TOCILIZUMAB - A PROMISING THERAPY IN THE MANAGEMENT OF MORPHEA IN CHILDREN

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Summary

Morphea is a rare autoimmune disease characterized by inflammation and fibrosis of the skin and soft tissue. Its etiology remains unknown, but several theories have been postulated and assert the interplay between genetic, environmental and immune factors. Currently, there is no cure for morphea. However, by investigating the cells, mediators, and pathways involved in disease pathogenesis, new potential therapies have been identified to prevent fibrosis, disfigurement, and physical impairment caused by disease progression. In the setting of COVID-19 pandemic, tocilizumab, an IL-6 antagonist, has gained attention due to a potential role in management of severe cases of infection with SARS-CoV-2. In recent years, several cases of morphea successfully treated with tocilizumab have been reported. This article reviews morphea cases treated with tocilizumab and provides new insights into its role in the management of the disease.

Keywords: *morphea, interleukin-6, tocilizumab.*

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Introduction

Morphea or localized scleroderma is an autoimmune sclerosing skin disease with unknown etiology that affects children and adults. Genetic factors, alterations of the immune response and environmental factors are involved in the pathogenesis of the disease [1]. Juvenile localized scleroderma has an estimated incidence rate of 3.4 per million children [2] and commonly affects children aged 2 to 14 years, being diagnosed more frequently in girls [3]. In about 50% of cases, spontaneous remission of the disease or skin softening occurs on average 3 years after onset. However, in many cases the sequelae caused by previously active lesions such as atrophy, contractures or hyperpigmentation persist [4]. The pathophysiological mechanisms are not fully elucidated, but it is known that the initial events are the alteration of micro-circulation and dysregulation of the immune response mediated by T cells, which are associated with abnormal collagen production and fibrosis [5]. Depending on the number, size, shape and location of the lesions, five main types of morphea were described including linear, circumscribed, generalized, pansclerotic and mixed type. Linear morphea is the most common type in children, usually involving the head and limbs. When the cephalic extremity is affected, ocular, dental, or neurological complications may occur [6].

The therapeutic approach in morphea is based on the following three principles, the activity of the disease, the depth of the lesions and the extent of the disease [1]. There is no consensus on the treatment of the disease and over time many regimens have been used. Topical therapies consist of corticosteroids,

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tacrolimus, calcipotriol or imiquimod. Topical therapy is reserved for patients diagnosed with circumscribed, superficial, and non-progressive lesions or linear scleroderma lesions that do not cross a joint [6]. Phototherapy is one of the most used treatments in morphea. However, it remains ineffective in the case of deep lesions that extend into the fascial and muscular compartments. It is recommended for patients over 12 years [1]. Systemic therapy is recommended for moderate and severe forms and includes immunosuppressants such as prednisone, methotrexate, mycophenolate mofetil or cyclosporine. Treatments with infliximab and imatinib have been associated with satisfactory results [7]. Other therapies that show promising results are abatacept and rituximab. Methotrexate alone or in combination with corticosteroids is the treatment of choice in the first 3 months [2]. In recent years, several cases of morphea in children treated with tocilizumab, an interleukin (IL)-6 antagonist, have been reported. In this review, we summarize these cases and emphasize the role of tocilizumab in morphea management.

