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Latent Tuberculosis Infection in Children with Pediatric Rheumatologic Diseases Treated with Canakinumab

Kanakinumab Tedavisi Alan Pediyatrik Romatolojik Hastalıklı Çocuklarda Latent Tüberküloz Enfeksiyonu

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Abstract

Objective: Knowledge of the long-term safety of canakinumab (CAN) regarding tuberculosis (TB) in pediatric rheumatologic diseases is limited. To determine the incidence and disease course of latent TB of patients treated with CAN in two centers from Türkiye.

Material and Methods: The hospital charts were analysed retrospectively. Tuberculin skin test (TST) and/or QuantiFERON-TB Gold (QFT-G) test were used to screen for TB. Chest X-rays were performed prior to therapy and then yearly. Patients were evaluated for symptoms of active TB.

Results: A total of 67 patients were investigated. The median duration of CAN use was three years (ranging from 2-4 years). Nine patients (9/67, 13.4%) had positive TST and one patient (1/11, 1.4%) had positive QFT-G with normal chest X-ray prior to therapy. They were given isoniazid (INH) prophylaxis for latent TB. During follow-up 11 patients (11/56, 19.6%) with TST conversion and two patients (2/22, 9%) with positive QFT-G were given INH prophylaxis. All patients receiving INH prophylaxis had normal chest X-rays and no active TB symptoms. One patient experienced persistent cough and fever at the fourth year of CAN therapy though TST and QFT-G test were negative prior to and during CAN treatment. Chest tomography revealed findings suggestive of pulmonary TB, anti-TB treatment was started. The remaining patients had not developed active TB disease during follow-up.

Öz

Giriş: Pediyatrik romatolojik hastalıklarda kanakinumabın (KAN) uzun dönemde tüberküloz (TB) açısından güvenliği hakkında yeterli bilgi bulunmamaktadır. Bu çalışmada, Türkiye'deki iki merkezde KAN ile tedavi edilen hastalarda latent TB insidansını ve hastalık seyrini değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Hastane kayıtları retrospektif olarak incelendi. TB taraması için tüberkülin deri testi (TDT) ve/veya QuantiFERON-TB Gold (QFT-G) testi kullanıldı. Tedaviden önce ve tedaviden sonra yıllık olarak akciğer grafileri çekildi. Hastalar aktif TB semptomları açısından değerlendirildi.

Bulgular: Çalışmaya 67 hasta dahil edildi. Ortalama KAN kullanım süresi üç yıldı (2-4 yıl). Dokuz hastada (9/67, %13.4) tedavi öncesinde pozitif TST ve bir hastada (1/11, %1.4) normal akciğer grafisi ile birlikte pozitif QFT-G vardı. Bu hastalara latent TB için izoniazid (İNH) profilaksisi verildi. Takip sırasında TST konversiyonu olan 11 hastaya (11/56, %19.6) ve pozitif QFT-G'si olan iki hastaya (2/22, %9) İNH profilaksisi verildi. İNH proflaksisi alan tüm hastaların akciğer grafileri normaldi ve aktif TB semptomları yoktu. Bir hastada KAN tedavisi öncesinde ve sırasında TST ve QFT-G testi negatif olmasına rağmen tedavinin dördüncü yılında inatçı öksürük ve ateş görüldü. Göğüs tomografisinde akciğer TB'sini düşündüren bulgular saptandı ve anti-TB tedavi başlandı. Diğer hastalarda takip sırasında aktif TB gelişmedi.

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Conclusion: This study suggests that although frequency of latent TB infection in children treated with CAN is not low in a TB endemic country, progression to TB disease under CAN treatment is not a common finding in our study.

Keywords: Canakinumab, latent tuberculosis, pulmonary tuberculosis

Sonuç: Bu çalışma, TB endemik bir ülkede KAN ile tedavi edilen çocuklarda latent TB enfeksiyonu sıklığının düşük olmadığını ancak KAN tedavisi altında TB hastalığına ilerlemenin de yaygın olmadığını göstermektedir.

