

Omalizumab in Severe Refractory Vernal Keratoconjunctivitis in Children: Case Series and Review of the Literature

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ABSTRACT

Introduction: Vernal keratoconjunctivitis (VKC) is a severe form of pediatric ocular allergy, characterized by acute and chronic corneoconjunctival inflammation that may lead to visual sequelae. Although topical immunosuppressive drugs such as cyclosporine are usually effective, some severe forms may be refractory and require prolonged steroid therapy. Very few papers report the use of

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omalizumab in VKC in the literature. In the present study, we describe our clinical experience with omalizumab in severe VKC children.

Methods: We retrospectively reviewed the files of four boys treated with omalizumab because of severe VKC, defined as persistent corneal inflammation despite continuous topical 2% cyclosporine and steroid eye drops. We also performed a literature review.

Results: Four boys, aged 7–13 years old, were treated. All children had asthma and one had severe lid eczema. Two patients had required intrapalpebral depot-steroid injections. Omalizumab was administered every 2 weeks by subcutaneous injections, at doses varying from 450 to 600 mg per injection. Three patients out of four responded to the treatment, with a decrease in global symptoms (median symptom rating decreasing from 89 to 29 on a 100-mm visual analog scale), frequency and in duration of the inflammatory flares, and also a decreased need for topical steroid. Their median clinical grade decreased from 4 to 3 (Bonini grading). However, the response was incomplete and they still had inflammatory corneoconjunctival flares despite continuous

topical cyclosporine. On the other hand, asthma and lid eczema were completely controlled in these three patients. The fourth child did not respond to omalizumab and needed oral steroids for his VKC and his asthma. Noticeably, this latter patient did not have detectable sensitization to any allergen, contrary to the other cases. The treatment was stopped in this refractory case, but is still ongoing in all other cases, with a median duration of 33 months (range 16–42 months). In the literature (four cases), omalizumab may have a more complete efficacy in some cases, but the results are still variable.

Conclusion: Omalizumab is an interesting treatment in severe refractory forms of VKC, but its efficacy is incomplete in these very severe cases.

Keywords: Children; Cyclosporine; IgE; Immunomodulation; Severe allergy; Steroids; VKC

INTRODUCTION

Vernal keratoconjunctivitis (VKC) is a severe form of ocular allergy occurring mainly in children. It is characterized by chronic corneoconjunctival inflammation with giant conjunctival tarsal papillae and/or limbal inflammation. Inflammatory flares are more frequent during the hot season, usually from March to October in temperate climates, but may be perennial in sunny/tropical climates or late forms. Symptoms such as ocular itching, burning, photophobia and sticky eyes with mucous ropy discharge, have an important impact on the quality of life of the children. Furthermore, corneal involvement such as dense superficial punctate keratitis, shield ulcers and vernal plaques, are very

symptomatic and may lead to neovascularized scars and visual sequelae.

Treatment of mild forms of VKC include wearing of sunglasses, ocular rinsing with balanced saline solution, and topical and systemic antihistamines H1 and topical mast cell stabilizers. In case of inflammatory flare with corneal involvement, topical steroids are needed. Dependence on steroids is very frequent, exposing children to unacceptable adverse effects such as ocular hypertension, glaucoma, cataract and infection. Besides, children are more susceptible to develop ocular hypertension than adults, and, also, monitoring of the ocular pressure may be difficult in non cooperative children. Topical immunosuppressive drugs are usually used in steroid-dependant cases. Cyclosporine A eye drops (0.5–2%; CsA) are the most frequently used and studied, and have been shown to have a steroid sparing effect with an excellent safety profile. However, a significant proportion of patients are intolerant to CsA, and 16% and 5% do not respond to this treatment at month 1 and 3, respectively [1]. There are very few options in these refractory cases: supratarsal steroid injections are very potent, but may induce severe iatrogenic complications [2]; systemic steroids may be used only for a limited time; tacrolimus 0.03% skin ointment is not approved for conjunctival application, although it seems to have a very interesting effect [3]; tacrolimus 0.1% eye drops are probably also potent, but are available only in few asian countries for the moment [4]; mild cryotherapy of papillae is also an option for some [5], but we believe that there is a risk of conjunctival atrophy and scarring after repeated applications.

