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# Extraordinary response to omalizumab in a child with severe chronic urticaria

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## KEY WORDS

*Chronic urticaria; omalizumab; ciclosporin; therapy*

## Summary

*A case of immediate and definitive response to a single dose of omalizumab in a child with severe ciclosporin-resistant chronic urticaria is reported.*

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An 11-year-old boy was recently seen at the allergy department of the Clinica San Carlo. He suffered from very severe urticaria with angioedema for 3 months (Urticaria Activity Score = 5) (1), and had a history of seasonal allergic rhino-conjunctivitis for several years, induced by both grass and pellitory pollen. The boy suffered from sensorineural deafness. At the first visit, the patient was taking Hydroxyzine 25 mg/day + Levocetirizine 5 mg/day + Montelukast 10 mg/day + Prednisone 25 mg/day with very little benefit. The chronic use of prednisone had caused an increase in body weight of 9 Kg during the last 3 months. Exams showed basopenia, an increase in RCP and normal total IgE, normal complement fractions and negative antinuclear antibodies and thyroid autoantibodies. In view of the sensorineural deafness and to exclude a Muckle-Wells disease, gene-sequencing analysis was carried out. Analysis of GJB2 and GJB3 genes showed a compound heterozygosity for V153I polymorphic mutation in GJB2 and a -3224G>A mutation in its promoter

UTR region. The two mutations were each present in heterozygote state in patient's parents, and it is improbable that, associated in trans, these might cause the bilateral sensorineural deafness present in patient. Sequencing of exon3 of gene CIASI/NLRP3 was also performed to exclude cold urticaria or Muckle-Well syndromes due to alterations in this gene and no pathogenic mutations were found.

In view of the very poor response to current treatment and of the severe side effects of oral corticosteroids, after an informed written consent was obtained by the parents, ciclosporin 3 mg/Kg/day was started, maintaining a single dose of levocetirizine 5 mg in the evening. Ciclosporin dosage was increased to 3.8 mg/kg/day after 2 weeks due to the insufficient response, and this dose (250 mg/day) led to an improvement of the clinical situation by 80-90%. A further increase in dosage of ciclosporin to 4.6 mg/kg/day (300 mg/day) led to the complete disappearance of both wheals and angioedema. After one month, some viral respirato-

ry infections were followed by a relapse of urticaria (UAS = 4), which did not respond to levocetirizine at higher than licensed dose. At this point, a marked increase in D-dimer plasma levels (2450 ng/ml; normal 500 ng/ml) and a moderate kidney failure were observed: BUN 70 mg/dl (normal range 19-50 mg/dl).

After an informed written consent was obtained by the parents, omalizumab (Xolair) 300 mg was administered subcutaneously. The dosing was based on the present recommendations for asthma. The day after the administration urticaria completely disappeared, and the boy is still completely urticaria free after 6 months.

The effectiveness of omalizumab (Humanized monoclonal anti IgE antibodies) in different subsets of CU/angioedema unresponsive to antihistamines is supported by several case-reports (2-11), and lately by some multi-center randomized placebo-controlled studies as well (12-14). Two points make our case novel. First, the fact that the patient was a 11-year-old boy, and second that the drug worked very quickly and apparently in a resolutive way in a patient that had not been satisfactorily controlled neither by systemic corticosteroids (plus leukotriene receptor antagonists and both first and second generation antihistamines) nor by ciclosporin. The mechanism by which omalizumab works in patients with chronic idiopathic urticaria is all but established. Previous studies showed that the binding of circulating IgE by the drug eventually leads to a down regulation of the high affinity IgE receptors, within 2 weeks on basophils and after 8 weeks on mast cells (15-17). Other authors showed that omalizumab induces eosinophil apoptosis, a down-regulation of inflammatory cytokines (18) and a reduction in B-cell activation and homing. (19). However these observations cannot explain a clinical response that occurs within few days in most cases.

