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Omalizumab is an effective and rapidly acting therapy in difficult-to-treat chronic urticaria: A retrospective clinical analysis

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ABSTRACT

Background: Omalizumab (anti-IgE) therapy is effective and safe in chronic urticaria (CU) in placebo-controlled clinical trials but real life clinical data are scarce.
Objective: To better understand the effects of omalizumab in CU patients treated outside of clinical trials.
Methods: In this retrospective clinical analysis, we assessed responder rates, optimal dosage, response to up-/downdosing, time to relief of symptoms, rates of return and time of relapse after omalizumab administration, and safety in 51 CU patients, 20 with chronic spontaneous urticaria (CSU) alone, 21 with different forms of chronic inducible urticaria (CindU) and 10 with both.
Results: Omalizumab treatment led to complete remission in 83% of CSU and 70% of CindU patients. When starting with 150 mg omalizumab 4 weekly, only 2/15 CSU and 7/17 CindU patients required updosing to achieve complete remission. In CSU, 57% of complete responses occurred within week one, all on the first day. Relapses were 2–8 weeks in all but six patients, where they were <4 months. Omalizumab was safe. Efficacy was not correlated to baseline IgE levels.
Conclusion: Clinical experience from more than 1250 injections in 51 patients over four years indicates that omalizumab is a rapidly acting, highly effective and safe drug in CSU and CindU patients. Our observations in a real life clinical setting support the recommendation of current EAACI/GA^{2}LEN/EDF/WAO guideline for the management of urticaria to use omalizumab to treat urticaria patients.

1. Introduction

Omalizumab, anti-immunoglobulin E (anti-IgE), is becoming increasingly recognized as an effective and rapidly acting therapy in antihistamine-resistant difficult-to-treat chronic urticaria (CU) even though it is, at present, being used off-label for this condition [1–3]. In Europe, more than five million people suffer from persistent urticaria symptoms [4], which severely impair quality of life [5], with negative effects on sleep, daily activities, school/work life and social interactions.

The current EAACI/GA^{2}LEN/EDF/WAO guideline for the management of urticaria states that the goal for the treatment of patients should be complete symptom control [6]. Although second generation H_1-antihistamines are the mainstay of symptomatic therapy in both chronic spontaneous (CSU) and inducible urticaria (CindU), increasing the dose up to fourfold above licensed doses still leaves up to a quarter of patients symptomatic [4]. For these patients, one of the options suggested by the guideline is the use of omalizumab [6].

Omalizumab is a recombinant humanized monoclonal anti-IgE antibody that binds to circulating free IgE but not to cell-bound IgE on mast cells or basophils. In the treatment of allergic asthma and allergic rhinitis, the postulated mechanism of action of omalizumab is a reduction of free IgE levels and the consequential down-regulation of FcεRI receptors on mast cells, basophils and dendritic cells [7]. In these conditions, there is a considerable delay of around 12–16 weeks for optimal reduction of symptoms [8].

Although only licensed for the treatment of moderate to severe asthma, omalizumab it is now widely used off-label for other allergic conditions, particularly severe allergic rhinitis [9] and chronic urticaria. Chronic urticaria patients were first described in 2006–2008 to benefit from omalizumab treatment in reports of individual cases of cold urticaria [10], cholinergic urticaria [11], solar urticaria [12] and CSU [13], a case series of CSU [14] and small trials of CSU [15,16]. In total, 19 case reports or small case series of 147 patients with CSU [2,17–20] and 10 case reports and one small case series of 17 patients with CindU treated with omalizumab have been published to date [2,21]. Furthermore, there are two published placebo-controlled randomized clinical trials using omalizumab in chronic spontaneous urticaria, one proof-of-concept trial [22] and one dose-ranging study [23] including a

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total of 139 patients. Most recently, a phase 3 multicentre, randomized, double-blind study has shown omalizumab at 150 mg and 300 mg, but not 75 mg, to significantly improve symptoms of 323 CSU patients who remained symptomatic despite therapy with licensed doses of H_1-antihistamines [1].

However, randomized controlled trials, while providing evidence of drug efficacy, do not reflect real life conditions. To address this, we present a retrospective analysis of the first 51 patients with chronic urticaria, both CSU and CindU, treated with omalizumab in a real life clinical setting in our specialist urticaria clinic in Berlin and provide details on doses needed for optimal control, the speed of onset of action and the rates and times of relapse after cessation of treatment.

2. Materials and methods

This report is a retrospective analysis of the effects of omalizumab therapy on the clinical progress of 51 unselected patients with difficult to treat chronic urticaria (14 male and 37 female, age range 20–82 years) who visited the specialist urticaria clinic at the Department of Dermatology and Allergy, Charité – Universitätsmedizin, Berlin, Germany between September 2008 and November 2012. Of the 30 patients with CSU, 10 also had one form and one had two forms of CindU. The remaining 21 patients were diagnosed with CindU, one of whom had both cholinergic and cold urticaria.

