A Systemic-Onset Juvenile Idiopathic Arthritis Patient with Reduced Anakinra Treatment Admitted with an Attack

Anakinra Tedavisi Azaltılırken Atakla Başvuran Sistemik Juvenil Idyopatik Artritli Hasta

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ABSTRACT

Interleukin-1 plays an important role in the pathogenesis of systemic-onset juvenile idiopathic arthritis (SoJIA), and the use of anti-interleukin-1 therapy has been increasing. We report a case of a 14-year-old male patient with SoJIA. He was in remission with anakinra treatment for almost 2 years. When we extended the therapeutic range and decreased the dose (1 mg/kg twice a week), he developed symptoms mimicking pulmonary embolism and cardiac ischemia. Increased cardiac enzyme levels and echocardiographic findings were interpreted as myopericarditis. Pulmonary computed tomography angiography revealed no thrombus. An SoJIA attack was considered because of high level of acute-phase reactants and clinical findings. Intensive immunosuppressive therapy with 2 mg/kg/day anakinra was reinitiated. Clinical and laboratory parameters began to improve on the fifth day of treatment. Thus, anti-interleukin-1 therapy is very important in patients with SoJIA. Although the treatment dose was gradually reduced and the therapeutic range was extended, it is noteworthy that the case progressed to a severe clinical condition. Broad prospective studies regarding whether, how long, and for what reasons the dosages of these drugs should be reduced in patients with SoJIA with no genetic disorders are required.

Keywords: Anakinra, interleukin-1, inflammation, systemic juvenile idiopathic arthritis, pulmonary embolism

ÖZ

Etyopatogenezinde interlökin-1 in önemli rol aldığı sistemik başlangıçlı juvenil idopatik artritte (soJIA); tedavide anti interlökin-1 kullanımı giderek artmaktadır. 14 yaşında soJIA tanılı bir erkek olgu sunuldu. Yaklaşık 2 yıldır anakinra tedavisiyle remisyonda olan olgunun, tedavi aralığı açılıp, doz azaltıldığında (1 mg/kg haftada 2 kez), pulmoner emboli ve kardiyak iskemiyi taklit eden bulguları gelişti. Artmış kardiyak enzimleri ve ekokardiyografik bulguları myo-perikardit olarak yorumlandı. Pulmoner BT anjiografide trombüs saptanmadı. Yüksek akut fazları ve kliniğiyle soJIA atağı kabul edilen hastaya, yoğun immunsupresif tedavi ve beraberinde 2 mg/kg/g anakinra tedavisi tekrar başlandı. Tedavinin 5. gününde klinik ve laboratuvar bulguları düzelmeye başladı. Bu olgu, soJIA'lı hastalarda anti-interlökin 1 tedavinin oldukça önemli olduğunu desteklemektedir. Tedavinin yavaş yavaş doz azaltılarak ve aralık açılarak kesilmiş olmasına rağmen, olgunun oldukça ağır bir klinikle başvurması dikkat çekicidir. Bu ilaçların, genetik bozukluğun olmadığı soJIA'lı hastalarda, ne kadar sürede ve nasıl kesilmesi gerektiğiyle ilgili, geniş kapsamlı prospektif çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Anakinra, interlökin-1, inflamasyon, sistemik başlangıçlı juvenil idyopatik artrit, pulmoner emboli

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Introduction

Systemic-onset juvenile idiopathic arthritis (SoJIA) is characterized by spiking fever, evanescent rash, hepatosplenomegaly, serositis, lymphadenopathy, and arthritis. The International League Against Rheumatism criteria has classified SoJIA as a subtype of JIA [1]. SoJIA is an often severe, potentially life-threatening inflammatory disease of childhood, the pathophysiology of which is poorly understood. Key players of the innate immunity system are involved in the pathophysiology of SoJIA, supporting the theory that SoJIA is an autoinflammatory syndrome [2].

According to Pascual and Hedrich, interleukin (IL)-6 and IL-1, involved in innate immunity, essentially contribute to the etiopathogenesis of SoJIA [2, 3]. The innate immunity and coagulation systems are known to have a common origin. Inflammatory cytokines and coagulation factors have been found

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to act together in sepsis and rheumatoid arthritis. In clinical SoJIA, cardiac involvement has been reported at a rate of 3%-9% [4].

The use of anti-IL-1 therapies for autoinflammatory diseases has been continually increasing, most often as an off-label therapy without standardized monitoring. Anakinra is an example of a short-duration recombinant form of an IL-1 receptor antagonist that inhibits the activity of IL-1 [5].

Randomized controlled trials of adult patients with rheumatoid arthritis revealed that anakinra, alone or with methotrexate, was an effective treatment [6]. However, there have been only a small number of studies in children, and these were non-controlled [7, 8]. Anakinra treatment in adult patients usually involves a dose of 100 mg/day, whereas in children, it varies between 1 and 6 mg/kg/day [7]. There is insufficient data in the literature about the doses and duration of biological agents in children with SoJIA.

In this study, we present a 14-year-old male patient with SoJIA undergoing reduced anakinra treatment who was admitted because of atypical attack symptoms. Anakinra treatment had previously achieved remission in this patient for almost 2 years.