Anahtar Kelimeler: Kanakinumab, latent tüberküloz, pulmoner tüberküloz

Introduction

The IL-1 cytokine family plays a central role in orchestrating the inflammatory response. It intricately controls a network of selected pro-inflammatory mediators and orchestrates the subsequent expression of integrins in both leukocytes and endothelial cells (1). Increasing knowledge about the pathogenesis of rheumatological diseases and understanding the effective therapeutic properties of IL-1 inhibitors has led to major advances in the management of rheumatic diseases (2,3). IL-1 inhibitors have therapeutic implications in autoinflammatory disease (AID), systemic-onset juvenile idiopathic arthritis (SJIA), adult-onset Still's disease and gouty arthritis. Moreover, their effectiveness was shown in conditions such as familial Mediterranean fever (FMF), Behcet's disease, uveitis, and idiopathic recurrent acute pericarditis (4-8). In pediatric rheumatic diseases (PRD), long-term drug safety monitoring is crucial as anti-IL-1 treatments are often required long-term. Given the prominent role of the IL-1 pathway in pathogen defense, theoretical concerns have emerged regarding the potential risk of serious or opportunistic infections with IL-1 blockade. Notably, animal studies indicate that IL-1 targeted therapies may increase susceptibility to active tuberculosis (TB) (9,10). Furthermore, the demonstration of IL-1β production in lung granulomas of individuals with active TB adds to these concerns (11). Additionally, specific single nucleotide polymorphisms in the IL-1β gene have been identified, affecting the risk of extrapulmonary TB in the general population (12).

Reporting of the use of anti-IL1 therapy in patients with latent TB infection are limited. Case reports suggest patients with latent TB treated with anti-IL therapy did not progress to active TB (13-15). The European Association of Clinical Microbiology and Infectious Diseases recommendation suggested that TB screening should be considered for patients using anti-IL-1 therapies (16). Whilst there are a few studies reporting the long-term efficacy of anti-IL-1 treatments in pediatric rheumatologic diseases with follow-up to five years; to the best of our knowledge, there is only one publication reporting a screening program and its results for latent TB in children using anti-IL1 treatment (17-20). The objective of this study is to assess the incidence of latent TB infection and examine the clinical course of patients undergoing treatment with canakinumab (CAN), a human immunoglobulin G1 (IgG1) anti-IL-1β monoclonal antibody (21). The study will be conducted at two pediatric rheumatology centers in Türkiye.

Materials and Methods

Study Population

The hospital charts of patients who were treated with CAN for at least one year in two referral pediatric rheumatology centers between February 2012 and March 2020 in İzmir, Türkiye (Dokuz Eylül University Hospital and Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital were retrospectively reviewed). In total 67 patients were investigated. Forty FMF, 16 SJIA, 6 mevalonate kinase deficiency (MKD) and five cryopyrin associated periodic syndrome (CAPS) patients were evaluated. Canakinumab was administered 2-4 mg/kg for every eight weeks in patients with FMF and every four weeks in patients with SJIA, CAPS and MKD. Patients up to 21 years of age were included, as this is the cut-off for transition to adult rheumatology care in Türkiye.

The following demographic and clinical characteristics were recorded: Age, gender, primary disease, other therapies administered, immunosuppressive drug use prior to CAN, duration of disease at the administration of CAN therapy, duration of CAN use, presence of latent TB infection (LTBI), and use of prophylactic anti-TB medication.

Follow-up Protocol

Patients underwent a thorough evaluation for signs and symptoms of active TB before initiating CAN therapy. None of the patients exhibited a history or current signs and symptoms of active TB during the screening process. Additionally, none of the patients reported recent close contact with an individual diagnosed with active TB.

Preliminary TB screening for patients involved the tuberculin skin test (TST) and/or the QuantiFERON-TB Gold (QFT-G) test. The Mantoux method was employed for TST, involving the intradermal injection of five tuberculin test units of purified protein derivative on the volar surface of the forearm. Results were evaluated based on the maximum diameter of induration (in millimeters) at 48-72 hours post-injection. For patients not previously treated with immunosuppressive therapy, a TST induration size of ≥15 mm (for those vaccinated with BCG) and ≥10 mm (for those not vaccinated with BCG) was considered a positive test. BCG vaccination status was determined by the presence of a scar on the upper arm. In cases of prior immunosuppressive drug use, the TST cut-off limit was set at ≥5 mm. Patients with either a positive TST or QFT-G result, but ruled out for active TB, received prophylactic isoniazid (INH) treatment (10 mg/kg/day, up to 300 mg/day) for latent TB for a minimum

