

Anti-TNF α therapy and switching in severe uveitis related to Vogt-Koyanagi-Harada syndrome

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Abstract

The study aimed to describe the effectiveness of switching the anti-TNF α agent when an acceptable clinical response has not been obtained with the first anti-TNF α agent in patients with uveitis in VKH syndrome. Patients diagnosed with VKH syndrome being evaluated from the uveitis unit of a single tertiary hospital from January 1, 2000, to October 30, 2015. Patients who presented uveitis with an inadequate response to a first anti-TNF α and required switching to a second anti-TNF α were selected. Complete clinical response was assumed in patients whose visual acuity was normal and those who showed absence of inflammatory findings (inflammatory cells in the anterior chamber and vitritis) or absence of macular thickening in upon OCT. A systematic review of the literature of anti-TNF α agents in VKH syndrome was performed. Five patients met the criteria of VKH syndrome. Two cases of VKH syndrome with uveitis and inadequate clinical response to an initial anti-TNF α (both IFX) were presented. After switching to Adalimumab (ADA), a satisfactory clinical response was noted in the first month. For the first time, we present two patients with severe uveitis due to VKH syndrome who after inadequately responding to the first anti-TNF α agent showed complete and maintained clinical improvement when switched to a second anti-TNF α agent.

Keywords: Uveitis, Vogt-Koyanagi-Harada disease, anti-TNF α



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Introduction

The Vogt-Koyanagi-Harada (VKH) disease is a multisystem autoimmune disorder mediated by T cells directed against the antigens of melanin-containing tissues, such as the eye, inner ear, meninges, and skin (1). Clinically, it is characterized by diffuse bilateral granulomatous panuveitis with exudative retinal detachment that can be associated with auditory, neurological, and cutaneous manifestations (1). Chee et al. (2) observed that more than one-half of the patients, despite receiving prompt and adequate immunomodulatory treatment, developed chronic disease, and in some cases, blindness occurred due to cataracts, glaucoma, cystoid macular edema, choroidal neovascularization. Anti-tumor necrosis factor alpha (anti-TNF α) agents have improved the prognosis of inflammatory uveitis, including the VKH syndrome. According to the "expert panel recommendations for the use of anti-TNF α drugs in patients with ocular inflammatory disorders," the use of infliximab (IFX, Inflectra, Pfizer) or adalimumab (ADA, Humira, Abbvie) may be considered in VKH disease patients intolerant or unresponsive to traditional immunosuppressive therapies (3). There is no information regarding switching to a second anti-TNF α agent when faced with an inadequate response to the first anti-TNF α drug. The objective of this study was to describe the effectiveness of switching to another anti-TNF α drug when an acceptable clinical response has not been obtained with the use of the first anti-TNF α drug in patients diagnosed with VKH disease.

Case Presentation

A review of all the patients diagnosed with VKH disease being evaluated from the uveitis unit of one tertiary hospital was carried out from January 1, 2000, to October 30, 2015. Patients who presented severe ocular involvement with inadequate response to a first anti-TNF α drug and required switching to a second anti-TNF α agent were selected. The diagnosis of VKH was performed in accordance with the criteria suggested by an international committee on nomenclature (4). Uveitis was classified anatomically and the degree of intraocular inflammation was evaluated according to the Standardization of Uveitis Nomenclature (SUN) Working Group (5). As previously described, patients were defined as having refractory uveitis when it was not in remission despite having received immunosuppressive drugs or when the use of these drugs was not sufficient to maintain the disease under control in the first 6 months (6-8). A complete clinical response to the treatment was assumed in those patients whose visual acuity was normal in both eyes and showed absence of inflammatory findings in the ocular fundus exam (inflammatory cells in the anterior chamber, vitritis, and choroiditis) or absence of

macular/choroidal thickening in optical coherence tomography (OCT). Since uveitis is an off-label indication for anti-TNF α therapy, written and informed consent was obtained from all patients.

Five patients met the criteria of complete diagnosis of VKH disease. Two of them required treatment with one anti-TNF α agent and later needed switching to a second anti-TNF α drug. In both cases, intravenous pulses of 1 g of methylprednisolone a day for 3 days were administered at the time of diagnosis. Subsequently, corticosteroids were used at a dose of 30 mg/day of prednisone with decreasing dosage along with cyclosporine. In both patients, adverse effects were observed related to the use of cyclosporine. In the two cases, IFX 5 mg/kg was the first anti-TNF α agent administered at weeks 0, 2, and 6 and then every 8 weeks. A switch was conducted to subcutaneous ADA standard dose 40 mg injection every 2 weeks, observing complete clinical response after up to 12 and 24 months of follow-up, respectively.

