Omalizumab, an Anti-IgE mAb, Receives Approval for the Treatment of Chronic Idiopathic/Spontaneous Urticaria

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Omalizumab, an anti-IgE mAb, has recently been approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of chronic idiopathic urticaria. Saini *et al.* (2014) (this issue) report on ASTERIA I, a 40-week randomized, double-blinded, placebo-controlled phase III trial evaluating omalizumab for the treatment of this disease.

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The burden of disease

In this issue, Saini *et al.* (2014) report on ASTERIA I, a phase III clinical trial of omalizumab for the treatment of chronic idiopathic urticaria (CIU) (also referred to as chronic spontaneous urticaria). CIU is a common dermatosis, with a prevalence of 0.5–1% and a peak incidence between 20 and 40 years of age, although patients of any age can be affected. Women are twice as likely as men to suffer from CIU (Maurer *et al.*, 2011). CIU is defined by itchy red patches and wheals (hives) affecting the skin; these can range from a few millimeters to several centimeters in diameter. Although individual wheals may come and go, typically lasting 2–24 hours, to meet the criteria of CIU, the condition must persist for over 6 weeks without any identifiable underlying triggers (e.g., drugs, physical stimulus, infection, or allergen). In addition to red patches and wheals, up to two-thirds of patients with CIU will have deeper swelling of the skin (known as angioedema), which typically affects the eyelids, lips, and genitals (Maurer *et al.*, 2011). Angioedema is more often painful than pruritic and may last 2–3 days. Patients may also have associated fatigue and arthralgias.

As well as being relatively common, CIU can have detrimental effects on a patient's quality of life, with some patients rating the impact of CIU as highly as ratings for ischemic heart disease (O'Donnell *et al.*, 1997). Furthermore, CIU may persist for 3–5 years in 50% of patients and for over 10 years in 20%. CIU is more likely to have a prolonged course in patients with (i) greater severity of disease, (ii) angioedema, (iii) a positive autologous serum skin test, and (iv) a physical trigger to their urticaria (Maurer *et al.*, 2011). CIU can also have significant economic costs; one study of patients treated with H_1-antihistamines (patients on corticosteroids and immunosuppressants were excluded) showed that the annual cost was >$2,000 per patient (the majority being direct costs, e.g., medication and hospital visits; indirect costs included loss of salary due to outpatient attendance or absence from work; Delong *et al.*, 2008).

CIU may have an underlying autoimmune basis in approximately 30–50% of patients; these patients demonstrate functional IgG autoantibodies against the high-affinity IgE receptor (FcεRI) or IgE. These antibodies induce the release of histamine and other mediators (including proteases, eicosanoids, and cytokines) from mast cells (the principal effector cell in urticaria) and basophils (Hide *et al.*, 1993). A group of patients, who produce IgE against autoantigens, including thyroid peroxidase, has also been identified (Altrichter *et al.*, 2011). CIU patients with autoantibodies reportedly have more severe urticaria compared with CIU patients without autoantibodies, and they may be more resistant to treatment (Sabroe *et al.*, 1999). Interestingly, CIU patients with detectable autoantibodies against the high-affinity IgE receptor or IgE have a strong association with HLA DRB1*04 (DR4) and its associated allele, DQB1*0302 (DQ8; O'Donnell *et al.*, 1999). Further evidence that CIU may have an underlying autoimmune mechanism, at least in some patients, comes from the observation that CIU is associated with several autoimmune conditions, including type I diabetes, rheumatoid arthritis, autoimmune thyroid disease, and systemic lupus erythematosus (Confino-Cohen *et al.*, 2012).

