Etanercept for the Treatment of Chronic Arthritis Related to Chronic Granulomatous Disease: A Case

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Introduction: Chronic granulomatous disease (CGD) is a rare primary immunodeficiency, in which infections are the main presenting symptoms. Moreover, patients may also experience inflammatory and autoimmune manifestations. With proper management of infections, patients now survive to adulthood, and inflammatory manifestations have become more prominent problems. Treatment of the inflammatory manifestations in CGD is challenging and requires a multidisciplinary approach. Since tumor necrosis factor (TNF)- α has been cited as having a possible role on inflammatory conditions in CGD, etanercept, an anti-TNF agent, may represent a major advance in the management of inflammatory manifestations.

Case Presentation: In this report, we described a 15-year-old boy, suffering concurrently both from human leukocyte antigen (HLA)-B27-positive chronic arthritis and CGD, whose arthritis did not respond to treatment with methotrexate and ibuprofen. Remission was achieved 6 months after etanercept initiation and during the next 18 months on medication, we did not encounter any signs of severe infections.

Conclusion: Treatment of inflammatory conditions in CGD patients is still challenging in view of the lack of evidence-based therapeutic options. In this study, we report the first pediatric CGD case, in which chronic arthritis was successfully treated with etanercept.

Keywords: chronic arthritis, HLA-B27 positivity, chronic granulomatous disease, etanercept

Introduction

CHRONIC GRANULOMATOUS DISEASE (CGD) is a rare primary immunodeficiency, affecting 1 per 250,000 individuals. The pattern of inheritance is either X-linked (XL), which accounts for 65%–70% of cases or autosomal recessive.¹ CGD results in increased susceptibility to severe and recurrent infections by catalase-positive bacteria, including *Staphylococcus aureus*, *Burkholderia cepacia*, and *Serratia marcescens*, and fungi such as *Aspergillus* due to a defect in the multicomponent nicotinamide adenine dinucleotide phosphate oxidase complex, which is an important enzyme in phagocytosis. This leads to the defective intracellular killing of phagocytosed organisms.¹ Because infections are the main presenting symptoms of CGD and may be life-threatening, they have been the major focus of CGD research so far.

With optimal preventive care and treatment of infectious complications, patients with CGD now survive into adulthood. It is noteworthy to mention that although nearly 90% affected children survive to the age of 10, only 55% are still alive by 30. Furthermore, the quality of life of the survivors

is still poor.² Although CGD mainly presents with recurrent infections, patients also experience inflammatory and autoimmune diseases, including sarcoidosis, chronic arthritis, systemic lupus erythematosus and a severe Crohn's-like inflammatory bowel disease, which together cause significant morbidity and mortality.^{1,3,4–9} Of these, Crohn's-like inflammatory bowel disease is the most common inflammatory manifestation.

Some authors have suggested that immune dysregulation in CGD extends beyond recurrent infections and formation of granulomas, and also proposed that autoimmune disorders occurring in CGD patients may not be coincidental findings and CGD might itself serve as a genetic cofactor which lowers the threshold for autoimmunity by a currently unknown mechanism.⁶ Moreover, recent studies suggested the central role of Treg in developing autoimmunity in CGD patients. In detail, deficiency in NADPH oxidase was held responsible for the impairment of reactive oxygen species production, which is necessary for macrophages to activate Treg cells.^{10,11}

Although infections in CGD have been well studied over recent decades, information on inflammatory conditions is

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insufficient. Autoimmune events are more common in patients with XL-CGD than in healthy individuals.⁸ In a single-center cohort study, the frequency of autoimmune manifestations in CGD patients was reported as 10.3%, of which arthritis contributed 2%.⁸ The coexistent predisposition to both infections and inflammatory conditions may lead to problems in diagnosis and management. Therefore, the treatment of inflammatory manifestations is more challenging in CGD patients and requires a multidisciplinary approach.

Even though treatment is still primarily based on corticosteroids, refractory manifestations in CGD patients may benefit from second-line therapies, including immunosuppressants and biologics such as antitumor necrosis factor (TNF)- α agents.^{8,12} However, the utility of these drugs is still controversial.¹² Despite meticulous antibiotic and antifungal therapy and treatment of inflammatory complications, CGD patients are still compelling disease-related mortality. Fortunately, resolution of the infections and inflammatory complications can be feasible currently, in thanks to newer treatment approaches including, hematopoietic stem cell transplantation (HSCT).¹³

Etanercept is a fully human, dimeric protein containing the extracellular domain of the human p75 TNF receptor fused to the Fc region of human IgG1. It prevents the interaction of TNF- α with its cell surface receptor by binding to trimers of TNF- α in the circulation, therefore, inhibits cell activation and perpetuation of the inflammatory cascade.¹⁴ Etanercept is the mostly used TNF- α antagonist in the treatment of juvenile idiopathic arthritis (JIA) and its effectiveness in JIA well proven. Moreover, it seems to be safer than other known anti-TNF- α agents.¹⁵⁻¹⁷

In the present report, we described a 15-year-old boy with CGD and human leukocyte antigen (HLA)-B27-positive chronic arthritis treated with etanercept effectively and safely. Therefore, we hypothesize that biologic agents might be promising treatment options in CGD with inflammatory manifestations, in which HSCT is unfeasible.

