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Poor Control of Sarcoidosis-Related Panuveitis with an Antibody to IL-23

Akshay S Thomas[1,2], **James T Rosenbaum**[1,3]

[1]Casey Eye Institute, Oregon Health and Science University, Portland, OR.

[2]Tennessee Retina, Nashville, TN

[3]Legacy Devers Eye Institute, Portland, OR

Abstract

Purpose: To report a case of uveitis worsening in a patient with sarcoidosis while receiving guselkumab (anti-IL-23) for dermatologic disease.

Methods: Case report.

Results: A 61-year-old gentleman had been diagnosed with plaque psoriasis in his 30s. He had been unsuccessfully treated with multiple conventional immunosuppressive agents as well as biologics. He was subsequently diagnosed with pulmonary sarcoidosis with confirmatory oropharyngeal biopsy. His presumed psoriatic skin lesions were subsequently biopsied and were consistent with cutaneous sarcoidosis. His ocular involvement from sarcoidosis had been minimal, requiring only occasional topical corticosteroids. He was started on the interleukin (IL)-23 inhibitor, guselkumab, for his cutaneous disease. Despite mild improvement in his cutaneous disease, he had a bilateral flare of uveitis requiring oral and topical corticosteroids.

Conclusions: IL-23 has been implicated in the pathogenesis of uveitis, but there are limited data supporting efficacy of inhibitors of IL-23 in the management of uveitis.

Keywords

Anti-IL-23; Guselkumab; IL-23; Sarcoidosis; Uveitis

INTRODUCTION

T helper (Th) 17 cells play a crucial role in chronic inflammation and autoimmunity as seen in uveitis. Stimulation of Th17 cells results in local inflammation through production of interleukin (IL)-17. IL-17 then induces the production of other inflammatory cytokines such as IL-1, IL-22, granulocyte-macrophage colony-stimulating factor (GM-CSF) and tumor necrosis factor alpha (TNFα). Upstream activators of Th17 cells include transforming growth factor-β (TGFβ), IL-6 and IL-23. While TGFβ and IL-6 promote the protective and non-pathogenic responses of Th17 cells, IL-23 induces the pathogenic Th17 cells implicated

CORRESPONDING AUTHOR/ADDRESS FOR REPRINTS: James T. Rosenbaum, MD, 3375 SW Terwilliger Blvd, Portland, OR 97239, rosenbaj@ohsu.edu, Phone: (503)494-5023, Fax: (503)494-6875.

in autoimmunity.[1] IL-17 has shown to be critical in the development of experimental autoimmune uveitis (EAU) in mice[2] and IL-23 knockout mice are protected against the development of EAU.[3] Inhibitors of IL-23 mediated Th17 activation and downstream inflammatory cytokines such as IL-17 are thus of interest in the management of uveitis. Herein we describe the first case to our knowledge of a patient whose uveitis worsened while receiving guselkumab, an IL-23 inhibitor.

CASE REPORT

A 61-year-old Asian-Indian gentleman presented for continued evaluation of sarcoidosis-related panuveitis. The patient's ocular disease had been minimal for several years, requiring only occasional limited courses of topical corticosteroids for flares of anterior uveitis. Inflammation in both eyes had been quiescent at his last evaluation 6 months prior. The patient had a long history of dermatologic disease with a presumptive diagnosis of plaque psoriasis since he was in his 30s. Management of his severe cutaneous disease over the years had been attempted with various therapeutics including methotrexate, infliximab, adalimumab, etanercept, hydroxychloroquine, secukinumab and ustekinumab. The patient was later diagnosed with sarcoidosis in 2013 following a computed tomography (CT) scan of the chest showing hilar and mediastinal lymphadenopathy and a subsequent confirmatory biopsy of an oropharyngeal lesion. A skin biopsy in 2016 was also consistent with cutaneous sarcoidosis, although the possibility of both cutaneous sarcoidosis and plaque psoriasis was not ruled out by his dermatologist. Owing to poor control of his cutaneous disease, he was started on guselkumab (100 mg subcutaneous on weeks 0, 4 then every 8 weeks) 4 months prior to presentation to the uveitis clinic. While on guselkumab, he noted slight improvement in his cutaneous symptoms. The patient had undergone cataract surgery in the right eye 2 months prior to presentation and felt that his vision had since declined. Prior to cataract surgery, his vision had been 20/40 in the right eye and 20/25 in the left eye and had since declined to 20/150 in the right eye and 20/40 in the left eye. Slit lamp examination revealed 1+ anterior chamber cell, a well-positioned intraocular lens and 2+ vitreous cell in the right eye and a quiet anterior chamber, mild cataract and no vitreous cell in the left eye. Funduscopy revealed 1+ vitreous haze in the right eye, a few new vitreous snowballs, cystoid macular edema (CME) and stable punched out chorioretinal lesions in the right eye as is characteristic of sarcoidosis. Funduscopy of the left eye revealed a quiet vitreous cavity and unchanged chorioretinal lesions. The flare of uveitis in the right eye was attributed to his recent cataract surgery and a course of oral corticosteroids was initiated. While the oral steroids improved the anterior chamber inflammation, persistent CME necessitated the addition of topical difluprednate (0.05%) 4 times a day to the right eye. Four months into the flare of the right eye, visual acuity had improved to 20/80, the anterior chamber inflammation had resolved, the vitritis had improved and the CME was largely gone, but the patient was still on difluprednate 4 times a day. Additionally, the left eye had now experienced a flare with 1+ anterior chamber cell with a slight reduction in visual acuity to 20/50.

