

the published paper. The trial registry was modified a number of times (see 'history of changes' on the ClinicalTrials.gov archive site); most notably, the primary and secondary end points listed were amended to correspond to the published article almost 6 months after publication.

While data providers are permitted to amend information on the clinical trials record at any time, the significance and timing of such changes is relevant. One of the principal objectives of trial registration is to enhance transparency by making key elements of clinical trials publicly available, thus reducing the risk of selective reporting bias.³

Overall assessment (including any potential application of the research to clinical practice)

This study suggests that higher doses of omalizumab (150 and 300 mg) are associated with an improvement in patient symptoms of CIU during the treatment period. However, it did not demonstrate a substantial modification of the basic underlying disease process in the study population during the follow-up period.

This is certainly an important study, which has offered a safe and effective therapeutic option for CIU in patients who do not respond to H₁-antihistamines. There is a clinically relevant treatment period of 12 weeks and an adequate follow-up of 16 weeks to assess efficacy. Areas of concern include some reporting issues, such as lack of information on recruitment and the study population (which brings into question the generalizability of the results), and discrepancies between outcomes registered and outcomes published (raising concerns about selective outcome reporting). Critical details regarding participant and clinician blinding should have been clearly described and longer term follow up is required to determine the adverse effect profile.

It is important to be aware that the pharmaceutical industry was heavily involved in all aspects of the study from design to reporting of the trial.

Studies investigating efficacy in nonwhite populations and comparative studies with other second-line treatments such as ciclosporin are still needed to determine the position of omalizumab in the management pathway of patients with CIU. In addition, daily clinical practice data and cost-effectiveness studies are also needed.

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Commentary: Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria

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Chronic urticaria affects approximately 0.1% of the population. The disease is not life threatening, but it is very disabling and has a significant effect on quality of life.¹ Approximately 50% of patients are unresponsive to H₁-antihistamines,² and commonly used second-line agents such as ciclosporin or prednisolone have marked adverse effects. Thus there is a need for a safe and effective second-line therapy. Omalizumab, a recombinant humanized monoclonal anti-IgE antibody that is effective in asthma and has a very good safety record,³ appears to fulfil this need. The main drawback at present is its cost.

In this multicentre, phase 3 study, Maurer et al.⁴ gave three different doses of omalizumab to 323 patients with chronic spontaneous urticaria (CSU) resistant to treatment with antihistamines. Short-term use of omalizumab produced a significant reduction in urticaria scores, particularly at the highest dose of 300 mg monthly, with little in the way of adverse events.

These findings reinforce data from two other large studies and multiple smaller studies and case reports.^{5,6} Altogether, provided there is no overlap in the study populations between any reports, omalizumab has been given to more than 800 patients with CSU, and found to be a very effective and safe short-term treatment. This is a much larger number of patients than for any of the other treatment options for antihistamine-resistant disease. Omalizumab thus seems a very attractive treatment option. However, there are still a number of areas of uncertainty.

The position of omalizumab in treatment guidelines appears to be moving. Previously omalizumab was generally used after failure not only of H₁-antihistamines, but also of leukotriene receptor inhibitors, and usually ciclosporin

or other agents such as dapsone.^{7,8} However, European guidelines have recently been updated to include the use of omalizumab after failure of high-dose antihistamines.⁹ In the new study discussed here,⁴ the entry criterion was resistance to antihistamines given at licensed doses only, so earlier still. Indeed, it is possible that omalizumab was given too early, and that a proportion of patients may have gone into spontaneous remission.

Earlier use of omalizumab may raise funding issues. The list price for 300 mg of omalizumab monthly for 12 months is over £6500 (British National Formulary price). Additionally, unlike many of the other subcutaneous biological agents, which can be given in the community, omalizumab is currently given in secondary care, which also increases its cost. For practitioners in the U.K., the landscape of commissioning is in flux and the opportunities of, or potential barriers to, funding of this treatment are still to be worked through.

While some other treatment options may be cheaper, costs for omalizumab are not that unreasonable compared with some immunosuppressants. Using typical doses of other agents with some evidence for their use, approximate annual costs (excluding monitoring) can be calculated. For methotrexate¹⁰ this is only £40 per annum, for prednisolone about £100 and mycophenolate¹¹ only £300, but for ciclosporin¹² the cost is up to £3000 and for dapsone¹³ about £1000. The very expensive intravenous immunoglobulins¹⁴ may be required for only a limited number of infusions, but the annual cost could be up to £90 000. A variety of other agents have also been tried in CSU or related conditions, including tumour necrosis factor- α inhibitors,^{15,16} agents that inhibit the actions of interleukin-1,^{17–19} and rituximab.^{20,21} Thus, when considering the limited effectiveness of some of these options and their substantial side-effect profiles, future cost-effectiveness appraisals may come down in favour of omalizumab. However, as yet there are no published studies comparing the efficacy of these second-line options with that of omalizumab, which would further inform the best choice of agents.