Current licensed treatment options for CIU are limited

Despite CIU being a relatively common and potentially debilitating disease, there are few licensed treatment options. International guidelines (Figure 1; Zuberbier *et al.*, 2014) recommend second-generation (non-sedating) H_1-antihistamines, on a regular basis, as first-line treatment for CIU. Although this is the mainstay of treatment for most patients, many do not experience adequate relief of symptoms. A sedating "classical" H_1-antihistamine, such as hydroxyzine, at nighttime, may be beneficial. Cooling topical treatments, such as menthol in aqueous cream, may provide symptomatic, soothing relief for some

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Abbreviation: CIU, chronic idiopathic urticaria

Clinical Implications

- H_1-antihistamines were previously the only therapy with regulatory approval for the treatment of chronic idiopathic urticaria (CIU), although many patients do not respond adequately to this treatment.
- Phase III clinical trials support the efficacy and safety of omalizumab for the treatment of CIU; it has now been approved by the US Food and Drug Administration and European Medicines Agency for this indication.
- Omalizumab, a recombinant humanized anti-IgE mAb, is recommended as third-line treatment (as are ciclosporin and leukotriene antagonists) for CIU. Until recently, this was an off-license indication.

patients. If symptoms persist after 2 weeks, guidelines recommend an increase of up to four times the normally prescribed dose of H_1-antihistamines. Studies investigating the effectiveness of higher doses of H_1-antihistamines for CIU are mixed, with responses ranging from 5 to 75% (Asero, 2007; Staevska *et al.*, 2010). The differences in response may, in part, be due to the different H_1-antihistamines prescribed. Furthermore, some studies may have been based in tertiary referral centers where there may be higher proportions of difficult-to-treat patients. In any case, the use of H_1-antihistamines above standard dosages is ''off-license''.

If symptoms persist, despite higher doses of H_1-antihistamines, guidelines recommend the addition of ciclosporin, montelukast (leukotriene antagonist), or omalizumab.(Zuberbier *et al.*, 2014). When these guidelines were written, all three third-line drugs (including omalizumab) were used ''off-label'' in the treatment of CIU. In addition to these treatments, other options reported in the literature include azathioprine, dapsone, hydroxychloroquine, Igs, methotreaxate, and sulfasalazine. Again, all these drugs are used off-label, with limited definitive evidence for their efficacy in CIU. Guidelines also suggest a short trial of systemic corticosteroids for exacerbations. One study showed that systemic corticosteroids could induce remission in ~50% of patients, although patients included in the study had not regularly used H_1-antihistamines above the licensed doses, and it was uncertain how long these patients had CIU prior to receiving systemic corticosteroid treatment. However, long-term use of systemic corticosteroids should be avoided, because of potential side effects associated with prolonged use, including hypertension, glucose intolerance, and osteoporosis.

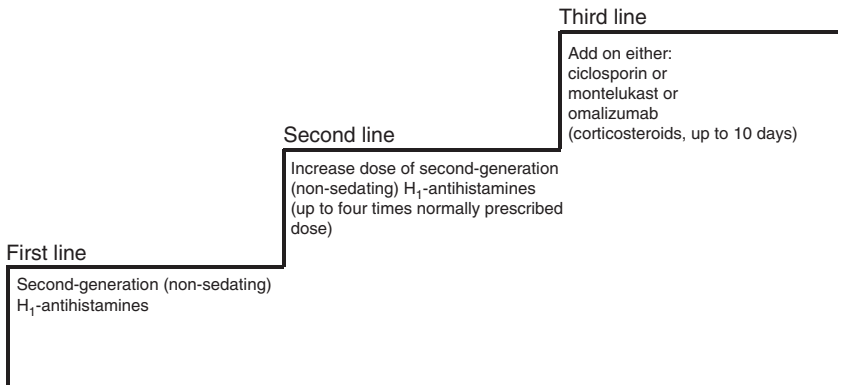

Figure 1. Treatment ladder for chronic idiopathic urticaria. H_1-antihistamines, on a regular basis, should be used as first-line treatment. If symptoms persist after 2 weeks, increase dose up to four times the normally prescribed dose, as second-line treatment. If symptoms continue after a further 1–4 weeks, add either ciclosporin, montelukast (leukotriene antagonist), or omalizumab (add-on therapies are listed in alphabetical order and do not represent ranking). Short courses of corticosteroids (up to 10 days) may be prescribed during exacerbations of chronic idiopathic urticaria if required. Adapted from the figure in the reference of Zuberbier *et al.* (2014).