The role of IL-6 in morphea

IL-6 was identified about 30 years ago and was originally described as a B-cell differentiation factor [8]. In fact, IL-6 is a potent pro-inflammatory cytokine, with numerous effects in the human body, being involved in inflammation, immune response and hematopoiesis. IL-6 has been associated for the first time with a disorder, in the case of a cardiac myxoma, an observation reported by Hirano et al. in 1987 [9]. Today, it is well known that IL-6 is associated with the development of various conditions, including autoimmune diseases, chronic inflammatory diseases, and neoplasms [10]. IL-6 binds to cells through a specific receptor complex including two proteins, IL-6 receptor α and gp130. Tocilizumab is a recombinant humanized monoclonal antibody directed against both soluble and membrane-bound interleukin 6 receptors (IL-6R) [11] and was first approved in Japan for the treatment of Castleman's disease [12]. The drug neutralizes IL-6 and IL-6R activity and therefore it blocks both classic and trans-signaling pathways. Tocilizumab exhibits the ability to dissociate the IL-6 – sIL-6R complex, but not the IL-6 – sIL-6R – sgp130 complex [12]. During the COVID-19 pandemic, tocilizumab was proposed as a possible therapeutic option for severe cases of infection with SARS-CoV-2. However, the meta-analysis by Lan et al. indicated that there is insufficient data to attest that tocilizumab may offer additional benefits for patients with severe COVID-19 and further studies are needed [13].

Profibrotic cytokines TGF beta, IL-4, and IL-6 play a crucial role in the pathogenesis of scleroderma, according to recent studies [14]. IL-6 modulates fibroblast activity, induces collagen production and inhibits collagenase synthesis [15]. Kurzinsky et al. reviewed studies on the cytokine profile in patients with localized scleroderma. Cytokines released by Th1, Th2 and Th17 cells have been shown to participate in the pathogenesis of the disease. Elevated serum IL-6 levels have been reported in patients with localized scleroderma compared to a control group. In addition, higher levels of IL-6 were detected in patients with localized scleroderma compared to those with systemic sclerosis. Elevated levels of IL-6 have been detected especially in patients with generalized and linear morphea. It has been observed that serum IL-6 levels decrease as the disease improves, suggesting that IL-6 may be considered a marker of disease activity. Furthermore, a positive correlation was found between serum IL-6 levels and the presence of antihistone antibodies, indicating that IL-6 may also be a marker of disease severity [16]. Włodarczyk et al. did not identify significant differences in serum IL-6 levels when comparing patients with localized scleroderma and healthy individuals. However, they observed a positive correlation between IL-6 and erythrocyte sedimentation rate among these patients, suggesting the possible involvement of IL-6 in chronic inflammation [17]. A recent study has shown that the abnormal expression of IL-6 is related to epidermal alteration in patients with localized scleroderma. Abnormal keratinocyte-derived IL-6 secretion contributes to the thickening of the epidermis and induces dryness [18].

The use of tocilizumab in morphea patients

Lythgoe et al. reported 5 cases of juvenile localized scleroderma refractory to classical therapies that had a favorable outcome following tocilizumab therapy. The patients were treated with tocilizumab for a period of 12 to 25 months. No serious adverse reactions were registered in any of the patients. Disease activity scores improved; a statistically significant improvement was achieved for the physician's global assessment of activity (PGA-A) at 6 months. However, no progress has been made in terms of disease damage and patient quality of life. It should be noted that changes in the course of the disease are often irreversible and the use of tocilizumab in earlier stages may have greater benefits [19]. In the following subsections we present the reported clinical cases of morphea treated with tocilizumab.

Linear scleroderma "en coup de sabre"

Two cases of linear scleroderma "en coup de sabre" with neurological manifestations, treated with tocilizumab have been described. Osminina et al. reported a case of linear scleroderma "en coup de sabre" associated with epilepsy and uveitis. The disease started in a girl of 2 years and 10 months with episodes of epilepsy. Later, the girl developed skin lesions of morphea and uveitis. Initially, she was treated with immunosuppressive agents (prednisone, methotrexate) and the evolution of the disease was favorable for 2 years. However, the lesions progressed and became refractory to conventional therapy. Treatment with tocilizumab was started and lasted for 26 months. One year after stopping the treatment with tocilizumab, there was no progression of the disease and the patient continued treatment with methotrexate [20]. Magro et al. reported a case of linear scleroderma "en coup de sabre" in a child who developed refractory epilepsy and cognitive impairment. Over a period of 7 years, a progressive neurological deterioration was observed and the disease becamerefractory to classical therapy. A brain biopsy was performed and the histopathological examination revealed acute and chronic cortical ischemia associated with small vessel lymphocytic vasculitis. Direct immunofluorescence examination showed C5b-9 and IgG depositsin endothelium. A positive anti-endothelial cell antibody assay was also present. The patient started tocilizumab, which led to satisfactory results. IL-6 seems to be involved in endothelial cell apoptosis [21]. Patschan et al. have shown that tocilizumab stimulates the population of endothelial progenitor cells, a group of cells involved in vasculogenesis in adults [22]. These 2 cases suggest the utility of tocilizumab in morphea with nervous system involvement.