of one month before initiating CAN, with a total treatment duration of nine months. Chest radiographs were performed prior to therapy and then yearly. All patients underwent TST screening before the initiation of CAN. For patients currently on immunosuppressive therapy, an additional screening with QFT-G was conducted before CAN administration. In cases where TST results were anergic, both chest X-ray and TST were repeated after three months. Throughout the CAN therapy period, patients were regularly monitored for signs and symptoms of active TB by an infectious disease specialist every three months, following the guidelines outlined by the Turkish Ministry of Health for the use of biologic agents (22). Tuberculin skin test and/or QFT-G, along with X-ray screenings, were conducted annually. Tuberculin skin test conversion was defined as a change ≥5 mm between two TSTs performed with an interval of at least three months. If TB was suspected during the study, comprehensive TB testing (TST, QFT-G, and chest radiograph) and examinations of sputum/early morning gastric fluid for acid-fast bacilli, as well as chest tomography imaging, were performed. Routine laboratory analyses, including complete blood count, alanine aminotransferase, and aspartate aminotransferase levels, were conducted every 4-8 weeks.

Statistical Analysis

Statistical analysis of the variables was conducted using SPSS software version 15. Normal distribution of the data was assessed through the Shapiro-Wilk test and variation. Descriptive analyses were presented with medians and interquartile range (IQR), while categorized variables were expressed as numbers and percentages. A significance level of 0.05 was considered statistically significant.

The study received approval from the Local Ethical Committee (Ethics approval number: 2020/03-43) and adhered to the principles outlined in the Declaration of Helsinki.

Results

The median age of starting CAN treatment was 10 (range 5-15) years. Thirty-nine (58.2%) patients were male. The median age was five years six months (ranging from 3 to 7 years) at diagnosis. The median time of diagnosis until start of CAN was three (range 2-4) years. The median duration of CAN use was three (range 2-4) years. Therapies used prior to CAN treatment included colchicine (n= 47), anakinra (n= 13), prednisolone (n= 16), methotrexate (n= 15), etanercept (n= 4), cyclosporine-A (n= 2), and sulphasalazin (n= 1) (Table 1). All patients were screened with TST. QFT-G was assessed in 11 patients before the initiation of CAN, with 10 out of 11 yielding negative results. Among the 67 patients, nine exhibited positive TST results, and one patient, with a negative TST result, tested positive for QFT-G, while also having a normal chest X-ray before therapy. Consequently, all individuals with positive TST or QFT-G results, excluding active TB, received INH prophylaxis for latent TB (Table 2).

Table 1. Demographics data of the patients (n= 67)

Gender, female/male	28/39
Current age (years)*	14 (10-18)
Median age at diagnosis (years)*	5.5 (3-7)
Median follow up (years)*	6 (3.5-11)
The median age at CAN onset (years)*	10 (5-15)
The median duration of CAN use (years)*	3 (2-4)
The median time of diagnosis until start of CAN (years)*	3 (1-7.5)
Disease, n (%)	
FMF	40 (59.7)
SJIA	16 (23.8)
MKD	6 (8.9)
CAPS	5 (7.4)
Drugs prior/with CAN, n (%)	
High dose prednisolone	16 (23.8)
Anakinra	13 (19.4)
Colchicine	47 (70.1)
Etanercept	4 (5.9)
Methotrexate	15 (22.3)
Cyclosporine-A	2 (2.9)
Sulphasalazine	1 (1.4)

CAN: Canakinumab, CAPS: Cryopyrin associated periodic syndromes, FMF: Familial Mediterranean fever, MKD: Mevalonate kinase deficiency, SJIA: Systemic juvenile idiopathic arthritis.
*Median (interquartile range).

All patients underwent screening with TST and/or QFT-G for LTBI during follow-up. Eleven patients experienced TST conversion over the follow-up period (three in the first year, six in the second year, and two in the third year). Additionally, QFT-G was assessed in 22 patients during follow-up, with two yielding positive results. One of them had previously received INH prophylaxis before CAN therapy, while the other had not undergone TST screening (Table 2).

Patients with a positive QFT-G test and those experiencing TST conversion were further evaluated for active TB. These individuals exhibited normal chest X-rays and reported no symptoms indicative of active TB (cough, fever, night sweats, and/or weight loss). Further diagnostic tests, including mycobacterial cultures and *Mycobacterium tuberculosis* polymerase chain reaction (PCR) of induced sputum (via hypertonic saline nebulization) or morning gastric aspirates, returned negative results. Consequently, they were prescribed INH prophylaxis for latent TB. Importantly, none of the patients developed elevated liver enzymes during TB prophylaxis.

