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Case Report

Vernal Keratoconjunctivitis: A Case of Anti-IgE Treatment with Short-Lasting Remission

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Keywords

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Abstract

Vernal keratoconjunctivitis (VKC) is a persistent, severe allergic eye disease, mainly occurring in children, that can lead to severe ocular complications including visual loss. The underlying etiology and pathophysiology of VKC remain unclear. Common therapies include topical antihistamines and mast cell stabilizers that are effective in mild-to-moderate forms of VKC but are often ineffective in severe forms that require topical or systemic corticosteroids. Dependence on steroids is common with potential adverse effects both local, as increased intraocular pressure, glaucoma, infection and cataract, as well as systemic ones, as reduction in child growth velocity. Alternative therapies are immunosuppressive drugs, like cyclosporine A and tacrolimus, that usually are effective but may also cause adverse effects. A promising therapeutic option is omalizumab, a recombinant anti-IgE humanized monoclonal antibody, currently used as add-on therapy for moderate to severe uncontrolled allergic asthma and chronic spontaneous urticaria. Here, we report the short-time duration of effective relief of symptoms

after the prolonged use of omalizumab in a patient affected by refractory VKC. However, in our case any apparent beneficial effect was short lasting, and we propose that the duration of the disease and the concomitant long-term use of steroids leads to iatrogenic damage; thus, the disease becomes refractory to anti-IgE treatment.

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Introduction

Vernal keratoconjunctivitis (VKC) is a persistent, severe allergic eye disease [1], mainly occurring in children and in warm climates, characterized by chronic corneoconjunctival inflammation that can lead to severe ocular complications such as glaucoma, corneal scarring, and blindness [2, 3]. Usually, it appears in boys (sex ratio, 3/1) during the first decade and often disappears during the end of the second decade of life [2, 4]. The most important symptoms are ocular itching, burning, redness, photophobia, and mucous discharge. The underlying etiology and pathophysiology of VKC remain unclear; however, clinical findings and immunohistochemical studies suggest a complex, immune-mediated pathogenesis [4]. Allergic sensitization is found in approximately 50% of patients and does not completely explain the severity and the clinical course of the disease. Common therapies include topical antihistamines and mast cell stabilizers that often fail to relieve signs and symptoms, so that topical or systemic corticosteroids are required. Dependence on steroids is common with potential adverse effects such as increased intraocular pressure, glaucoma, infection, cataract as well as reduction of growth velocity, taking into account that patients often start receiving systemic steroids in childhood. Alternative therapies are immunosuppressive drugs, like cyclosporin A and tacrolimus, which usually are effective but may also cause adverse effects [5, 6]. Recently, a few reports on the use of the anti-IgE monoclonal antibody omalizumab in severe VKC, for a total of 17 patients treated, showed encouraging results [6–13]. Currently, omalizumab has been licensed for use in severe allergic asthma and chronic spontaneous urticaria. Nevertheless, the knowledge of its mechanisms of action, which appear to affect not only IgE-triggered events, explains why there is so much interest in the use of this drug in other diseases, not only in those in which IgE plays a central role. In recent years, omalizumab has been investigated for several off-label uses, as confirmed by clinical trials that in one-third of cases focused on the use of Omalizumab in conditions other than severe asthma and chronic urticaria [14]. Here, we describe the use of omalizumab in a patient affected by VKC who showed only transient benefit at a long-term follow-up.

Case Report

The patient, a 24-year-old male, was affected by severe keratoconjunctivitis and intermittent-mild allergic rhinitis since the age of 5 years. He also suffered from mild atopic dermatitis (AD), treated with moisturizing creams, occasionally topical steroids and cetirizine to control itch. AD completely disappeared by 18 years of age. The rhinoconjunctivitis was treated with cetirizine (then levocetirizine), and topical mometasone furoate nasal spray during spring and summer months. Allergen sensitization towards olive and cypress pollens was detected by

skin tests at the age of 6 years; however, ocular symptoms extended well beyond the pollen season. Recurrent bilateral corneconjunctival inflammation characterized by giant conjunctival tarsal papillae unresponsive to antihistamine treatment was diagnosed at 8 years of age and prompted cryotherapy of giant tarsal papillae (two separate interventions at 1-year interval). At this age, visual acuity was 10/10 and 9/10 (right and left eye, respectively), with corresponding tonometry 15 and 13 mm Hg.

