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Can omalizumab be used effectively to treat severe conjunctivitis in children with asthma? A case example and review of the literature

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Abstract

A 14-year-old girl with poorly controlled asthma attended the difficult-to-treat asthma clinic for review. Although she has eosinophilia and significantly raised immunoglobulin E levels, she is not currently a candidate for omalizumab (Xolair). She also suffers from chronic urticaria, eosinophilic eosophagitis and severe conjunctivitis. You wonder if omalizumab would be effective in treating her multiple atopic conditions, in particular her troublesome conjunctivitis. PubMed was searched using the following search terms: (Omalizumab) or (Xolair) and (conjunctivitis). Searches were conducted in November 2020. Abstracts were selected for full text review if the study population identified asthma as a comorbidity. Non-paediatric studies and those that were not written in English were excluded. The use of omalizumab has the potential to be effective in the treatment of conjunctivitis associated with asthma and other atopic conditions. However, research is needed to address the question, in the form of multicenter, double-blind randomized control trials.

Key Words: Omalizumab; Conjunctivitis; Allergy; Asthma; Pediatrics; Atopy

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Core Tip: Asthma is often associated with multiple atopic conditions which can be more debilitating than the asthma itself. The use of omalizumab has the potential to be effective in the treatment of conjunctivitis associated with asthma and other atopic conditions. However, research is needed to address the question, in the form of multicenter, double-blind randomized control trials.

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INTRODUCTION

Scenario

A 14-year-old girl with poorly controlled asthma attended the difficult-to-treat asthma clinic for review. Although she has eosinophilia and significantly raised immunoglobulin E (IgE) levels, she is not currently a candidate for omalizumab (Xolair) due to poor adherence. She attends immunology clinic for spontaneous urticaria which has not improved despite high dose antihistamine. Gastroenterology are treating her for eosinophilic oesophagitis with proton pump inhibitors. During the consultation, you note that she also has severe vernal keratoconjunctivitis (VKC). She reported itching, burning and tearing of her eyes and it was evident at the review that she had marked conjunctival hyperaemia and blepharitis. Although adherence has been an issue in relation to her asthma treatment, she is reportedly compliant with both enteral and topical antihistamine therapy for her conjunctivitis.

You wonder if omalizumab would be effective in treating her multiple atopic conditions, in particular her troublesome conjunctivitis.

STRUCTURED CLINICAL QUESTION

Does treatment with omalizumab (intervention) in children with allergic conjunctivitis as a comorbidity of asthma (population) improve their conjunctivitis symptoms (outcome) compared to current treatment (control)?

SEARCH

PubMed was searched using the following search terms: (Omalizumab) or (Xolair) and (conjunctivitis). Searches were conducted in November 2020.

RESULTS

The literature search returned a total of 31 studies. Abstracts were selected for full text review if the study population identified asthma as a comorbidity. Non-paediatric studies and those that were not written in English were excluded. Following abstract review, 5 papers were deemed relevant for full text analysis and all were felt to address the question. Included studies are summarized in [Table 1](#) and graded according to the Oxford Centre for Evidence-based medicine Levels of Evidence[1].

Table 1 Studies assessing the use of omalizumab in conjunctivitis as a comorbidity

Ref.	Study group	Study type (level of evidence)	Intervention	Outcome	Results
Doan <i>et al</i> [13], 2017	4 patients with severe VKC, asthma, rhinitis and AD	Non-controlled, open-label, retrospective case series (Level 4)	2 weekly treatment with Omalizumab for range of 16-42 mo	Ocular VAS scale. Bonini grading. ACT score	3/4 had improvement in VAS score and Bonini grading. 3/4 had total control
Sánchez and Cardona [18], 2012	1 patient. 16 years old with severe refractory VKC, asthma, AD and rhinitis	Case report (Level 4)	2 weekly treatment with Omalizumab for 18 mo	Ocular VAS scale. Objective physician evaluation including cessation of immunosuppressive therapies	Ocular VAS improvement. Reduction of red eyes, photophobia and papillae. Cessation of ciclosporin and corticosteroids
de Klerk <i>et al</i> [19], 2013	1 patient. 12 years old with severe refractory VKC, asthma and rhinitis	Case report (Level 4)	Monthly treatment with Omalizumab for 18 mo	Juniper's rhinoconjunctivitis QOL score. Reduction in immunosuppressive ocular therapy	Improvement in Juniper's rhinoconjunctivitis score. Cessation of ciclosporin and olapatidine
Occasi <i>et al</i> [20], 2015	1 patient. 15 years old boy with asthma, severe VKC and AD	Case report (Level 4)	2 weekly treatment with Omalizumab for 3 mo	Achieving asthma control. Resolution of AD and VKC symptoms	Asthma control achieved at 3 mo. Resolution of VKC symptoms at 3 mo
Rossberg <i>et al</i> [11], 2020	2 patients with severe VKC, asthma and AD	Case report (Level 4)	2 weekly treatment with Omalizumab for 11 mo and 6 mo	Bonini grading	Improvement in Bonini grading

