

Critically appraised research paper

Ligelizumab for chronic spontaneous urticaria

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Chronic spontaneous urticaria (CSU) is a very disabling condition. It can be difficult to treat. Less than 50% of people respond to licensed dosages of H₁ antihistamines, although up dosing where safe increases the response rate. Additionally, only a small proportion respond to the addition of the leukotriene receptor antagonist (LTRA) montelukast.^{1,2} Recently, the recombinant humanized monoclonal anti-IgE antibody, omalizumab, has become established as a second-line treatment option for people with severe CSU inadequately responsive to the above-mentioned first-line treatments. Its efficacy (about two-thirds respond) and excellent safety profile make it attractive.^{1,2}

Ligelizumab is a new high-affinity humanized monoclonal anti-IgE antibody. Maurer et al. have published the first study on the use of ligelizumab for the treatment of CSU.³ This pharma-funded phase IIb multicentre randomized double-blind placebo-controlled study examined responses of people with CSU to varying doses of ligelizumab and compared these responses with a standard omalizumab regimen.³ In total 382 participants were included, aged 18–75 years. Their disease was inadequately controlled by approved or increased doses of H₁ antihistamines alone or in combination with H₂ antihistamines or LTRAs, all of which were continued without alteration during the trial. A weekly urticaria score, a weekly hive score and an in-clinic urticaria activity score needed to be above 16 out of 42, 8 out of 21 and 4 out of 6, respectively, during the 7 days before randomization for inclusion.

At week 12, complete symptom control was achieved in 30%, 44% and 40% of people treated with monthly ligelizumab 24 mg, 72 mg or 240 mg, respectively, and in 26% and 0% of those given 300 mg omalizumab or placebo monthly, respectively. In a separate arm of the study, a single dose of 120 mg of ligelizumab was given, and the beneficial effects appeared to last for 8 weeks. Indeed, the median times to loss of response on treatment withdrawal were 3, 4 and 10.5 weeks for ligelizumab 24 mg, 72 mg and 240 mg, respectively, and 4 weeks for omalizumab. There were no safety concerns. Injection-site reactions appeared more commonly in those receiving 72 mg or 240 mg of ligelizumab.

Thus, ligelizumab was shown to be effective in the treatment of CSU. At doses ≥ 72 mg, it appeared more effective than omalizumab. Another advantage of ligelizumab may be less frequent injections (if given at doses > 72 mg) than for omalizumab, but the final dosing regimen has yet to be chosen.³ Ligelizumab may offer similar advantages in asthma.⁴ A new theory is emerging for IgE-mediated 'autoallergy' in CSU, where IgE antibodies against a component of 'self' are thought to be able to trigger mast cell release when crosslinked by the appropriate antigen.⁵ People with IgE-mediated disease may respond particularly well to anti-IgE therapies.^{6,7}

There are a few things to consider. Firstly, the complete response rate to omalizumab was lower than might be expected from a meta-analysis of previous trials (36%),⁸ and, although higher, the response rate to ligelizumab was also perhaps slightly disappointing. However, this may have been due to the inclusion of people with more severe CSU.

Secondly, as omalizumab and ligelizumab work through the same mechanism, it seems likely that a similar cohort will respond to either. This may leave a residual unresponsive group. Some may respond to ciclosporin. Indeed, it is thought that people with functional histamine-releasing IgG autoantibodies (against the high-affinity IgE receptor or against IgE), may respond better to ciclosporin than to anti-IgE therapies.⁶ Conversely, a high total IgE level may indicate a higher probability of early disease responsiveness to anti-IgE therapies.⁷

Thirdly, confirmatory studies are needed to establish the dose regimen, safety and cost-benefit ratio, to treat people for longer periods, and to compare ligelizumab with other established treatments, particularly ciclosporin.

There is still a need for better understanding of the underlying pathogenic mechanisms of CSU and for the development of further new treatments with good safety profiles. Currently, if anti-IgE therapies and/or ciclosporin fail, people with CSU progress to treatments of which their track record is less well defined and which have the potential for significant side-effects (e.g. mycophenolate mofetil, azathioprine, dapsone or methotrexate). Drugs in use or development which may prove helpful in the future include new tyrosine kinase inhibitors, dupilumab, histamine 4 receptor antagonists, C5a receptor antagonists and drugs targeting inhibitory mast cell receptors.⁹

Of note, this study looked at CSU only. In the UK, funding has not been approved for the use of omalizumab in people with severe inducible urticarias whose disease has responded inadequately to H₁ antihistamines. We are still lacking effective treatments to offer this group.

Thus, the results of this trial are encouraging. Ligelizumab's apparent increased efficacy and greater convenience (if injections are required less frequently) compared with omalizumab, along with the absence of safety concerns reported in this study, will make it an attractive option. New safe treatment options for debilitating severe urticaria are to be welcomed.

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