The patient was treated with nedocromil eye drops, ketotifen, and low-dose fluocinolone topical therapy, with the use of soft lenses (Bausch & Lomb) during spring and summer seasons to minimize corneal exposure.

Two years later, intolerance to the use of soft lenses and rapid development of ocular hypertension (45 mm Hg) occurred, and both limbal inflammation and generalized keratitis with corneal ulcers were detected in the right eye. Admitted to a specialized ophthalmic center, the patient was treated with betamethasone (despite ocular hypertension). Reepithelialization started already on the third day of treatment, and normalization of ocular pressure was obtained with combined therapy.

Definitive diagnosis of VKC was established the following month, and the patient was discharged with the following therapy: cyclosporine A 50 mg twice daily, ketotifen eye drops, ketotifen 2 mg/day and prednisone 5 mg/day (oral therapy to be taken 5 days/week). This treatment was followed for the next 8 years, with withdrawal of oral ketotifen and reduction of prednisone to alternate days.

At age 20 years, topical cyclosporine 1% was started as an attempt to substitute for oral cyclosporine, but a few months later the oral formulation was reintroduced 6 days/week for worsening of symptoms, in addition to topical cyclosporine.

In March 2017, he was referred to our outpatient clinic, where laboratory tests were requested, including complete blood cell count, which revealed normal eosinophils (140 cells/ μ L), autoantibodies (antinuclear antibodies absent), complement levels (normal) and allergy screening that revealed total IgE levels of 128 IU/mL, specific IgE (kUA/L) to nOle e1 1.17, nCup a1 3.10, thus confirming the allergic sensitization diagnosed at age 5, and below 0.01 for cat and dog epithelia, *Alternaria* spp., *Parietaria* and grass pollens. Eosinophil cationic protein (ECP) in tears was <2 μ g/L (left eye) and 10.90 μ g/L (right eye). We therefore decided to attempt treatment with omalizumab, 300 mg s.c. every 4 weeks, according to weight and total serum IgE level. At the time of starting this treatment, the patient was also taking oral prednisone (5 mg/b.i.d. reduced to once a day).

Since the first administration of omalizumab, the patient reported benefits such as reduced ocular dryness and redness. In August, ocular hypertension developed in the right eye; therefore, oral steroid was stopped, and hypotensive treatment started with beta blockers for topical use. Despite this, in October 2017 he was subjected to implantation of glaucoma valve to reduce right eye intraocular pressure. After that, he experienced a worsening of ocular symptoms (burning, photophobia, and ptosis) but only to the right eye, as a consequence of the surgical intervention.

In January 2018, a scarring lesion was observed, and then treated with topical steroid, until resolution. In June again, he suffered burning, pain, and photophobia in the right eye, and a corneal ulcer was found (Fig. 1). Omalizumab was administered at 4 weekly intervals until September, for a total of 19 months, while receiving topical cyclosporine and antibiotic treatment. Due to the recurrent symptoms and persisting ocular lesions, we decided to discontinue

omalizumab and follow the patient under standard therapy. The patient gave informed consent to the off-label treatment with omalizumab and to the use of his medical records for scientific purpose.

