

DR. FRANCESCA OCCASI (Orcid ID : 0000-0001-9160-5782)

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VERNAL KERATOCONJUNCTIVITIS TREATED WITH OMALIZUMAB: A CASE SERIES.

Francesca Occasi 1. MD.

Marzia Duse 1. Professor, MD.

Marcella Nebbioso 2. Professor, MD.

Giovanna De Castro 1. Professor, MD.

Marco Di Fraia 1. M.D.

Giulia Capata 1. M.D.

Valeria Lollobrigida 1. MD.

Anna Maria Zicari 1. Professor, MD.

1 “Sapienza” University of Rome, Department of Pediatrics, Rome, Italy .

2 “Sapienza” University of Rome, Department of Sense Organs, Rome, Italy .

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Corresponding author:

Marcella Nebbioso

“Sapienza” University of Rome

Work address: Viale Regina Elena , 324- 00161 Rome, Italy

Mail: marcella.nebbioso@uniroma1.it

+39 06 49979333

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VERNAL KERATOCONJUNCTIVITIS TREATED WITH OMALIZUMAB: A CASE SERIES.

To the Editor,

We report the cases of 4 children affected by Vernal keratoconjunctivitis (VKC) treated with Omalizumab with resolution of ocular signs and symptoms. Vernal keratoconjunctivitis (VKC) is a chronic conjunctivitis, not responding to topical antihistamines and frequently misdiagnosed and mistreated.

Patient 1 was a 6 years old male who referred to our center for a severe photophobia, dramatically affecting his activities during the last year, and he was diagnosed with VKC by an ophthalmologist reporting intense conjunctival hyperemia and giant papillae in the upper palpebral conjunctiva. Patient 2 was a 8 years old male with severe itching, photophobia, tearing and the evidence of giant papillae in both eyes. Patient 3 was a female aged 11 years referring severe ocular symptoms since the last two years and tarsal and limbal papillae with Trantas dots at the ocular evaluation. Patient 4 was a male aged 9 years with numerous tarsal papillae, abundant ocular watery secretions and perilimbar edema.

The diagnosis of VKC was given by an ophthalmologist investigating ocular signs (conjunctival hyperemia, tarsal and/or limbal papillae, giant papillae, corneal involvement) and subjective ocular symptoms (itching, photophobia, tearing, foreign body sensation, and burning sensation). Signs and symptoms have been classified using two disease severity scales graded from '0' absent to '2' severe, as previously described.¹

All children have been previously unsuccessfully treated with topical antihistamines and had a corneal involvement with de-epithelialization, while patient 1 had a severe corneal keratitis and he has been also treated with topical vancomycin for 15 days. Of note, all patients underwent Skin Prick Test to the main airborne and food allergens and serum specific IgE testing without any evidence of allergic sensitization. Concerning comorbidities, no patient had concomitant asthma although patient 1 referred eczema and patients 4 and 5 persistent rhinitis.

After the diagnosis all children underwent topical treatment with 1% cyclosporine (1 drop/eye twice daily) prepared strictly respecting sterility criteria, by the Chemistry Service Institute at the 'Sapienza' University of Rome, following a formulation including one part of commercially available cyclosporine solution for intravenous infusion (Sandimmun_Novartis Farma S.p.A.S.S., Varese, Italy), diluted in aqueous vehicle (Vismed Light_TRB Chemedica, Haar/Munich, Germany) for 1 month without significant improvement of symptoms and ocular signs, followed by Tacrolimus eyedrops at 0.1% (1 drop/eye twice daily) obtained by diluting one part of Prograf vial [5 mg/ml (Astellas Pharma)] in the aqueous vehicle and administered for another month, without resolution. Considering the unsuccessful outcome of these therapies, a subcutaneous therapy with Omalizumab (Novartis, Basel, Switzerland) was administered at the dosage scheduled for patients with asthma based on weight and total serum IgE level for 6 months. During the first weeks of treatment with Omalizumab, all children experienced an improvement of ocular symptoms and clinical signs with a resolution of conjunctival hyperemia, tarsal and limbal papillae, giant papillae and, after 3 months, a visible corneal re-epithelialization. No relapse was observed after treatment suspension. Ocular scores and IgE levels graded before treatment with Omalizumab and after 3 and 6 month of therapy are summarized in figure 1. Serum IgE levels were detected by ImmunoCAP (Thermo Fisher Scientific, Uppsala, Sweden).