Case

A 15-year-old boy was referred to our pediatric rheumatology department with left knee swelling and back pain for the last 2 months. He had been born to a nonconsanguineous parents and received the XL-CGD (*CYBB*; c.1461+1G>T Hemizygote mutation) diagnosis at the age of 4. Previous medical treatment for CGD included methylprednisolone, interferon gamma, cotrimoxazole, and itraconazole. Unfortunately, HSCT treatment was unfeasible due to the lack of a suitable donor. Moreover, he had suffered from morning stiffness for the previous 2 months. General physical examination was normal apart from developmental delay in both height and weight. Musculoskeletal examination revealed left knee swelling with pain and reduced range in movement and mild pain in both hip joints. Laboratory studies disclosed elevated acute phase reactants, including leukocytosis (10,920/mm³), thrombocytosis (427,000/mm³), mild anemia (10.9 g/dL), C-reactive protein (7.7 mg/dL), and erythrocyte sedimentation rate (47 mm/hr), and also HLA-B27 positivity. Magnetic resonance imaging revealed an effusion extended to the suprapatellar bursa and intra-articular area of the left knee, and in both hip joints in addition to bilateral active sacroiliitis. In the presence of arthritis lasting more than 6 weeks and HLA-B27 positivity, he was

diagnosed with HLA-B27-positive chronic arthritis and treated with methotrexate plus ibuprofen. After an ineffective 6 months course of methotrexate and gastrointestinal intolerance, methotrexate was discontinued and subcutaneous weekly etanercept (0.8 mg/kg per dose) was commenced. Methylprednisolone, cotrimoxazole, and itraconazole were continued during etanercept treatment. Six months after etanercept initiation, the pain and morning stiffness did resolve, musculoskeletal examination revealed no signs of arthritis and acute phase reactants were normal. The patient was monitored regularly for the efficacy and side effects of anti-TNF- α treatment. During 18 months under etanercept treatment, we have not encountered any severe side effects, although the patient has had mild upper respiratory tract infections. Timeline indicating the clinical course of the patient and the changes in acute phase reactants during follow-up are detailed in Figs. 1 and 2, respectively.

Discussion

JIA is characterized by arthritis lasting at least 6 weeks in children younger than the age of 16 years.^{18,19} Other well-known etiologies of arthritis are infections, malignancies, and systemic diseases. Moreover, chronic arthritis may be a manifestation of immunodeficiencies, including CGD occasionally.^{5-7,20}

TNF- α is a proinflammatory cytokine, which has been often cited as a possible cause of the inflammatory state of CGD.^{18,21,22} TNF- α inhibitors can be administered either as monotherapy or in combination with other anti-inflammatory agents in the treatment of chronic inflammatory diseases. There are several TNF- α inhibitors in clinical practice, including 4 anti-TNF- α monoclonal antibodies (infliximab, adalimumab, golimumab, and certolizumab pegol) and 1 fusion protein (etanercept). TNF- α inhibitors may increase the risk of infections as an adverse effect, particularly opportunistic infections such as tuberculosis and human immunodeficiency virus. Reactivation of latent tuberculosis infection and the overall risk of opportunistic infections should be considered before the beginning of TNF- α inhibitor treatment. Monoclonal antibodies, particularly infliximab, which is an antireceptor fusion protein, appear to be responsible for the increased risk of infections.^{14-17,23}

Etanercept is currently indicated for children with JIA, aged at least 2 years, and long-term continuous treatment appears to be safe.^{15,16,24} The most common adverse events have been reported as being upper respiratory tract infections during etanercept.²⁵ Treatment of autoimmune diseases with biologic agents in children with CGD is challenging owing to the predisposition to infections and increased risk of treatment-related infections. TNF- α inhibition might be a reliable approach for the inflammatory conditions in CGD since TNF- α is the prominent proinflammatory cytokine, which is excessively secreted from inflammatory cells of the patients with CGD.^{26,27} There is an increased off-label use of anti-TNF- α agents in CGD-induced inflammatory diseases, with variable outcomes.²⁸ Uzel et al. have reported 5 patients with CGD-related Crohn's-like inflammatory bowel disease treated with infliximab and found a high incidence of infections, including 2 patients with fatal consequences.²⁰ On the contrary, infliximab has been successfully used to treat granulomatous diseases in 5 common variable immunodeficiency patients without notable adverse reactions or increased susceptibility to infections

FIG. 1. Timeline indicating the clinical course of the patient with chronic arthritis and CGD. CGD, chronic granulomatous disease.

by Franxman et al.²⁹ Moreover, Magnani et al. have reported improvement in 2 out of 4 patients with XL-CGD and gastrointestinal inflammation treated with anti-TNF agents.⁸ The only report we have found on successful treatment of arthritis with etanercept was demonstrated in an adult patient.⁶

In the present report, we described the co-occurrence of HLA-B27-positive chronic arthritis and XL-CGD in a 15-year-old boy, in whom chronic arthritis was treated with etanercept effectively and safely. While this cannot be proven, we believe that both HLA-B27 positivity and underlying CGD may have contributed to the inflammatory process of this patient. We preferred to use etanercept in view of its well-known effectiveness and long-term safety profile in JIA

patients. However, due to insufficient data on this topic, there is still a great deal to learn about choosing the effective biologic agents in inflammatory conditions of CGD patients.

To our knowledge, our case is the first reported pediatric CGD patient, in whom HLA-B27-positive chronic arthritis has been successfully treated with an anti-TNF- α agent. We propose that underlying primary immunodeficiencies should not restrict the consideration of biologic agents for the treatment of the autoimmune disease, particularly for patients in whom HSCT is unfeasible or contraindicated. Etanercept might be an effective and safe treatment option in such scenario. However, further long-term studies are needed to clarify the safety and efficacy of etanercept in chronic arthritis with CGD.

FIG. 2. A diagram revealing the favorable improvement in acute phase reactants of the patient with chronic arthritis and CGD during follow-up.

Take-home points

- (1) Chronic arthritis can be seen as an inflammatory manifestation in CGD patients.
- (2) An anti-TNF- α agent, particularly etanercept might be an effective and safe treatment option for treating those patients.

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Confirm Consent

A confirm consent was taken from his parents.

Author Disclosure Statement

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