Discussion

We report the short duration of effective relief of symptoms after the prolonged use of omalizumab, an anti-IgE monoclonal antibody, in a patient affected by refractory VKC. The patient suffered from a particularly severe form of VKC, a disease whose pathogenesis is not completely understood, and where IgE are involved although with an unclear role. In this case, antihistamines, steroids and immunosuppressive drugs had failed to arrest the multiple flares and to effectively relieve symptoms. Omalizumab has been proposed as rescue therapy, and several reports have been published in recent years for the treatment of VKC [6–13]. Omalizumab has a mechanism of action that is beyond the simple blocking of IgE binding, so it may provide additional benefit by inhibiting the perpetuation of type 2 inflammation [14]. Moreover, no patient experienced severe adverse effects during treatment with omalizumab, which is a well-tolerated and safe drug. Ocular signs affect palpebral and/or limbal region, so three VKC phenotypes can be distinguished (tarsal, limbal, and mixed). Pathognomonic signs are represented by papillary hyperplasia of the upper tarsal conjunctiva (ranging from papillae of 1 mm of diameter to typical giant or cobble stone papillae) and infiltration of the limbal tissue with frequent recognizable excrescences, known as Horner-Trantas dots [2]. Corneal involvement includes superficial punctate keratitis, shield ulcers, and vernal plaques that may cause permanent reduction in visual acuity. Eosinophils are the predominant cells found in tears and eye discharge, while tear levels of ECP, interleukin-5 and eotaxin seem to be related to disease severity [2]. In our patient, the disease was predominantly affecting the right eye, where tear ECP was measurable, whereas in normal conditions it is absent. Reviewing the literature on the use of omalizumab in VKC, of all the patients treated with the drug, 11 showed complete control of the disease, 4 patients a partial control, and 2 patients did not respond to the therapy (Table 1). The period of observation was up to 4 years. Although 1 of the 2 nonresponding patients was nonatopic, the lack of allergic sensitization would not seem to be the discriminating reason for a possible failure of therapy. Indeed, some authors [7, 10, 11] reported cases of patients with VKC, who were successfully treated with omalizumab, although they were not allergic. The anti-IgE monoclonal antibody omalizumab is a humanized IgG1 able to bind selectively free serum IgE, specifically in the Cε3 region of the Fc fragment. For this reason, it prevents IgE binding to high-affinity receptor FcεRI of many cell types, including basophils and mast cells. This results in a reduction of total free IgE, with the resulting inability to trigger mediator release from these cell types. Moreover, the reduction of available IgE induces a decrease in FcεRI expression on the surface of mast cells, basophils, and dendritic cells, thus leading to a decrease of the allergic inflammation and ultimately to a lower production of IgE [14]. Clinical evidence suggests that VKC usually subsides during puberty. In our case, the patient continued to show severe allergic inflammation even later, requiring long-term corticosteroid therapy due to failure of a steroid-free treatment with only cyclosporine A. This was the immediate cause of the increase in intraocular pressure, a complication that would seem more frequent in the mixed-type VKC [15], and it was treated with antiglaucoma

drugs and surgery. During the treatment with omalizumab, the patient initially experienced an improvement of ocular symptoms, but this was not long lasting, and it never allowed the discontinuation of other therapies. At the time of this patient's treatment, other biologic therapies such as mepolizumab or benralizumab were not available to us. Despite the relevance of interleukin-5 and the strong eosinophilic inflammation characterizing VKC [2], we found no reports of their use in the treatment of this disorder. In our patient, ECP was detectable at low levels only in tears from the right eye; so, we did not attempt to try anti-interleukin-5 after discontinuation of omalizumab, when these new biologics became available. We may hypothesize that early treatment with anti-IgE could have avoided the side effects due to prolonged steroid therapy. This is particularly important in childhood, since prolonged oral steroid use may severely impact growth velocity. However, this should be validated by some direct experience, since the patient arrived at our clinic at the age of 23 and without signs of impaired growth. In conclusion, omalizumab seems to be a safe drug but not an effective therapy in severe VKC, where the duration of the disease and the concomitant long-term use of steroids lead to iatrogenic damage, and the disease becomes refractory to other forms of treatments.

Statement of Ethics

The study reported was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The patient gave informed consent to the treatment and the use of medical records for publication.