According to our knowledge, this is the first case series in children affected by resistant VKC and successfully treated with Omalizumab. The assumption of its effectiveness in this severe ocular disease was based on a previous experience of our study group,² also supported by a recently published case report.³ Interestingly, while in the first report² we described the case of a young male affected by VKC associated with severe atopic dermatitis and uncontrolled asthma, in the last report³ the authors reported the case of a girl affected by a severe VKC without any manifestation of allergy or asthma in the first decade of her life. Of note, other two groups reported the effectiveness of Omalizumab in VKC although in patients with comorbidities.^{4,5}

VKC is classified as a chronic ocular allergic disease. Although Th1 and Th2 mechanisms have been implied⁶, the role of IgE has always been disputed. Omalizumab is a recombinant humanized monoclonal antibody binding free IgE, reducing the expression of the IgE receptor and controlling the release of soluble mediators, approved for patients older than 6 years suffering from moderate to severe uncontrolled allergic asthma. Considering the uncertain role of IgE in the pathogenesis of VKC, the mechanism this recombinant antibody exercises its effect on ocular inflammation is yet to be clarified. Noga O. et al.⁷ showed an increased eosinophil apoptosis, a reduction of IL-2 and IL-13 producing lymphocytes and of serum IL-13 in patients with asthma treated with omalizumab.

However, this increased apoptosis might be the result of the direct interaction with eosinophils or a secondary effect related to an alteration of secreted cytokines as well. Also the finding that IL-5, an important survival factor for eosinophils, was not significantly influenced by Omalizumab underlines that its effect on lymphocytes should be better investigated. In this perspective, although eosinophils and mast cells are the most represented cells in the conjunctival scraping of patients affected by VKC⁴ other cells might play a crucial role in its pathogenesis. Of note, Heffler E. et al.³ reported a reduction of eosinophils in the conjunctival scraping of two patients treated with Omalizumab. However, also IgE might exert a role in directly maintaining eosinophils and, hence the IgE elimination might also result in an increased apoptosis of eosinophils. In the present case series we documented a reduction of total IgE in line with symptoms improvement. Although measurements of free IgE after Omalizumab administration is still debated, even in the presence of interfering omalizumab, total IgE measurements can be effectively used to detect changes that may aid in evaluating treatment efficacy.⁸ In this perspective, Ballou M. et al.⁹ detected specific IgE in tears of some patients with negative Skin prick test and serum specific IgE supporting the concept that specific IgE antibodies can be produced locally by the target organ. This phenomenon, also known as “entopy”, is the object of longstanding controversies, and has been studied especially in the nose where different phenotypes of allergic rhinitis have been investigated.¹⁰ In this sense, the existence of different phenotypes of ocular allergy might be hypothesized and should be studied in the light of symptoms severity.

In conclusion, the effect of Omalizumab in patients with VKC should be better investigated and well-designed studies are warranted to prove its efficacy. Not only might these studies be useful in order to provide new therapeutic strategies especially in patients resistant to Cyclosporine and Tacrolimus, but also they could help to clarify the pathogenesis of this severe ocular disease.

Occasi F., M.D., Department of Pediatrics, Policlinico Umberto I – “Sapienza” University of Rome, Italy

Duse M., Professor, M.D., Department of Pediatrics, Policlinico Umberto I – “Sapienza” University of Rome, Italy

Nebbioso M., Professor, M.D., Department of Sense organs, Policlinico Umberto I – “Sapienza” University of Rome, Italy

De Castro G., Professor, M.D., Department of Pediatrics, Policlinico Umberto I – “Sapienza” University of Rome, Italy

Di Fraia M., M.D., Department of Pediatrics, Policlinico Umberto I – “Sapienza” University of Rome, Italy

Capata G., M.D., Department of Pediatrics, Policlinico Umberto I – “Sapienza” University of Rome, Italy

Lollobrigida V, M.D., Department of Pediatrics, Policlinico Umberto I – “Sapienza” University of Rome, Italy

Zicari AM., Professor, M.D., Department of Pediatrics, Policlinico Umberto I – “Sapienza” University of Rome, Italy

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