The pathophysiology of VKC combines IgE-mediated allergic reactions to

non-IgE-mediated reactions [6]. IgE-mediated reactions characterize the classical immediate allergic reaction, also called anaphylaxis. As a prerequisite, sensitization to specific allergens such as pollen, dust mites, animal dander, mold, food allergens, leads to the production of specific immunoglobulins E (IgEs). When the allergen binds to specific IgEs present at the surface of a conjunctival mast cell, a degranulation of preformed mediators such as histamine, chymase and tryptase by the mast cell occurs. These mediators are responsible for the classical symptoms and signs of the early allergic phase: itching, redness and edema. A late phase occurs after 6 h, as a result of the production of postformed inflammatory mediators such as leukotrienes and prostaglandins by the mast cell, leading to the infiltration of eosinophils, neutrophils and macrophages in the tissue. Eosinophils play a major role in inflammation and in tissular lesions such as epitheliopathy in VKC. CD4+ TH2 cells seem to drive these IgE-dependant reactions in VKC [7]. However, only 50% of VKC patients have identified sensitization to specific allergens. Indeed, several types of non-IgE-mediated reactions also occur in VKC, among which direct activation of T cells, dendritic cells, enzymatic systems, metalloproteases, and non-specific hyper-reactivity are included [8].

Omalizumab is a monoclonal chimeric anti-IgE antibody that binds to the Cε3 domain of free circulating IgE, resulting in inactive immune complexes that are cleared from the plasma [9]. It can reduce circulating free IgE up to 99%, thus suppressing the activation of mast cells [10] and down-regulating the expression of the IgE receptors FcεRI at the surface of basophiles and mast cells. Hence, the IgE-mediated reactions are less likely to occur [11].

Several studies have shown the efficacy of omalizumab in allergic asthma since the initial publications in 1999 [12], leading to the approval of omalizumab for this indication in the USA in 2003 and in France in 2006. In patients with moderate to severe allergic asthma with dependence on inhaled steroids, the addition of omalizumab reduces asthma exacerbations and decreases inhaled corticosteroid and rescue medication use. Furthermore, a few studies have shown the efficacy of this molecule in seasonal allergic rhinitis [13, 14].

Omalizumab is administered systematically by subcutaneous injections every 2–4 weeks, according to the weight and the level of blood total IgEs. It has initially been authorized for the treatment of severe asthma. Few case reports suggest its efficacy in VKC and atopic keratoconjunctivitis [15, 16]. The purpose of this study is to report our clinical experience with omalizumab in severe refractory cases of VKC in children, and to review the literature.

METHODS

Design

This was a non-controlled, open-label, retrospective case series.

We reviewed the files of four boys (eight eyes), suffering from severe VKC, and who were treated with omalizumab.

For each patient, we collected the ocular and extra-ocular data concerning their allergic diseases.

At each visit, a global symptom score was assessed by a visual analog scale (from 0 if no symptoms to 100 mm if maximum symptoms).

VKC severity was graded according to Bonini's classification [17]: grade 0: no

symptoms, no superficial punctate keratitis (SPK); grade 1: mild symptoms, no SPK; grade 2: photophobia, no SPK; grade 3: photophobia, moderate SPK; grade 4: photophobia, severe SPK or corneal ulcer.

Response to treatment was graded as follows: total control: no inflammatory flare; partial control: decrease in the number and/or intensity of the inflammatory flares; failure: no change in the evolution.

The retrospective analysis was approved by the institutional ethical committee of Fondation A de Rothschild. The parents provided written informed consent for publication of clinical data.

RESULTS

Patients were aged 7–13 years. They all suffered from very severe VKC, with symptom scores ranging from 72 to 100 mm, and a clinical grade of 4 in all cases, according to Bonini's classification. Their disease was resistant to topical steroids and topical cyclosporine 2% eye drops, with persistent superficial punctate keratitis despite these treatments for more than 2 years (at least 8 months per year; Table 1). Patient #2 developed a shield ulcer on the left eye, requiring corneal scraping 2 years earlier. In patients #2 and 4, supratarsal depot triamcinolone injections had even been performed once a year for the 2 previous years, and were the only way to control corneal inflammation at this moment.

