary TB was present in 54%, extrapulmonary TB was 17.% and both pulmonary TB and extrapulmonary TB were present in 28% of the children between 2015 and 2018, from 22 hospitals in China [26]. Gender was not found to be a risk factor for extrapulmonary TB in children in both studies [25, 26]. A higher rate of low birth weight, worse diagnosis at first visit, and worse hospitalization plan were found to be associated with extrapulmonary TB, which we could not evaluate these parameters in our study [26]. These differences between the countries may be related to different TB incidences and diagnostic and therapeutic approaches to TB.

In children using biological agents, pulmonary involvement was more common in children with rheumatological diseases and extrapulmonary involvement was more common in children with other systemic inflammatory and immune-mediated diseases. There is no explanation for this finding in the literature. Most of the children in our study had rheumatological diseases, and inflammatory bowel diseases in our study, however, we did not have detailed clinical data on underlying diseases. We can speculate that in children receiving biological agents, although all clinicians are alert for pulmonary TB, symptoms related to TB in organs other than the lung, may be overlooked. This may be attributed to symptoms associated with the primary systemic disease, such as Crohn's, and ulcerative colitis, for example. Also, underlying inflammation and impaired tissue integrity may facilitate TB in these organs.

Naproxen was found to increase the pulmonary TB risk in children using biological agents in our current study. A population-based study from Taiwan showed that traditional NSAIDs increased the risk of TB whereas COX-2 selective inhibitors did not increase it [27]. Although they did not explain the causative mechanisms, it is a controversial study about NSAIDs in the literature. Ibuprofen is another non-selective COX inhibitor and is frequently used to alleviate TB-related symptoms. A study in mice showed that Ibuprofen administration reduced bacillary load and affected lung area, leading to an increase in survival [28, 29]. However, recently controversial studies have been published, which suggest potential unfavorable effects with impaired macrophage capacity to control mycobacterial growth in patients with TB receiving COX-2 inhibitor treatment [30]. Another study showed that COX inhibitor (celecoxib and ibuprofen) treatment impairs the formation of immune memory, reduces Type 1 helper T cell function/differentiation, and diminishes the protective capacity of CD4 T cells which can pose a risk of TB progression in *M. tuberculosis-infected* subjects [31]. However, there is no study in the literature about naproxen and TB in children. We must keep in

mind that all these studies were conducted in mice and adult patients and that children's immune systems may differ.

There are some limitations of this study. As a retrospective study utilizing a national database, inherent challenges include selection bias, potential data recording errors, and limited access to detailed clinical information. Additionally, due to the relatively small proportion of children using biological agents (1.9% of the total cohort), the statistical power of subgroup analyses is limited, which may impact the robustness and generalizability of the findings. Furthermore, while national TB surveillance systems ensure systematic case reporting, variations in clinical practice and data completeness may influence the interpretation of results. Nevertheless, this is one of the largest pediatric studies on tuberculosis in children using biological agents, contributing valuable insights that may support ongoing public health efforts in TB prevention and management.

In conclusion, we present the findings of children with TB using biological agents in a moderate-level TB-prevalent country. The low frequency of TB in children using biological agents may be due to effective TB and TBI screening before starting treatment, and close surveillance during the therapy. The age at diagnosis was greater; pulmonary and extrapulmonary TB involvement was more common in children using biological agents, which may be related to the immunosuppressive effect of drugs. Also, children using biological agents, especially those who are also using naproxen, should be closely followed for any development of pulmonary TB. Electronic health database systems are useful for the follow-up of chronic diseases. It is important to analyze the clinical data obtained from patients and develop relevant and effective health policies regarding diagnosis, treatment, and follow-up. With the improvement of these electronic systems, we can have more detailed, accurate data about pediatric patients and diseases.

Abbreviations

COX	Cyclooxygenase COX
TB	Tuberculosis
TNFα	Tumor necrosis factor-α

Author contributions

TSE, ATA, NA had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. VM, SC, MMU and SB contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript. All authors approved the final version to be published.

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Data availability

All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

This study was conducted according to the Declaration of Helsinki and received approval from the Turkish Ministry of Health with a waiver for informed consent for retrospective data analysis and the health information privacy law (Date:11/27/2019, Number:95741342-020).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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