Disclosure Statement

The authors declare that they have no conflict of interest in relation to the content of this study.

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Author Contributions

A.G., L.D.V., and A.F. collected the case history; they, together with G.S. A.L., E.C. and M.D.G. collected records and provided medical care during the therapeutic and follow-up period; A.G. and R.P. reviewed the literature on VKC treatment; A.G. and R.P. wrote the manuscript; M.D.G. and R.P. provided the revision. All co-authors read and approved the final version of the manuscript.

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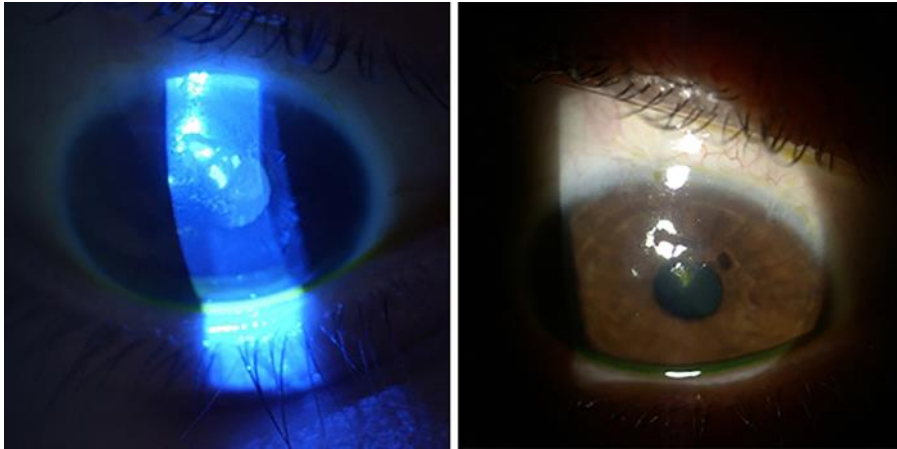


Fig. 1. Shield ulcer staining positive with fluorescein.

Table 1. Case series on VKC patients treated with omalizumab

First author [Ref.]	Patients	Age, years/sex	Atopic condition	Allergic sensitization	Omalizumab schedule	Duration of therapy	Control of VKC
Williams [6]	3	33/M	A, R, AD	Not specified	Based on weight and total serum IgE	Not specified	Total control
		67/F	A, R, AD	Not specified		Not specified	No changes
		59/F	A, R, AD	Not specified		Not specified	Total control
Sanchez [7]	1	15/M	A, R, AD	Dust mites	300 mg/2 weeks	9 months	Total control
de Klerk [8]	1	12/M	A, R, E	Not specified	300 mg/month	18 months	Total control
Occasi [9]	1	15/M	A, AD	Dust mites, <i>Lolium perenne</i> , cypress, Betulaceae	600 mg/2 weeks	3 months	Total control
Heffler [10]	2	9/F	None	None	300 mg/month based on weight and total serum IgE	6 months	Total control
		21/M	AD	None		6 months	Partial control
Occasi [11]	4	6/M	E	None	Based on weight and total serum IgE	6 months	Total control
		8/M	None	None		6 months	Total control
		11/F	R	None		6 months	Total control
		9/M	R	None		6 months	Total control
Doan [12]	4	13/M	A, R	Grasses, Fagaceae, <i>Alternaria</i> , cat dander	600/2 weeks	16 months	Partial control
		10/M	A, R	Grasses, dust mites, <i>Alternaria</i>	600/2 weeks	33 months	Partial control
		7/M	A, R, AD	Grasses, birch	450/2 weeks	42 months	Partial control
		7/M	A	None	600/2 weeks	6 months	No change
Santamaria [13]	1	15/F	R	Dust mites	225 mg/2 weeks Reduced to 150/2 weeks after 24 months	54 months	Total control with relapses in case of discontinuation

A, asthma; R, rhinitis; AD, atopic dermatitis; E, eczema.