A seven-year-old female patient developed constitutional symptoms as well as cough. This patient experienced persistent cough, fever, night sweats and chest pain despite two-weeks of ceftriaxone and clarithromycin treatment at the fourth year of CAN therapy. Her medical history was notable for a diagnosis of mild asthma and recurrent bronchopneumonia. Bronchopneumonia episodes were diagnosed by the

Table 2. Results of LTBI screening

Prior to CAN, n (%)	Positive TST	9*/67 (13.4)
	Positive QFT-G test	1*#/11 (9.0)
	Isoniazid prophylaxis	10/67 (14.9)
During CAN, n (%)	Positive TST	11*/56 (19.6)
	Positive QFT-G test	2*¥/22 (9.0)
	Isoniazid prophylaxis	13/67 (19.4)
Total, n (%)	LTBI positive	23/67 (34.3)
	Active Mtb infection	-

CAN: Canakinumab, LTBI: Latent tuberculosis infection, Mtb: *M. tuberculosis*, QFT-G: QuantiFERON-TB gold, TST: Tuberculin skin test.
*Their chest X-rays were normal. None of them had active TB symptoms, such as; cough, fever, night sweats and weight loss. The mycobacterial cultures, *M. tuberculosis* PCR of induced sputum (via hypertonic saline nebulization) or morning gastric aspirates were negative in these patients. These patients were administrated isoniazid prophylaxis for latent TB.
#One who had negative TST had positive QFT-G.
¥One already had received INH prophylaxis prior to CAN, one other was not screened with TST.

department of pediatric chest diseases and reviewed by allergy and immunology specialists. The lymphocyte panel and immunoglobulin A, G and M levels were normal for age. The TST was anergic and QFT-G test was negative. The chest X-ray revealed paracardiac infiltration on the right lung and increased nodular opacity in the left perihilar area. Therefore, chest tomography was performed and revealed multiple lymph nodes (the largest 1 cm diameter) of the right paratracheal, subcarinal and bilateral hilar area, suggesting TB. As the tomography findings indicated possible TB, anti-TB treatment (INH, ethambutol, rifampicin, pyrazinamide) was started and CAN was stopped. The mycobacterial cultures and *M. tuberculosis* PCR of sputum of three consecutive days were negative. The diagnosis of TB was therefore not microbiologically confirmed. The patient completed a-12-months course of anti-TB therapy and CAN was readministered after the 3rd month of anti-TB therapy. The findings of the chest computed tomography recovered at the follow-up after three months. Canakinumab was not stopped, and the patient has had seven years treatment without any additional problems to date.

Discussion

The findings from this study indicate that, despite the relatively high prevalence of LTBI among children receiving CAN treatment, likely influenced by the endemic risk in the study country, the use of CAN does not seem to be linked to an elevated risk of active TB. Notably, only one case of TB disease was observed during the course of CAN treatment. To the best of our knowledge, this study represents the first investigation into the incidence of latent TB infection in pediatric patients undergoing CAN therapy. Additionally, the follow-up protocol for latent TB infection has not been previously outlined for CAN treatment.

Many studies have been reported investigating LTBI/TB infection during anti-TNF treatment in the pediatric population. Brunelli et al. reported that LTBI screening with TST was positive in three of 69 patients with JIA (23). None had active TB. In another study of 221 pediatric patients treated with anti-TNF drugs, three cases of LTBI were detected. While all three were positive for QFT-G, one was positive for TST. They did not report any cases of active TB (24). Kılıç et al. evaluated 144 pediatric patients with JIA and FMF treated with anti-TNF-α treatment in terms of LTBI (25). They reported 21 (14.5%) patients with positive TST prior to anti-TNF treatment, and during follow-up, seven patients (4.8%) with positive TST. These patients were given prophylaxis and TB was not observed in any patient after nine months. Türkiye, although being a low-risk region for *M. tuberculosis* infection, exhibits a high rate of LTBI among patients using anti-TNF drugs (26). However, the detection rate of active TB appears to be low in these patients. This low detection rate of active TB may be attributed to the regular screening of LTBI patients and the administration of prophylactic anti-TB treatment. Similarly, in the present study, nine patients (9/67, 13.4%) had positive TST, and one patient (1/11, 9%) had positive QFT-G prior to CAN. During follow-up eleven patients (11/56, 19.6%) with TST conversion and two patients (2/22, 9%) with positive QFT-G were given INH prophylaxis. Thirty four point five percent patients (23/67) were developed LTBI during the study period. One patient with MKD was treated with anti-TB treatment due to the tomography findings. It was shown that MKD patients have some kind of immune deficiency (not shown easily by basic immunology screening tests) and have a tendency to develop recurrent lung infections irrespective of the immunosuppressive drugs (27). In a retrospective multicenter study by the Paediatric Tuberculosis Network European Trials Group, including patients <18 years who developed TB disease during anti-TNF-α therapy, 19 patients were reported to develop active TB. Three-quarters had miliary TB, which was associated with significant morbidity and mortality. They reported that LTBI screening was performed in 15/19 patients prior to anti-TNF-α therapy, but only one

