

Failure of omalizumab in cholinergic urticaria

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Summary

Cholinergic urticaria is one of the more common physical urticarias. Although it is often fairly mild, severe treatment-resistant disease may occur, with significant associated disability. Omalizumab, a monoclonal IgG anti-IgE antibody licensed for use in severe asthma, has recently been used successfully in several types of urticaria, including in one case of cholinergic urticaria. This paper reports a patient with severe cholinergic urticaria, unresponsive to antihistamines and multiple other treatments, whose disease was also unresponsive to omalizumab.

Cholinergic urticaria consists of small weals with a large surrounding red flare, occurring after a rise in core temperature caused by heat, exercise or emotion. Weals occur within 10–15 min of the stimulus and last for < 1 h. Most patients present with a rash only, but if the disease is severe, angio-oedema and symptoms of anaphylaxis may occur.¹ Cholinergic urticaria, like other forms of urticaria, can lead to high levels of disability and a markedly reduced quality of life.² Most patients adapt their lifestyle, but some patients have continuing disease for up to 30 years.¹

Report

A 27-year-old man presented in 2004 with a 5-year history of small itchy papules (Fig. 1), lasting for 30–60 min, and precipitated by heat, exercise, hot baths and emotion. The patient also gave a history of flushing, but had no other systemic symptoms and no angio-oedema. He was allergic to cats.

A hot-bath test confirmed the diagnosis of cholinergic urticaria. Results of full blood count, erythrocyte sedimentation rate, urea and electrolytes analysis, and liver function tests were normal, except for a slightly high

bilirubin level on occasion (up to 44 µmol/L; normal range 5–28), consistent with a known history of Gilbert's syndrome.

Before referral, the patient had been treated with cetirizine, loratadine, desloratadine, mizolastine, hydroxyzine, fexofenadine with ranitidine, fexofenadine with chlorpheniramine, montelukast, nifedipine, ketotifen and prednisolone without success. He was then prescribed cimetidine (but only for 2 weeks), levocetirizine 5 mg once daily, low-dose propranolol for 3–4 weeks, doxepin up to 50 mg at night, danazol, probanthine, sodium cromoglicate, gabapentin, ultraviolet B TL01 treatment (not tolerated) and ciclosporin (2.5 mg/kg initially, increased to 4 mg/kg) for 3 months, all to no avail.

By 2008, the patient had been unable to work for 2.5 years because of the severity of his symptoms. He was unable to do even mild exercise or any mental activity without weals. He also reported nausea, dizziness, palpitations, breathlessness and slight wheeze with attacks. He had become housebound and depressed. His general practitioner offered the patient psychiatric help, which he declined because he felt that the urticaria was the cause of his problems. His Dermatology Life Quality Index (DLQI) was 30/30 and he also scored 49/49 every week on an urticaria severity scoring system (daily score 0–4 for number of weals and 0–3 for severity of itching).

The patient was then given omalizumab 300 mg subcutaneously every 2 weeks for 4 months [at this

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Figure 1 Multiple small wheals with a large surrounding flare, typical of cholinergic urticaria, on the patient's back.

point, his weight was 84 kg and total IgE 1523 kU/mL (normal range < 120)], with no clinical benefit and no alteration in DLQI or urticaria severity score. He had no treatment-related adverse effects. Treatment was funded by Rotherham Primary Care Trust (£4098.40 excluding value added tax).

Treatment of cholinergic urticaria is aimed at symptom control. The avoidance of trigger factors may help, and menthol (1–2%) in aqueous cream may provide transient relief from itching. Orally, many patients gain benefit from H1 antagonists. Low-sedating antihistamines, such as cetirizine are usually most suitable but hydroxyzine has also been shown to be effective.¹ In patients unresponsive to H1 antagonists, treatment becomes more difficult. There is little or no evidence to support the use of H2 antagonists, leucotriene receptor antagonists or doxepin, although a trial of their use could perhaps be justified on the basis of the beneficial effects in other forms of urticaria. Ketotifen was reported as effective in four patients but its use is limited by its sedative effects. There are also case reports or small studies demonstrating the successful use of beta-

blockers, scopolamine, danazol, ultraviolet B, prednisolone and most recently omalizumab.^{3,4}

Omalizumab is a humanized monoclonal IgG anti-IgE antibody manufactured by recombinant DNA technology. It is licensed only for use in asthma. It has relatively few and mild adverse effects, the commonest being mild to moderate reactions at the site of injection and headache (manufacturer's datasheet).

There is now some evidence to support the use of omalizumab in urticaria. Two case reports have shown the highly successful use of omalizumab 300 mg every 2³ or 4⁴ weeks, in patients with cholinergic urticaria. There are also case reports of the successful use of omalizumab in cold urticaria,⁵ solar urticaria,⁶ chronic spontaneous urticaria⁷ and idiopathic angio-oedema.⁸ Additionally, in a small study of the use of omalizumab in 12 patients with chronic autoimmune urticaria, 7 patients achieved complete resolution and only 1 did not respond.⁹

The mechanism of action of omalizumab in urticaria is unknown. However, it reduces the amount of free IgE, which in turn downregulates the expression of FcεRI on mast cells, which could be important in chronic spontaneous or autoimmune urticaria. How it might act in cholinergic urticaria is unclear, particularly as the pathogenesis of cholinergic urticaria is poorly understood. Mast-cell degranulation and histamine release are thought to occur, and acetylcholine also seems to be involved.¹ Some authors suggest that a type I hypersensitivity reaction to sweat might be causative, and if this is the case, it might provide a rationale for the use of omalizumab.⁴

It is possible that the lack of response in this patient was related to his high IgE level, and that a higher dose of omalizumab might have been more successful. The maximum IgE for which dosages of omalizumab are recommended is 700 IU/mL. However, successful use has been described in patients with atopic dermatitis with IgE levels of up to 8396 IU/mL, although the dose required was difficult to estimate and ranged between 150 and 450 mg on alternate weeks.¹⁰ The complete absence of response in this patient discouraged repeat treatment using a higher dose.

Suitable treatment options are still lacking for patients with severe disabling H1 antagonist-resistant urticaria of all subtypes. Reports of the successful use of omalizumab are encouraging, but more work is required to clarify which patients are most likely to respond.

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