QOL: Quality of life; VKC: Vernal keratoconjunctivitis; VAS: Visual analogue scale; ACT: Advanced communication training.

DISCUSSION

Hypersensitization of IgE plays an important role in many allergic diseases. This means that patients often have multiple atopic conditions (multimorbidities). Patients with allergic asthma frequently present with other atopic conditions including: Rhinoconjunctivitis/allergic rhinitis, atopic dermatitis, food allergies, chronic spontaneous urticaria, eosinophilic oesophagitis and allergic bronchopulmonary aspergillosis [2]. Having these multimorbidities adversely impacts on asthma control and can contribute significantly to the overall burden of the disease[2].

IgE secreted by plasma cells in response to an exposure to allergens play an integral role in the allergic inflammatory cascade. Allergen-specific IgE binds to the surface of mast cells, causing degranulation of certain mediators (including histamine, chymase and tryptase) which are responsible for the classic symptoms of itching, redness and oedema. Omalizumab is a recombinant monoclonal antibody that sequesters free IgE and accelerates the dissociation of the IgE-Fcε receptor I complex[3]. This disrupts the IgE-mediated inflammatory cascade. Based on an extensive body of evidence, NICE now recommends use of omalizumab for patients with asthma and chronic spontaneous urticaria (CSU) who meet specific criteria[4,5] (Table 2). Guidance for its use in chronic rhinosinusitis with nasal polyps is expected[6]. These conditions are considered in isolation and current guidelines do not account for patients with multiple severe atopic conditions.

Dosing of omalizumab in Asthma is based on age, baseline, pre-treatment serum IgE levels and body weight[7]. As a result, a mg/kg dosing value is not usually given. Usual doses range from between 75-600 mg and depending on weight and serum IgE levels, dosing intervals may be fortnightly or monthly. At the upper extremes of weight and serum IgE levels, the theoretical dose *via* extrapolation is not licensed and therefore not recommended[7]. Currently, there is no guidance for this situation, however other biologics targeting different pathways may be trialed. Dosing in CSU is not dependent on serum IgE levels or body weights[7]. Recommendations are to administer 150 mg or 300 mg by subcutaneous injection every 4 wk. Dosing tables for asthma and chronic idiopathic urticaria are included in the appendix.

VKC is a chronic, relapsing condition mainly affecting children. Its pathophysiology involves both IgE and non-IgE mediated reactions[8]. The binding of specific allergens to specific IgE's causes degranulation of mediators leading to symptoms of redness and itching. Later, mediators cause infiltration of eosinophils, neutrophils and macrophages into the tissue. Eosinophils in particular play a major role in inflammation and tissue lesions such as epitheliopathy in VKC[9]. The mainstay of treatment is topical immunosuppressive medications and topical steroids. However, these are

Table 2 Current Indications for prescribing omalizumab

Ref.	Age	Previous treatment
NICE[4]	> 6 yr	Optimised standard treatment with documented compliance Continuous or 4 or more courses of oral steroids in the previous year
NICE[5]	> 12 yr	Poor response to standard treatment with H1-antihistamines and leukotriene receptor antagonists Objective severity score (weekly urticaria activity score) > 28

associated with significant side effects including ocular hypertension, glaucoma and cataract formation. Additionally, a large prospective study by Bonini *et al*[10] showed that 31% of patients with VKC requiring treatment with topical steroids had no improvement[10].

Four case reports and one case series followed a total of 9 patients with severe conjunctivitis as a comorbidity of asthma. Prior to omalizumab, all patients had worsening ocular symptoms despite topical and oral medications including immunosuppressants and corticosteroids. Omalizumab was associated with clinical improvement in 8 out of the 9 children including a reduction in the use of topical steroids and immunosuppressive therapies. Associated allergic multimorbidities also improved in 6 patients. Asthma control was achieved and lid eczema and atopic dermatitis completely resolved.