LTBI was identified. They suggested that LTBI screening was frequently falsely negative, likely due to immunosuppressants impairing test performance (28). Moreover, since most of these patients had inflammatory bowel disease, they need more immunosuppressive treatment that makes them more susceptible to any opportunistic infection. In our study, there were 16 patients who received immunosuppressive treatment prior to CAN, and only one had positive TST. Three patients had TST conversion during follow-up. None of them had active TB.

The relationship between anti-TNF drugs and LTBI/TB was reported by many studies; however, studies regarding the relationship between IL1 inhibitors and LTBI/TB was limited. The impact of CAN was investigated in 144 patients diagnosed with systemic juvenile idiopathic arthritis during the five-year long-term extension of the phase III pivotal trials. The results of this study revealed four opportunistic infections (toxoplasmosis, cytomegalovirus infection, Salmonella gastroenteritis, and adenovirus infection) in a single patient. The investigator suspected that two of these events were related to CAN. Fortunately, all events were successfully resolved following appropriate treatment. Notably, no cases of TB were reported (29). In addition, the presence of activated TB was not reported in two large cohort studies examining the long-term surveillance of patients using biological agents diagnosed with SJIA (30,31). The study reported from Türkiye, it was reported that among 162 JIA patients treated with various biologicals; among them were 13 JIA patients treated with CAN, two of them developed lung TB over time (32). A randomized, double-blind trial of CAN, the CANTOS trial, included more than one thousand adult patients who had a persistent pro-inflammatory response with previous myocardial infarction. Canakinumab was administered in these patients for evaluating whether it could prevent recurrent vascular events. Six TB cases were reported during the trial however, the rates were similar in CAN group and the placebo group (33). However, no LTBI screening was performed in these studies.

Studies of LTBI screening in relation to the use of anti-IL-1 drugs are limited to case reports, with the exception of one study. The study reported on 121 PRD patients treated with different biologicals, including 18 PRD patients treated with CAN. Three of 12 CAN patients were reported to have a TST conversion during follow-up (25%). The results are similar to our study (20). A single case report documented the reactivation of a prior pulmonary *M. tuberculosis* infection in a patient with rheumatoid arthritis after 23 months of treatment with anakinra (34). Lopalco et al. reported that an adult patient with Schnitzler syndrome was found to have LTBI and was treated with anakinra. They reported that the patient could not take prophylactic anti-TB medication INH due to the development of serious adverse effects, and she did not have LTBI reactivation (35). Migkos et al. reported a case of tuberculous pyomyositis in an 85-year-old patient with rheumatoid arthritis who had been undergoing treatment with anakinra and corticosteroids for 11 years (36).

The study is a retrospective study and has some limitations. Since both TST and QFT-G could not be applied to all patients in LTBI screening in patients using CAN, it is difficult to interpret in terms of reliability between tests. However, the results of this study suggested that both TST and QFT-G along with chest X-ray is a safe method for screening LTBI. In the present study, although 34% (23/67) patients had LTBI, and one patient had anti-TB treatment under CAN treatment.

Conclusion

In conclusion, the frequency of latent TB infection in children who were treated with CAN is not low in a TB-mild burden country. The risk of active TB in patients treated with CAN is low. Although regular screening of these patients for active TB and appropriate prophylactic treatment for latent TB is important, it should be noted that the sensitivity of culture and PCR for mycobacteria is limited. Close follow-up of children treated with CAN for TB by the pediatric infectious disease department is important for early detection of TB.

Ethics Committe Approval: This study was obtained from Dokuz Eylül University non-Invasive Researches Ethics Committee (Decision no: 2020/03-43, Date: 03.02.2020).

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