All patients suffered from asthma, and also from severe rhinitis in three cases (#1, 2 and 3) and severe atopic dermatitis with periocular involvement in case #3. All patients were polysensitized, except patient #4 for whom no sensitization was found. Total serum IgE ranged from 141 to 8000 KUI/L.

Omalizumab was primarily introduced because of the severe ocular involvement. It was administered every 2 weeks by subcutaneous injections, at doses varying from 450 to 600 mg per injection.

In three children (cases #1, 2 and 3), the ocular response to omalizumab was graded as a partial control: symptom scores dropped down to values ranging from 30 to 52 mm at 8 weeks months and from 21 to 31 mm at the end of follow-up. Clinical grading decreased from grade 4 to grade 3 in these 3 cases (Fig. 1). However, inflammatory flares with dense punctate superficial keratitis (3–5 episodes per year) still occurred but were much shorter and easily controlled with topical steroids, which were then only needed during the inflammatory flares for a short course, and not continuously as before omalizumab treatment. Corneal inflammation returned to zero between the inflammatory flares, which was never the case before treatment. Topical cyclosporine was continued in cases #1 and 2, and stopped in case #3 because of allergy to the eye drops, without consequence. No palpebral steroid injections were needed in any of those three cases.

In these three responder cases, asthma was totally controlled after 4 months, and eczema also healed completely after 9 months in case #3. Rhinitis was only partially controlled, with still noticeable nasal obstruction and intermittent need for nasal steroids.

Omalizumab was stopped after 16 months in case #1, and has been administered for 33 and 42 months, still ongoing in cases #2 and 3, respectively.

Case #4 did not respond at all to omalizumab, which was stopped after 6 months. Asthma and VKC still needed high doses of topical steroids, and also oral steroid

Table 1 Demographic features and outcome in VKC patients treated with omalizumab in the present case series and in the literature

Authors	n	Patient #	Before omalizumab		Allergy (prick tests + specific seric IgE)	Blood total IgE (KUI/L)	Ocular history	Previous treatments	
			Age	Gender					Atopy
Current paper									
Doan et al. [1]	4	1	13	Male	Asthma rhinitis	Grass pollens, fagaceae, alternaria, cat dander, cow milk, eggs	146	Palpebral form	Continuous topical steroids and CsA
		2	10	Male	Asthma, rhinitis	Grass pollens, dust mites, alternaria, nuts	1655	Palpebral and limbal form Vernal plaque OS Supratarsal steroid injections	Topical steroids 8 months/year and continuous topical CsA supratarsal steroid injections OS
		3	7	Male	Asthma, eczema, rhinitis	Grass pollens, birch, peanuts, eggs, kiwi	8000	Palpebral and limbal form	Continuous topical steroids and CsA
		4	7	Male	Asthma	None	141	Palpebral form Supratarsal steroid injection OS	Continuous topical steroids and CsA supratarsal steroid injections OS
Literature review									
Sanchez et al. [18]	1	5	15	Male	Asthma, eczema, rhinitis	Dust mites	340		Tacrolimus ointment on lids and eyes
	de Klerk et al. [15]	1	6	12	Male	Asthma, eczema, rhinitis	?	Vernal plaque OR Supratarsal steroid injections	CsA OU supratarsal steroid injection OR
Heffler et al. [19]	2	7	9	Female	None	None	?		Topical steroids, CsA, tacrolimus; oral steroids
		8	21	Male	Eczema	None	?		Topical steroids, CsA, tacrolimus; oral steroids