In the case report by Rossberg *et al*[11], effect on asthma symptoms was not reported. One patient required commencement of Dupilumab (an alternative monoclonal antibody that inhibits Interleukin-4 and Interleukin-13 signalling[12] mainly due to worsening AD, and reached complete control[11].

One patient in the case series by Doan *et al*[13] did not respond to omalizumab for either their conjunctivitis or their associated atopic conditions[13]. Notably, this patient did not have detectable sensitization to any allergen. This shows the complex and multifactorial pathogenesis of VKC, of which IgE plays a role[8,9].

A study by Heffler *et al*[14] in 2016 discusses treatment with omalizumab in 2 patients with severe VKC[14]. They did not meet our inclusion criteria as neither patient had concomitant asthma, however one patient was a child, in her first decade of life. Omalizumab was administered at 300 mg *per* month for 6 mo. Ocular visual analogue scale (VAS) scores, ophthalmologic examination and conjunctival scrape smears for cytologic examination were the outcomes measured. This is the first case report where cytologic examination has been used as an outcome. After 6 mo, the patient experienced improvement in all outcomes. Ocular VAS scores improved from 8 to 0, eye redness and cobblestone papillae were abolished, and eosinophil levels decreased from 69% to 3% on cytologic examination.

None of the five studies in this literature review report any adverse effects to treatment with omalizumab in children for conjunctivitis. The most common previously reported adverse effects to omalizumab include upper respiratory infections, headaches, arthralgia, pain, fatigue and abdominal discomfort[15]. The risk of anaphylaxis is 0.14% in patients receiving omalizumab, similar to other biologic drugs [16]. The British National Formulary reports further, rarer side effects, including eosinophilic granulomatosis with polyangiitis (usually associated with reduction of oral corticosteroids) and hypersensitivity reactions[17].

These findings are limited as the studies available were heterogeneous and of low quality. Sample size was small, with only case reports or small case series conducted. The dose, duration and frequency of omalizumab varied between the studies. Some studies used omalizumab as a single therapy and others as combination therapy. An array of different outcome measures were used and different grading systems were applied. Compliance to medication prior to commencing omalizumab was a concern in one case report, making conclusions of symptom improvement due to omalizumab more difficult.

CONCLUSION

The use of omalizumab has the potential to be effective in the treatment of conjunctivitis associated with asthma and other atopic conditions. However, research is needed to address the question, in the form of multicenter, double-blind randomized control trials.