DISCUSSION

Intraocular levels of chemical mediators and products of the Th17 pathway of autoimmunity such as IL-17 and IL-23 have been shown to be increased in uveitis.[1] Guselkumab (Tremfya, Janssen, Beerse, Belgium) is a monoclonal antibody which targets the p19 subunit of IL-23. It is currently approved by the Food and Drug Administration (FDA) for the treatment of plaque psoriasis. There are currently no reports on its efficacy in uveitis and no recruiting clinical trials designed to answer this question. Ustekinumab (Stelara, Janssen, Beerse, Belgium) is a monoclonal antibody targeting the IL-12p40 subunit of both IL-23 and IL-12. There are currently 2 registered, recruiting phase II clinical trials (NCT02911116 and NCT02648581) evaluating the efficacy of ustekinumab in non-infectious intermediate, posterior or panuveitis and Behçet's disease-related uveitis respectively. Secukinumab (Consentyx, Novartis, Basel, Switzerland) is a monoclonal antibody directed against IL-17A. It is FDA-approved for the treatment of plaque psoriasis, psoriatic arthritis and ankylosing spondylitis. Subcutaneous (SC) secukinumab was not found in 3 phase III clinical trials (SHIELD, INSURE, ENDURE trials) to significantly reduce rates of uveitis flares with withdrawal of a concomitant immunosuppressive agent.[4] While findings of these studies were quite surprising, a multicenter, randomized, placebo-controlled dose ranging phase II clinical trial found that secukinumab delivered intravenously at either 30 mg/kg or 10 mg/kg was more effective than the standard 300 mg SC dose in both treatment response rates (72.7%, 61.5% and 33.3%, respectively) and rates of inducing remission of uveitis (27.3%, 38.5%, 16.7%, respectively).[5] Thus it is was proposed that higher, well tolerated, doses of intravenous secukinumab may be needed to obtain therapeutic concentrations for the treatment of uveitis.

The patient presented in this report had been on guselkumab for 4 months prior to onset of a uveitic flare in the right eye. While this flare was likely precipitated by preceding cataract surgery, control of the flare required sizeable doses of oral and topical corticosteroids. Additionally, the nonsurgical left eye also experienced a flare, albeit less severe, 8 months into guselkumab therapy. It should be noted that while our patient historically had not had severe ocular sarcoidosis, it may have been masked by the variety of immunosuppressive agents he received over the years. Nevertheless, guselkumab monotherapy appeared inadequate to prevent a uveitic flare in this patient. Given the heterogeneity of uveitis and the complex interplay of cytokines in autoimmunity, inefficacy of guselkumab in this patient could have many explanations which include medication dosage, cause of uveitis, a paradoxical response to therapy, variable responsiveness of organ systems to targeted therapy, polymorphisms of the IL-23 receptor which render guselkumab less efficacious, or the uniqueness of the patient's disease. For example, studies have shown inefficacy of ustekinumab, an IL12/23 inhibitor, and the tumor necrosis factor (TNF)-inhibitors golimumab and etanercept for the treatment of pulmonary and cutaneous sarcoidosis.[6,7] Additionally, there have been reports of a more favorable response to infliximab in those with predominantly extrapulmonary sarcoidosis compared to those with predominantly pulmonary sarcoidosis.[8]

Despite the disappointing response in this case report, we and others[1] believe that IL-23 deserves further study as a target in the treatment of uveitis.

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DECLARATION OF INTEREST:

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