Table 1 continued

Authors	n	Patient #	Outcome on omalizumab			Ocular signs
			Delay for improvement	Dosing of OMZ	Efficacy on VKC	
Current paper						
Doan et al. [1]	4	1	3 months	600 mg every 2 weeks	Partial control	VAS 89 => 31 (16 months). Grade 4 => 3 Still some inflammatory flares
		2	6 weeks	600 mg every 2 weeks	Partial control	VAS 72 => 21 (33 months). Grade 4 => 3 Still some inflammatory flares
		3	2 months	450 mg every 2 weeks	Partial control	VAS 90 => 29 (42 months). Grade 4 => 3 Still some inflammatory flares
		4	NA	600 mg every 2 weeks	Failure	VAS 100 => 100 Grade 4 => 4
Literature review						
Sanchez et al. [18]	1	5	6 weeks	300 mg every 2 weeks	Total control	Disappearance of giant papillae
de Klerk et al. [15]	1	6	8 weeks	300 mg every month	Total control	Disappearance of keratitis and giant papillae
Heffler et al. [19]	2	7	2 months	300 mg every month	Total control	Disappearance of symptoms Disappearance of redness and giant papillae
		8	5 months	600 mg every month	Partial control	Partial reduction of symptoms Disappearance of giant papillae, reduction of redness

Table 1 continued

Authors	n	Patient #	Outcome on omalizumab	Treatment associated with OMZ	Asthma	Eczema	Rhinitis	Duration of OMZ treatment (months)
Current paper								
Doan et al. [1]	4	1	Rescue topical steroids 6 weeks/year continuous topical CsA, MCS and AHI	Total control ACT 24/25 => 24/25 (1 month)	NA	NA	Partial control SFAR 15/16 => 10/16 (16 months)	16 (stopped)
		2	Rescue topical steroids 4 weeks/year continuous topical CsA, MCS and AHI	Total control ACT 20/27 => 24/27 (4 months)	NA	NA	Partial control SFAR 14/16 => 13/16 (33 months)	33 (ongoing)
		3	Rescue topical steroids 8 weeks/year continuous MCS and AHI	Total control ACT 27/27 => 27/27 (1 month)	Total control SCORAD 56 => 5 (9 months)	NA	Partial control SFAR 15/16 => 11/16 (42 months)	42 (ongoing)
		4	Continuous topical steroids, CsA, MCS and AHI + oral steroid pulses	Failure ACT 3/27 => 5/27 (6 months)	NA	NA	NA	6 (stopped)
Literature review								
Sanchez et al. [18]	1	5	Continuous topical tacrolimus	Total control after 2 months	Total control after 6 months	?	Total control	18
de Klerk et al. [15]	1	6	None	Marked improvement	Partial control	Total control	Total control	18
Heffler et al. [19]	2	7	Rescue topical antihistamines	NA	NA	NA	NA	6 (stopped)
		8	Rescue topical antihistamines	NA	NA	NA	NA	6 (stopped)

NA non-applicable, OMZ omalizumab, MCS mast cell stabilizers, AHI antihistamines HI, CsA cyclosporine A eye drops, VAS Visual Analog Scale, RQLQ Rhinoconjunctivitis Quality of Life Questionnaire, ACT Asthma Control Score, according to [22]—the higher the better, SFAR Score For Allergic Rhinitis, according to [23], SCORAD Score for Atopic Dermatitis, according to [24]