If omalizumab is to be used routinely, then more work will be needed to establish the frequency and duration of treatment, whether it will remain effective with long-term treatment, and how and when to withdraw it. Whereas dosing in asthma is well established, the lack of certainty over the mechanism of action in CSU, and the potential for spontaneous resolution of the disease complicate matters. However, both phase 3 studies would indicate that long-term treatment may well be required as, within 2–3 months of treatment withdrawal, treated patients on average had similar disease activity scores to those given placebo.^{4,6}

The current study includes patients with CSU as a whole.⁴ It is not known whether patients with autoimmune CSU (with antibodies to the high-affinity IgE receptor, Fc ϵ RI) respond differently from those without, or whether disease severity or duration make any difference to outcome. Of interest, omalizumab appears to work by reducing circulating IgE levels and downregulation of Fc ϵ RI,²² and has actions in nonatopic

asthma²³ that may also be mediated through downregulation of Fc ϵ RI on immune cells. These data would suggest that actions may be across the spectrum of disease phenotypes, but this remains to be determined. Similarly, use of omalizumab in other subtypes of urticaria, such as the physical urticarias, would benefit from more detailed investigation, as small studies to date are encouraging.^{24–26}

In summary, this study⁴ provides good evidence for the efficacy and safety of omalizumab for the treatment of CSU, albeit given short term to patients resistant to only standard doses of antihistamines. For a nonlife-threatening disease, a drug without immunosuppression or severe adverse effects is a genuine advance. Perhaps one of the greatest challenges at present may be to put treatment into an appropriate position in guidelines. Future studies evaluating its cost-effectiveness and its potential place against commonly used second-line agents, or defining in more detail the subgroups likely to show the best response, would be valuable. Additionally, its use needs to be proportional to severity. This may require the application of minimum disease severity and/or minimum quality-of-life scores, and/or the prior failure of drugs with a low likelihood of adverse effects. This would be similar to the U.K. guidelines for use of biological drugs in other diseases such as psoriasis, which have been produced after appraisal by the National Institute for Health and Care Excellence.

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Response to: 'Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria: a critical appraisal'

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Durack and Matin¹ have written a critical appraisal of our article² and we appreciate the opportunity to respond to their concerns regarding our study methodology. We would like to thank the authors for their thorough evaluation of our phase 3 study of omalizumab in patients with chronic idiopathic urticaria or chronic spontaneous urticaria (CIU/CSU) and appreciate their bringing this analysis to the attention of a dermatology audience.

With regard to the exclusion of German participants < 18 years of age, German health authorities do not allow the participation of adolescents in phase 3 studies unless the study drug is being used for an approved indication. However, there are data from adolescents from other countries that would allow for generalization to the German adolescent population.

Regarding the concerns raised regarding eligibility, recruitment and assessment during the screening period, the Study Design section of the article indicates the length of the screening period (14 days before randomization, and two visits conducted at day –14 and day –7 to assess eligibility). During screening, patients had to have an in-clinic physician-assessed Urticaria Activity Score (UAS) ≥ 4 on one of the screening-visit days, had to use an approved dose of an H₁-antihistamine for the treatment of CIU/CSU for at least three consecutive days immediately before day –14, and had to complete an electronic symptom diary (eDiary) twice daily throughout the screening period to establish the patient's UAS over 7 days (UAS7). Patients were eligible for inclusion in the study if they had no missing eDiary entries in the 7 days before randomization, to ensure accurate capture of the severity of disease. All patients were recruited from specialty and/or research centres.

Use of H₁-antihistamines and other medications for CIU/CSU before enrolment was collected as part of the patient-reported history during screening.

Concerns were raised regarding the randomization and medications used before enrolment. The authors are confident that the Interactive Voice and Web Response System (IxRS) used to randomize patients successfully distributed patients evenly across the four treatment groups. Please note that patients who were enrolled in the trial may not have received immunosuppressants or steroids for 30 days before the first day of screening. The differences in medication before enrolment were not stratified; however, we did evaluate previous