Patient 1

The first case was of a 38-year-old male with decrease in his visual acuity due to bilateral exudative retinal detachment and panuveitis. Once the patient met the diagnostic criteria for VKH disease, treatment with cyclosporine was initiated at 100 mg every 12 hours. However, 3 months later, he experienced nausea and occasional vomiting with cyclosporine; hence, it was suspended, and treatment with azathioprine with a progressive dose of 3 mg/kg/day was initiated. A month later, due to the persistence of active uveitis, IFX 5 mg/kg was added to the treatment at weeks 0, 2, and 6 and then every 8 weeks. Complete clinical response and visual acuity improvement (from the first month until normal values are attained) were observed. During follow-up (2 years later), the patient presented with left eye choroiditis thus leading to IFX suspension and initiation of subcutaneous ADA 40 mg every 2 weeks with complete clinical remission from the first month and up to 2 years after the initiation of treatment.

Patient 2

The second case was of a 42-year-old female who was admitted with decrease in visual acuity due to bilateral exudative retinal detachment and panuveitis. During her hospital stay, the patient reported bilateral hearing loss. Due to initial suspicion of the VKH disease, a lumbar puncture was performed and noticeable pleocytosis was detected. She met the diagnostic criteria for VKH, and treat-

ment was initiated with intravenous pulses of methylprednisolone 1 g once a day for 3 days and then continued with prednisone 30 mg a day (reducing dosage to 2.5 mg until present day) and of cyclosporine 5 mg/kg/day, showing progressive clinical improvement. However, 4 months later during follow-up, the patient presented with hirsutism and bilateral anterior uveitis, therefore leading to cyclosporine suspension and initiation of IFX 5 mg/kg at weeks 0, 2, and 6 and then every 8 weeks combined with azathioprine 3 mg/kg/day. Clinical response was observed from the first month until it progressively became complete response. After 5 years of effectiveness, IFX was suspended because of severe fatigue and dizziness. Treatment with subcutaneous ADA was then initiated at 40 mg injections every 2 weeks, maintaining complete clinical response for the next 12 months. No adverse effects were observed in any of the two patients included in this study.

Discussion

Two cases of VKH disease with severe ocular involvement and inadequate clinical response to an initial anti-TNF α drug were presented. After switching to ADA and after the first month of treatment, a satisfactory clinical response is noted. Switching between anti-TNF α biologic agents has been described as successful in other inflammatory disorders, such as rheumatoid arthritis, psoriasis, ankylosing spondylitis or juvenile idiopathic arthritis. However, no information was found in the existing literature related to switching between anti-TNF α agents in VKH disease. The VKH disease etiology remains unknown. High levels of TNF α have been detected in patients with autoimmune uveitis (9). Therefore, the main objective is to suppress intraocular inflammation and prevent visual acuity loss. Thus, early and aggressive administration of corticosteroids is the most widely accepted treatment, and specific guidelines regarding immunosuppressive therapy have not been established, rendering that part of treatment to individual assessment. A variety of immunosuppressive drugs has been used in the treatment of VKH disease. Cyclosporine A is probably the most accepted medication as the first-line treatment. Azathioprine is another drug proven efficient, and in severe cases, azathioprine plus cyclosporine have been used. Other drugs that have been used less successfully are methotrexate and chlorambucil (10). Despite these treatment options, refractory cases have been reported, and anti-TNF α drugs could be an adequate alternative. A review of patients with VKH disease treated with an-

ti-TNF α therapy was conducted in PubMed, Embase, and Medline. Nine articles were found in which a total of twenty-five patients with VKH disease treated with anti-TNF α drugs (16 with ADA and 9 with IFX) were described. In all the cases, patients were refractory to conventional immunosuppressive treatments. Clinical response was observed in 15 of 16 patients (94%) treated with ADA and eight of nine patients (89%) treated with IFX. There is no reference to switching from one anti-TNF α drug to another in any of the articles. The benefit of a second anti-TNF drug could be because some patients present secondary failure to the first anti-TNF either by the production of anti-drug antibodies or by loss of efficacy. For the first time, we present two patients with severe uveitis due to VKH disease who after inadequately responding to a first anti-TNF α agent show complete and maintained clinical improvement upon switching to a second anti-TNF α drug. In both cases, the switching was performed from IFX to ADA.

Ethics Committee Approval: The ethics committee approval for this study was obtained from the ethics committee of Hospital Marqués de Valdecilla, Santander.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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