Meneghetti et al. presented the case of a 4-year-old child with Pary Romberg syndrome associated with scleroderma "en coup de sabre" successfully treated with tocilizumab. The patient had significant damage to the jaw. Magnetic resonance imaging showed resorption of the dental root and severe periodontal bone inflammation. Studies have shown that the inflammatory process plays a crucial role in the activity of morphea, and the decrease in the inflammatory process could slow its progression [23]. Tocilizumab and mycophenolate mofetil were initiated. After 6 months, oral pain and dysphagia improved, magnetic resonance imaging revealed a reduction in periodontal bone edema, and the scores for disease assessment decreased [23].

Pansclerotic morphea

Ventejou et al. reported the case of an 8-year-old girl diagnosed with pansclerotic morphea, a rare subtype of localized scleroderma. The patient was treated with corticosteroids, methotrexate, and tocilizumab, and complete and sustained remission was achieved. The authors suggest that early administration of tocilizumab may lead to complete cure. Since the patient received triple therapy, it is difficult to show the exact role of tocilizumab. However, the unsatisfactory course of the disease under conventional immunosuppressive therapy should be considered [15]. Zhang et al. presented the case of a 6-year-old girl with refractory pansclerotic morphea to classical immunosuppressive therapies, who had a favorable evolution following methotrexate in combination with tocilizumab. The authors consider that the addition of

tocilizumab to methotrexate may be useful in refractory morphea [24].

Martini et al. reported 2 cases of pansclerotic morphea treated with tocilizumab. The first case is of a 16-year-old girl diagnosed with mixed morphea (pansclerotic morphea on her right limb and deep morphea on her trunk). The disease started at the age of 4 years. Over time, she underwent treatments with prednisone, methotrexate, and mycophenolate mofetil with encouraging results. Later, in the course of the disease, new lesions were observed on her trunk and worsening of fibrosis on her right limb. The patient refused treatment with methotrexate or mycophenolate mofetil, consequently, treatment with imatinib was started, but in the last 4 years the disease continued to worsen significantly. Disease activity and damage index LoSCAT was 58 (mLoSSI15, LoSDI 43]. The patient was given tocilizumab, and after 18 months of treatment a significant improvement was observed (LoSCAT 47, mLoSSI 7, LoSDI 40) [25]. The second case refers to a patient who had also been diagnosed at the age of 4 years. She was initially treated with prednisone and methotrexate, but when the lesions worsened, the therapy was shifted to the mofetil mycophenolate regimen. Over the next three years the evolution was favorable, but subsequently the lesions extended and became refractory to immunosuppressive therapy (LoSCAT 57, mLoSSI 24, LoSDI 33). She was treated with tocilizumab for 6 months, and 24 months from the last dose of tocilizumab, the disease was still inactive (LoSCAT 43, mLoSSI 10, LoSDI 33) [25].

Conclusions

Morphea is an inflammatory skin condition that can evolve into severe lesions that cause disfigurement and abnormal mobility, and is associated with a significant impact on quality of life. The current therapies are disappointing. However, biological therapies seem to bring hope into the field. Therapy with tocilizumab, an IL-6R antagonist, shows encouraging results in several cases of severe morphea in children, refractory to conventional immunosuppressive therapies. Data are still scarce and further studies are needed to establish the recommendations, timing and duration of tocilizumab regimen and the need for combination with immunosuppressive therapies.

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Conflict of interest
NONE DECLARED

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