Case Report

A 14-year-old male patient with SoJIA arrived in the emergency room with sudden-onset knifing chest and back pain in the left hemithorax. He reported that in the previous two days he had suffered progressive dyspnea with activity, irritating cough, and fever. This pain started initially in the front wall of the chest and then spread to the entire wall of the chest and back. He had difficulty breathing because of the pain. In his physical examinations, he was tachypneic (35/min) and tachycardic (120/min) and had a body temperature of 38.4°C, and his blood pressure was 60/40 mmHg. Respiratory sounds were normal at first examination. There was no sign of deep venous thrombosis of the lower extremities. He was taken to the intensive care unit.

He had been referred to our hospital at the age of 10, when he was diagnosed with JIA after presenting with a fever at 39°C, weakness, transient joint pain, salmon-colored rashes, and cervical lymphadenopathy. We excluded infections, malignancy, vasculitic diseases, systemic lupus erythematosus, and polyarteritis nodosa at that time. SoJIA was considered as a primary diagnosis with clinical and laboratory findings of a total leukocyte count (WBC) of 38,090/μL, a C-reactive protein (CrP) level of 254 mg/L, an erythrocyte sedimentation rate (ESR) of 79 mm/h, an immunoglobulin G (IgG) level of 1227 mg/dL, and a ferritin level of 7139 ng/mL in the patient. Steroid, methotrexate, tumor necrosis

Table 1. Laboratory results and therapeutic follow-up of the patient

Variable	Pre-anakinra	Post-anakinra treatment 1 month	Post-anakinra treatment 12 months	Attack	Post-attack (1 month)
Hemoglobin (g/dL)	10	11.2	12.3	12.4	14.1
Platelet count/μL	225,000	312,000	235,000	331,000	254,000
White cell count/μL	38,090	15,020	10,040	30,900	7,800
ESR (mm/h)	79	25	15	104	14
CrP (mg/L)	254	45	6	427	1.1
Ferritin (ng/mL)	2139	300	45	550	35
Anakinra	No	Yes (2 mg/kg/d)	Yes (2 mg/kg/d)	Yes (1 mg/kg twice a week)	Yes (2 mg/kg/d)
Steroid	Yes	No	No	Yes (30 mg/kg every day)	Yes (2 mg/kg/d)
Cyclosporin A	Yes	No	No	Yes (3 mg/kg/d)	Yes (3 mg/kg/d)
Hyper-immunoglobulin	Yes	No	No	Yes (1 g/kg/d)	No

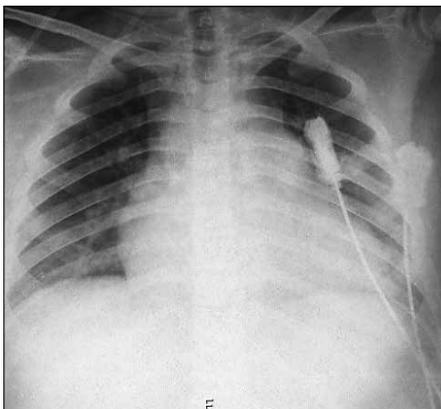ESR: erythrocyte sedimentation rate; CrP: c-reactive protein

Figure 1. Left pleural effusion on chest X-ray.

Figure 2. No pulmonary thrombus on pulmonary. CT angiography
CT: computed tomography

factor-alpha receptor inhibitor, and cyclosporine treatments were given, respectively, but there was an incomplete recovery. Later, two years after being diagnosed, anakinra at 2 mg/kg/day subcutaneously was started as well. In the first month of this treatment, acute-phase reactants and clinical symptoms were fully improved (Table 1). All the other treatments were then discontinued. In the twelfth month of follow-up, anakinra was tapered down. First, it was reduced to 1 mg/kg every day for 3 months, then 1 mg/kg every other day for another 3 months, and finally the treatment was set at a dosage of 1 mg/kg twice a week. There was no worsening in clinical symptoms or acute-phase response in the patient when treated with anakinra alone for approximately two years. The patient was admitted with marked dyspnea, tachypnea, chest pain, tachycardia, and hypotension in the second year of treatment, even though anakinra was being used twice a week at 1 mg/kg. Initially, we thought it might be a

combination of pulmonary embolism (PE) and cardiac ischemia.

His laboratory examination results were as follows: Hb, 12.4 g/dL; WBC, 30,900/mm³; Plt, 331,000/mm³; CrP, 427 mg/L; ESR, 84 mm/h; ferritin, 550 ng/mL; IgG, 3882 mg/dL; PT, 14 (10-14) s; APTT, 38.2 (22.8-31) s; D-dimer, 1794 (0-550) ng/mL; and troponin-I 30 (0-0.08) ng/mL (Table 1). The arterial blood gas measurement results were as follows: pH, 7.46; pO₂, 52 mmHg; and pCO₂, 26 mmHg. His chest X-ray showed a left pleural effusion (PE; Figure 1). No viral infections were detected and lung perfusion scintigraphy was found to be normal. Owing to the continuation of marked chest pain and tachypnea, a pulmonary computed tomography (CT) angiography was performed. This was interpreted as showing mild pericardial effusion and pleural fluid was measured to be

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10 mm thick, and it did not show any level of pulmonary artery thrombus (Figure 2).