To be started on omalizumab therapy, patients had to have been shown to be unresponsive to H_1-anthistamines. Table 1 shows that all patients had received second generation H_1-antihistamines at up to fourfold higher than the licensed dose in an attempt to control their condition. Some patients had even received five or more different antihistamines. Also, many had received second and third line therapy as defined in the EAACI/GA^{2}LEN/EDF/WAO guidelines on the management of urticaria [6]. Furthermore, for omalizumab therapy to be initiated, successful applications for funding by health insurers were necessary so that the patients themselves did not have to meet the costs of treatment. The only exclusion criterion was that patients who were participating in clinical trials were not included.

Clinical diagnoses were made based on patient history and clinical picture. In some patients skin biopsies of urticarial lesions were taken and histological analyses were performed to rule out urticarial vasculitis. Initial diagnoses of CSU and CindU were made from patient history and clinical symptoms. The diagnosis of CSU was based on the spontaneous and sudden appearance of itchy wheals resolving within 1–24 h [24]. In physical urticaria, specific provocation tests were performed to verify the diagnosis, and respective threshold testing was performed to assess disease severity [25]. Provocation tests and threshold testing were performed using FricTest (Moxie, Berlin) for symptomatic dermographism [26], TempTest (Emo Systems, Berlin) for cold and heat urticaria [27], light-provocation test (Saalmann-Multitester SBC LT 400) with UVA and UVB for solar urticaria, physical exercise provocation tests for cholinergic urticaria, and weighted metal rods for delayed pressure urticaria [25].

To evaluate the effectiveness of treatment, 21 CSU patients were given a diary in which the number of wheals and the severity of pruritus were recorded daily for the 7 days immediately before the commencement of therapy and for eight weeks afterwards. From these records, the weekly and daily Urticaria Activity Scores (UAS7 and UAS1) were calculated as recommended by the 2009 guidelines on the diagnosis of urticaria [24].

In CSU, ''complete response'' to omalizumab was defined as a reduction of 90% or more in the UAS7, ''significant improvement'' as a reduction in the UAS7 of 90%-30% and ''no significant improvement'' as less than 30% reduction in the UAS7. In CindU, ''complete response'' was defined as the absence of wheals after respective provocation testing or absence of symptoms as assessed by patient global assessment, ''significant improvement'' as a 50% or more reduction in provocation thresholds or more than 50% improvement of symptoms, and ''no significant improvement'' as a less than 50% reduction in provocation thresholds or improvement of symptoms. In addition, in both conditions, complete responders showed no requirement for H_1-antihistamines while on omalizumab treatment and patients with significant improvement required H_1-antihistamines only for mild exacerbations while being treated with omalizumab.

Autologous serum skin test (ASST) was performed by intradermal injection of autologous serum as described previously [28]. Total serum IgE was measured using the ImmunoCAP system (Phadia 250, Phadia, Sweden).

Skin prick tests were performed on the volar surface of the forearm using histamine (10 mg/ml) and codeine (9 mg/ml). Responses were quantified by measuring the largest diameter (in mm) of the resultant wheal 15 min after provocation. Serum tryptase was measured using the ImmunoCAP tryptase assay (Phadia, Uppsala, Sweden).

2.1. Statistics

The relationship between total serum IgE and the final omalizumab dose required to suppress symptoms was assessed by the non-parametric Spearman rank correlation method. The results of skin prick tests to histamine and codeine were not normally distributed. Consequently these are expressed as median (with 25% and 75% percentiles) and statistical differences explored using the Wilcoxon signed-rank test.

3. Results

Because this was a retrospective study of clinical practice, the doses used were variable and patient dependent and often differed between clinicians. Patients started on omalizumab before 2011 were dosed according to their weight and circulating IgE levels with 150, 225 or 300 mg of omalizumab every 2–4 weeks. In 2011 we changed protocols and now use an initial dose of 150 mg regardless of patients' weight and circulating total IgE levels. Patients were updosed or downdosed according to their response to therapy.

3.1. Omalizumab in chronic spontaneous urticaria

Of the 30 CSU patients treated with omalizumab, 25 (83%) gained complete remission of their symptoms (Table 2). A further 3 patients showed significant improvement leaving only 2 patients with no significant improvement.

Table 1
Previous medication taken by patients before being prescribed omalizumab.

Types of medication	Number of patients
SGAHs	51
SGAHs Updosed fourfold	51
Updosed SGAHs + H_2-AHs	42
Updosed SGAHs + H_2-AHs + LTRAs	39
Oral corticosteroids	21
FGAHs	9
Cyclosporin	7
Dapsone	3

SGAHs, second generation H_1-antihistamines; H_2-AHs, H_2-antihistamines; LTRAs, leukotriene receptor antagonists; FGAHs, first generation H_1-antihistamines.

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