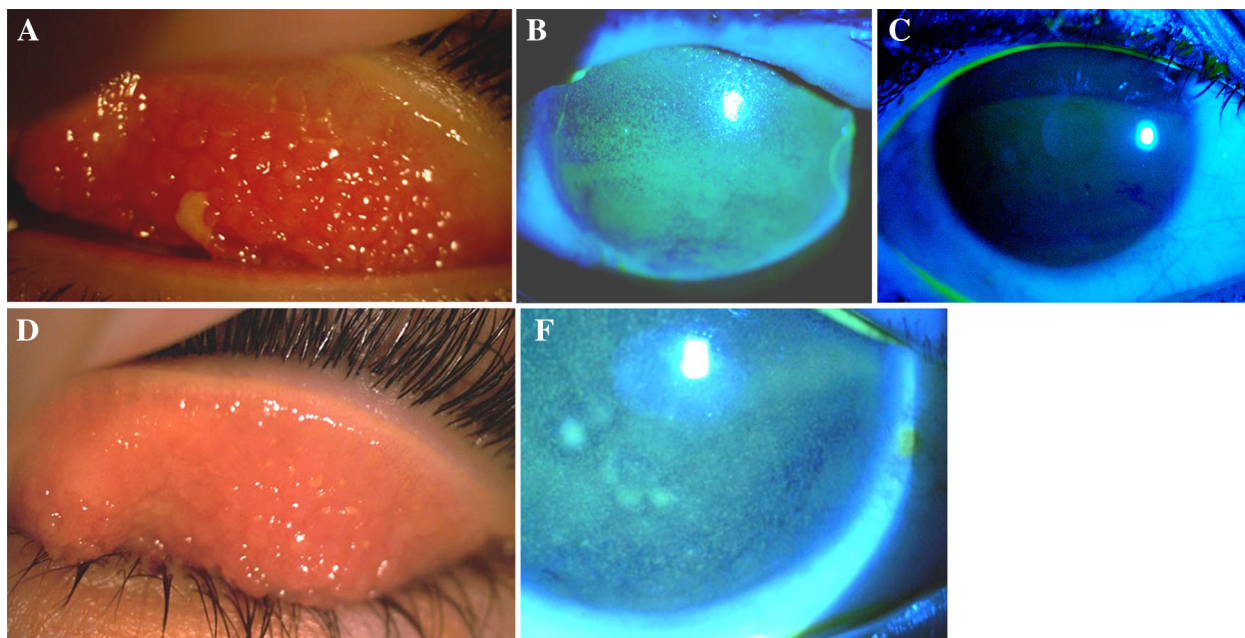


Fig. 1 Patient #3, before treatment (**a, b**) and after 3 months of omalizumab (**c**). At month 4, a recurrence of corneal inflammation occurred (**d, e**). Superior palpebral conjunctival papillar hypertrophy (**a, c**) and corneal fluorescein staining (**b, d, e**), showing partial diminution

of inflammation. In this patient, several episodes of corneal inflammation occurred on omalizumab, but were less frequent and easier to control, compared to before omalizumab treatment

pulses in order to control pulmonary and ocular inflammation. Noticeably, this patient was the only one to have no evident sensitization at allergy workout. His serum IgE level was 141 pre-treatment, and 77 post-treatment.

Omalizumab was well tolerated in our four patients, and no adverse effects were noted.

LITERATURE REVIEW

We performed a literature search in PubMed. The keywords were vernal keratoconjunctivitis, atopic keratoconjunctivitis, allergic conjunctivitis, and omalizumab. There were only case reports, with a total of four children with VKC who were treated with omalizumab. The cases are summarized in Table 1.

Sanchez et al. described the first VKC patient treated with omalizumab in 2012 [18]. This severe case had unsuccessfully been treated with

topical steroids/cyclosporine, then topical tacrolimus 0.03% ointment for more than 2 years. Although this latter treatment had been maintained, omalizumab clearly allowed for a major reduction of the symptoms after 3–6 months, with a disappearance of the conjunctival tarsal giant papillae after 10 months. No steroid treatment was needed while on omalizumab. Extra ocular involvement (asthma, atopic dermatitis and rhinitis) also improved with the treatment. The effects were still present after 18 months of treatment.

In 2013, de Klerk et al. [15] described the second case of VKC, who had developed a corneal shield ulcer despite topical steroids on the right eye, leading to a subtarsal injection of triamcinolone. Omalizumab was introduced because of non-controlled severe asthma and rhinitis. After 2 months of treatment, ocular

symptoms had improved, as well as asthma and rhinitis. After 18 months, the ocular involvement was completely controlled, with a disappearance of the giant conjunctival papillae and of the keratitis. Asthma and rhinitis were completely controlled, although eczema was still moderately active. Although this child had had a severe corneal complication, it is difficult to grade the real severity of his case, for topical cyclosporine had been prescribed for a very short time before omalizumab was initiated for a non-ocular reason.