Omalizumab as a treatment option for CIU

In light of CIU being a relatively common disease that can impact negatively on quality of life, and with limited licensed treatment options, there is clearly an unmet demand for treatment. The article by Saini *et al.* (2014) in this issue, reporting the results of ASTERIA I, a randomized, double-blinded, placebo-controlled phase III trial of omalizumab for the treatment of CIU, is therefore of great interest. Omalizumab, a recombinant humanized mAb, is already licensed for the treatment of moderate–severe allergic asthma, with an established safety record for its use in this condition. Omalizumab binds to free IgE in serum and inhibits IgE binding to FcεRI on effector cells, including mast cells and basophils (it cannot bind to FcεRI-bound IgE; Chang *et al.*, 2014). Although omalizumab has no direct effect on FcεRI expression, sequestration of free IgE results in downregulation of FcεRI on effector cells. It is beyond the scope of this study to discuss the downstream effects of these actions, but a comprehensive commentary on this subject has recently been published (Chang *et al.*, 2014).

Two phase III clinical trials on omalizumab for the treatment of CIU have been published by the same, well-regarded, Consortium. Supplementary Table S1 online of the article (Saini *et al.*, 2014) summarizes the key design features of these studies, but briefly (i) the GLACIAL study (Kaplan *et al.*, 2013) evaluated the safety of omalizumab in patients already receiving typical second-line therapy (e.g., four times approved doses of H_1-antihistamines, H_2-antihistamines, or leukotriene antagonists), and the primary outcome was the percentage of participants with adverse events (AEs); (ii) the ASTERIA II study (Maurer *et al.*, 2013) evaluated the

efficacy of three different doses of omalizumab, in patients who remained symptomatic despite approved doses of H_1-antihistamines, over a 12-week treatment and 16-week observation period, and the primary outcome was the change in the weekly itch severity score (ISS) from baseline to week 12 of treatment. A critical appraisal of ASTERIA II has been recently published (Durack and Matin, 2014).

ASTERIA I is a similar, although separate, study from ASTERIA II, but with a treatment period that is twice as long (24 weeks vs. 12 weeks); the follow-up periods were the same in both studies (16 weeks). As with ASTERIA II, the primary outcome was the change in weekly ISS from baseline to week 12. All three omalizumab treatment groups achieved a lower weekly ISS at week 12 compared with placebo (Supplementary Table S2 online), this appeared to be dose dependent. These results were consistent with the primary end point of ASTERIA II (Maurer *et al.*, 2013). Interestingly, although improvements in ISS are maintained after 12 weeks, there does not appear to be any further improvement in this end point after this period (Supplementary Tables S2 and S4 online). No group returned to their baseline mean weekly ISS after the 16-week observation period, including the placebo group (Supplementary Figure S2 online). As the authors point out, this could suggest that a proportion of patients experienced ''spontaneous'' remission (or at least remission while on standard doses of H_1-antihistamines).

Safety

AEs, which were suspected to be caused by omalizumab, appeared to be dose dependent (Supplementary Table S3 online), although the authors state ''the dose-dependent trend was not clustered by a specific AE type''. No statistical analysis was reported on these figures, as safety was not a primary outcome in ASTERIA I. However, the previously published phase III GLACIAL study primarily evaluated the safety of omalizumab in patients already receiving standard combination CIU treatment and found the incidence of AEs to be similar between placebo and treatment groups (e.g., the proportion of patients with $\geq$1 AE suspected to be caused by study drug was 13.3% in the placebo group compared with 11.1% in the omalizumab 300 mg group; Kaplan *et al.*, 2013).

The future

Undoubtedly, the well-conducted phase III clinical trials and recent FDA/EMA approval of omaluzimab for CIU are exciting. It will be interesting to see how writers of guidelines and health economists view the recent approval and whether this will affect the availability and ranking of omalizumab in the management of CIU. However, as with other biologics, omalizumab has significant cost implications, and its effectiveness compared with other third-line agents (ciclosporin or montelukast) has yet to be established. Furthermore, not all patients responded to omalizumab treatment; future studies could be directed at investigating biomarkers to predict responses to therapy. Finally, it may be interesting to investigate the effects of omalizumab in other diseases characterized by elevated IgE levels, which in dermatology could include atopic dermatitis and bullous pemphigoid.

CONFLICT OF INTEREST

KCPW is currently undertaking a Wellcome Trust funded PhD, with GlaxoSmithKline (GSK) acting as an Industrial Partner, he does not receive any salary from GSK. ZJL states no conflict of interest.

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