The patient's description of the pain was compatible with ischemic chest pain; electrocardiography (ECG) and cardiac enzymes were evaluated. On ECG, ST-T changes were not detected, but excessively high troponin-I levels of 30 (0-0.08) ng/mL were reported. In echocardiographic findings, myocardial functions were normal and the ejection fraction was determined to be 65%. Mild hypokinesia of the right ventricular apex and increased pulmonary artery width were detected. However, pulmonary artery pressure was normal. In addition, echocardiography showed no pulmonary artery thrombus. By a combination of the current clinical and echocardiographic findings and the elevation in cardiac enzymes, the patient was diagnosed with myopericarditis. We excluded PE in the light of this information. Written informed consent was obtained from patients who participated in this study.

Consequently, the patient was presumed to be suffering an SoJIA attack. Pulse steroid therapy, cyclosporine at 3 mg/kg/day, hyper-immunoglobulin, and anakinra at 2 mg/kg/day were administered. On the fifth day of treatment, the patient had a better clinical status and acute-phase reactants and cardiac enzymes were decreased.

Discussion

In classically drug-unresponsive cases of SoJIA, there are many case reports in the literature of achieving complete remission with biological agents [5, 7, 9]. However, in patients with SoJIA, there are no prospective studies that address for how long and at which pharmaceutical dose should these biological agents be used. In patients with no known genetic disorders, biological drugs could be discontinued after a period of time. The use of anakinra in auto-inflammatory diseases of children has been mostly recorded in the form of case reports or short-term prospective studies [7-9].

Symptomatic PE has been described in 3%-5% of patients with rheumatoid arthritis, but the rate of pleural involvement on plain chest radiograms is much higher [10]. Most patients with rheumatoid PE (RPE) are asymptomatic unless the effusion becomes large enough to cause pleuritic chest pain and dyspnea [10]. However, this patient had minimal pleural and pericardial fluid in combination with unusually severe chest pain. Cough is not a regular feature of RPE and generally indicates underlying lung disease. We initially suspected PE and myopericarditis because of severe pleural pain, cough, hypocapnia, high D-dimer levels, and elevated cardiac enzyme levels. PE and deep vein thrombosis in patients with rheumatoid arthritis have been reported to increase relative to the risk in the general population [10]. If PE is suspected

because of the non-specificity of symptoms, it is often necessary to rely on imaging tests to confirm the diagnosis. The scintigraphy test of our patient was negative; owing to the low sensitivity of scintigraphy and the ongoing chest pain in the patient, we added CT angiography to the diagnostic process. CT pulmonary angiography of our patient was negative for PE; therefore, we excluded PE. We initiated treatment with pulse MPZ, cyclosporine, and 2 mg/kg/day anakinra following the diagnosis of SoJIA attack and myopericarditis. The clinical and laboratory improvements with this treatment confirmed the diagnosis.

Pascual et al. [2] demonstrated that IL-1β is an important cytokine in the pathogenesis of SoJIA and that this cytokine is important for the treatment of SoJIA. The use of anti-IL-1 treatments for these conditions is most often in an off-label context and without standardized monitoring. Thus, data on their medium- and long-term effectiveness and side effects are lacking [7]. The comprehensive study by Ilowite [9] reported that the short-term use of the drug, similar to its use in adult patients with rheumatoid arthritis, is safe, that very few side effects of the drug have been observed during the entire treatment course, and there are only a few cases that require withdrawal of the drug [9]. A recent study revealed that anakinra can be used as a second treatment option for SoJIA and that systemic symptoms and joint symptoms had high rates of recovery in this case series [9]. The results of pharmacokinetic studies showed that 1 mg/kg/day anakinra provides sufficient exposure in patients with SoJIA. Moreover, very high plasma levels of anakinra are observed in children than in adults when anakinra is administered at a daily dose of 100 mg [9].

A prospective study was conducted in France at a rheumatology center; 189 patients attended between 2011 and 2013 (50 of whom were children) [7]. In this study, the efficacy and tolerance of anti-IL-1 treatment were evaluated. A total of 185 patients used at least one anakinra treatment (dose for adults was 100 mg/day and for children 1-6 mg/kg/day). Most of them used daily medication, and for a few other patients in remission the dosage range differed. Of 26 children with SoJIA, complete remission was reported in 42.3% of cases and partial remission in a further 46.2%. It was also stated that anakinra treatment was stopped in 5 children with SoJIA with persistent remission [7].

Our patient had approximately two years of full remission when treated with anakinra. During the drug discontinuation phase, he was again admitted to the hospital with a serious attack of the disease.

In conclusion, we think that anti-IL-1 treatment is quite important in children with SoJIA. However, in patients with SoJIA with no genetic disorders, there are no prospective studies of

biological agents that address the effective duration of treatment and the recommended pharmaceutical dose that should be used. Clearly, there is a need for such studies.

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