## References

- Zuberbier T, Asero R, Bindslev-Jensen C, Canonica GW, Church MK, Gimenez-Arnau A, et al. EAACI/GA2LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria. *Allergy*. 2009;64:1417-26.
- Boyce JA. Successful treatment of cold-induced urticaria/anaphylaxis with anti-IgE. *J Allergy Clin Immunol*. 2006;117:1415-8.
- Spector SL, Tan RA. Effect of omalizumab on patients with chronic urticaria. *Ann Allergy Asthma Immunol*. 2007;99:190-3.
- Sands MF, Blume JW, Schwartz SA. Successful treatment of 3 patients with recurrent idiopathic angioedema with omalizumab. *J Allergy Clin Immunol*. 2007;120:79-81.
- Kaplan AP, Joseph K, Maykut RJ, et al. Treatment of chronic autoimmune urticaria with omalizumab. *J Allergy Clin Immunol*. 2008;122:569-73.
- Dreyfus DH. Observations on the mechanism of omalizumab as a steroid-sparing agent in autoimmune or chronic idiopathic urticaria and angioedema. *Ann Allergy Asthma Immunol*. 2008;100:624-5.
- Godse KV. Omalizumab in severe chronic urticaria. *Indian J Dermatol Venereol Leprol*. 2008;74:157-8.
- Waibel KH, Reese DA, Hamilton RG, Devillez RL. Partial improvement of solar urticaria after omalizumab. *J Allergy Clin Immunol*. 2009;125:490-1.
- Vestergaard C, Deleuran M. Two cases of severe refractory chronic idiopathic urticaria treated with omalizumab. *Acta Derm Venereol*. 2010;90:443-4.
- Krause K, Ardelean E, Kessler B, et al. Antihistamine-resistant urticaria factitia successfully treated with anti-immunoglobulin E therapy. *Allergy*. 2010;65:1494-5.
- Ferrer M, Gamboa P, Sanz ML, et al. Omalizumab is effective in nonautoimmune urticaria. *J Allergy Clin Immunol*. 2011;127:1300-2.
- Maurer M, Altrichter S, Bieber T, Biedermann T, Brautigam M, et al. Efficacy and safety of omalizumab in patients with chronic urticaria who exhibit IgE against thyroperoxidase. *J Allergy Clin Immunol*. 2011;128:202-9.
- Saini S, Rosen KE, Hsieh HJ, Wong DA, et al. A randomized, placebo-controlled, dose-ranging study of single-dose omalizumab in patients with H1-antihistamine-refractory chronic idiopathic urticaria. *J Allergy Clin Immunol*. 2011;128:567-73.
- Maurer M, Rosen K, Hsieh HJ, Saini S, Grattan C, Gimenez-Arnau A, Agarwal S, Doyle R, Canvin J, Kaplan A, Casale T. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med*. 2013; 368:2340-1.
- Beck LA, Marcotte GV, MacGlashan D, Togias A, Saini S. Omalizumab-induced reductions in mast cell Fc epsilon RI expression and function. *J Allergy Clin Immunol*. 2004;114:527-30.
- Eckman JA, Sterna PM, Kelly D, et al. Effects of omalizumab on basophil and mast cell responses using an intranasal cat allergen challenge. *J Allergy Clin Immunol*. 2010;125:889-95.
- MacGlashan DW, Bochner BS, Ademan DC, et al. Down-regulation of Fc(epsilon)RI expression on human basophils during in vivo treatment of atopic patients with an anti-IgE antibody. *J Immunol*. 1997;158:1438-45.
- Noga O, Hanf G, Brachmann I, et al. Effect of omalizumab treatment on peripheral eosinophil and T-lymphocyte function in patients with allergic asthma. *J Allergy Clin Immunol*. 2006;117(6):1493-1499.
- Iemoli E, Piconi S, Fusi A, Borgonovo L, Borelli M, Trabattoni D. Immunological effects of omalizumab in chronic urticaria: a case report. *J Investig Allergol Clin Immunol*. 2010;20(3):252-254.