REFERENCES

- 1 **CEBM.** Oxford Centre for Evidence-Based Medicine: Levels of Evidence 2009. [cited 20 January 2021]. Available from: <https://www.cebm.ox.ac.uk/resources/Levels-of-evidence/oxford-centre-for-evidence-based-medicine-levels-of-evidence-march-2009>
- 2 **Humbert M,** Bousquet J, Bachert C, Palomares O, Pfister P, Kottakis I, Jaumont X, Thomsen SF, Papadopoulos NG. IgE-Mediated Multimorbidities in Allergic Asthma and the Potential for Omalizumab Therapy. *J Allergy Clin Immunol Pract* 2019; **7**: 1418-1429 [PMID: 30928481 DOI: 10.1016/j.jaip.2019.02.030]
- 3 **Sanchez J,** Ramirez R, Diez S, Sus S, Echenique A, Olivares M, Cardona R. Omalizumab beyond asthma. *Allergol Immunopathol (Madr)* 2012; **40**: 306-315 [PMID: 22264640 DOI: 10.1016/j.aller.2011.09.011]
- 4 **NICE.** Omalizumab for treating severe persistent allergic asthma, 2013. [cited 2 January 2021]. Available from: www.nice.org.uk/guidance/ta278
- 5 **NICE.** Omalizumab for previously treated chronic spontaneous urticaria, 2015. [cited 2 January 2021]. Available from: www.nice.org.uk/guidance/ta339
- 6 **NICE.** Omalizumab for treating chronic rhinosinusitis with nasal polyps 2021. [cited 20 January 2021]. Available from: <https://www.nice.org.uk/guidance/indevelopment/gid-ta10558>
- 7 **Genentech USA IaNPC.** XOLAIR [prescribing information]2020 02.02.2021]. [cited 20 January 2021]. Available from: <https://www.xolairhcp.com/starting-treatment/dosing.html>
- 8 **Leonardi A,** Bogacka E, Fauquet JL, Kowalski ML, Groblewska A, Jedrzejczak-Czechowicz M, Doan S, Marmouz F, Demoly P, Delgado L. Ocular allergy: recognizing and diagnosing hypersensitivity disorders of the ocular surface. *Allergy* 2012; **67**: 1327-1337 [PMID: 22947083 DOI: 10.1111/all.12009]
- 9 **Leonardi A,** DeFranchis G, Zancanaro F, Crivellari G, De Paoli M, Plebani M, Secchi AG. Identification of local Th2 and Th0 lymphocytes in vernal conjunctivitis by cytokine flow cytometry. *Invest Ophthalmol Vis Sci* 1999; **40**: 3036-3040 [PMID: 10549670]
- 10 **Bonini S,** Bonini S, Lambiase A, Marchi S, Pasqualetti P, Zuccaro O, Rama P, Magrini L, Juhas T, Bucci MG. Vernal keratoconjunctivitis revisited: a case series of 195 patients with long-term followup. *Ophthalmology* 2000; **107**: 1157-1163 [PMID: 10857837 DOI: 10.1016/s0161-6420(00)00092-0]
- 11 **Rosberg S,** Pleyer U, Lau S. Omalizumab in three children with severe vernal keratoconjunctivitis. *Allergo J Int* 2020; **29**: 181-186 [DOI: 10.1007/s40629-020-00128-4]
- 12 **Matsunaga K,** Katoh N, Fujieda S, Izuhara K, Oishi K. Dupilumab: Basic aspects and applications to allergic diseases. *Allergol Int* 2020; **69**: 187-196 [PMID: 32007360 DOI: 10.1016/j.alit.2020.01.002]
- 13 **Doan S,** Amat F, Gabison E, Saf S, Cochereau I, Just J. Omalizumab in Severe Refractory Vernal Keratoconjunctivitis in Children: Case Series and Review of the Literature. *Ophthalmol Ther* 2017; **6**: 195-206 [PMID: 27909980 DOI: 10.1007/s40123-016-0074-2]
- 14 **Heffler E,** Picardi G, Liuzzo MT, Pistorio MP, Crimi N. Omalizumab Treatment of Vernal Keratoconjunctivitis. *JAMA Ophthalmol* 2016; **134**: 461-463 [PMID: 26795360 DOI: 10.1001/jamaophthalmol.2015.5679]
- 15 **Casale TB,** Condemi J, LaForce C, Nayak A, Rowe M, Watrous M, McAlary M, Fowler-Taylor A, Racine A, Gupta N, Fick R, Della Cioppa G; Omalizumab Seasonal Allergic Rhinitis Trail Group. Effect of omalizumab on symptoms of seasonal allergic rhinitis: a randomized controlled trial. *JAMA* 2001; **286**: 2956-2967 [PMID: 11743836 DOI: 10.1001/jama.286.23.2956]
- 16 **Tan LD,** Schaeffer B, Alisma A. Parasitic (Helminthic) Infection While on Asthma Biologic Treatment: Not Everything Is What It Seems. *J Asthma Allergy* 2019; **12**: 415-420 [PMID: 31849501 DOI: 10.2147/JAA.S223402]
- 17 **Formulary BN.** Omalizumab: Side effects 2021. [cited 20 January 2021]. Available from: <https://bnf.nice.org.uk/drug/omalizumab.html#sideEffects>
- 18 **Sánchez J,** Cardona R. Omalizumab. An option in vernal keratoconjunctivitis? *Allergol Immunopathol (Madr)* 2012; **40**: 319-320 [PMID: 21975146 DOI: 10.1016/j.aller.2011.08.002]
- 19 **de Klerk TA,** Sharma V, Arkwright PD, Biswas S. Severe vernal keratoconjunctivitis successfully treated with subcutaneous omalizumab. *J AAPOS* 2013; **17**: 305-306 [PMID: 23607979 DOI: 10.1016/j.jaapos.2012.12.153]
- 20 **Occasi F,** Zicari AM, Petrarca L, Nebbioso M, Salvatori G, Duse M. Vernal Keratoconjunctivitis and immune-mediated diseases: One unique way to symptom control? *Pediatr Allergy Immunol* 2015; **26**: 289-291 [PMID: 25692810 DOI: 10.1111/pai.12350]



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