Recently, Heffler et al. reported two cases, aged 9 (girl) and 21 (man) [19, 20]. The particularities of their study are that none of the patients had asthma, and the efficacy was assessed by clinical parameters, but also by eosinophil count on conjunctival scrape smears. The cases were unresponsive to topical corticosteroids, cyclosporine and tacrolimus, and partially responsive to oral steroids. The younger patient completely responded to omalizumab within 2 months in terms of symptoms and eye redness. The older patient only responded partially and progressively within 5 months. He also suffered from eczema, and, given his age, might have, in fact, a frontier form between AKC and VKC. The eczema was not modified by omalizumab. Giant papillae disappeared after 6 months in both cases. The eosinophil count on conjunctival smears was also dramatically reduced after 6 months of treatment, from 69% in the child and 51% in the young man to 3% and 0%, respectively. Omalizumab was stopped after 6 months in both cases, without recurrence after 4 months.

Williams et al. published an expert review in 2005, where they reported six patients with severe AKC [21]. Unfortunately, the description of their cases was incomplete. Although three patients were qualified as VKC in their summary

table, it is likely that all patients were, in fact, AKC patients, as stated in the text, for their age ranged from 27 to 71 years. All patients were on topical and systemic steroids. It seems that symptoms and signs decreased globally, although some fluctuation was noted, following the evolution of the general allergy symptoms. The need for topical steroids was decreased in all patients but one. No patient received topical cyclosporine.

DISCUSSION

Omalizumab seems to be a potent treatment for refractory forms of VKC. It allows a reduction of symptoms and corneoconjunctival inflammation. Its efficacy is, however, variable among patients. One patient out of eight did not respond at all. Response was considered as partial in four patients, and complete in three. This variability could reflect the incomplete responsibility of IgE-mediated mechanisms in VKC, as proposed in the new classification of allergic eye diseases published in a position paper of the European Academy of Allergy and Clinical Immunology written by Leonardi et al. [6]. Case #4, for whom omalizumab failed, was the only child of our series without any allergic sensitization. Absence of allergy might be a risk factor of treatment failure, although the two patients reported by Heffler et al. were also non-allergic but responded well to the treatment. Besides, elevated total IgE blood levels did not seem to be a predictive factor of ocular response in these patients.

In patients with very high inflammatory levels, omalizumab may only have a partial effect. However, the patients are very happy with the treatment, because the inflammatory flares become more seldom and easily controlled with topical steroids (cases #1, 2 and 3) or antihistamines (cases #7 and 8).

Patients #1, 2 and 3 also suffered from rhinitis, which was only partially controlled by omalizumab, whereas asthma and eczema totally healed within 4 months. Omalizumab might have a lower effect on the eyes and nose, compared to the lungs and skin, although patient #8 did not show any improvement of his eczema on omalizumab. The mechanisms of nasal and ocular inflammation may be more IgE-independent than asthma and eczema.

Several questions remain concerning the optimal therapeutic scheme in VKC patients. The dosing of omalizumab varied from 300 mg every month to 600 mg every 2 weeks, which represents a four-fold variation between different teams, but there are no data available in these patients for a dose–effect relation.

Among all the publications, our patients have the longest duration of treatment by omalizumab, up to 42 months. However, VKC is seasonal in 70% of patients, with an increase of inflammatory flares between February and October. It is not clear whether omalizumab could be stopped during winter, but it seems that this practice has been adopted by some teams.

The cost of omalizumab remains a concern (several thousand euros in Europe), but in most severe cases of VKC, we believe that such a cost is justified. Although the effect was partial in our patients, the occurrence of severe corneal complications was prevented, and the quality of life of the patients much better. In the future, other key mechanisms such as those involving eosinophils should be targeted by new treatments.

CONCLUSION

Omalizumab is an interesting treatment for refractory forms of VKC. Its efficacy can be

partial in most severe forms, but reduction of signs, symptoms and anti-inflammatory treatment is almost always noted. The best patient profile and treatment regimen are yet to be determined. Controlled studies are needed in the future.

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Compliance with Ethics Guidelines. The retrospective analysis was approved by the institutional ethical committee of Fondation A de Rothschild. The parents provided written informed consent for publication of clinical data.

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