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Omalizumab re-treatment rates in chronic spontaneous urticaria

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The review paper by Tonacci A and colleagues highlights the fact that re-treatment with omalizumab for patients with chronic spontaneous urticaria (CSU) is not unusual, which adds significantly to costs of treatment (1). Our experience with use of omalizumab in CSU has been similar and treatment responses with re-treatment rates are presented. The study was part of an outcome reporting audit aimed to document (1) efficacy; (2) safety profile; (3) failure rates; and (4) identification of factors relating to efficacy or resistance to omalizumab, and was approved by the Clinical Audit and Effectiveness team of the Hull University Teaching Hospitals NHS Trust.

The health records of patients with resistant CSU who received XolairÒ (Omalizumab, Novartis) between the years 2017-2019 were reviewed. Omalizumab 300mg was administered subcutaneously with antihistamines every 4 weeks for 6 months, followed by an 8-week treatment interruption. In case of recurrence, further doses were approved after clinic review. Patient demographics, laboratory features (autoantibody status, IgE level, tryptase), weekly urticaria activity score (UAS7) during treatment were analysed. UAS7 at zero was considered complete remission (CR), UAS7 1-28 as partial remission (PR), UAS7>28 as non-responder (NR). Descriptive statistics including parametric and non-parametric tests were done using GraphPad Prism version 7.00 for Windows, GraphPad Software, La Jolla California USA.

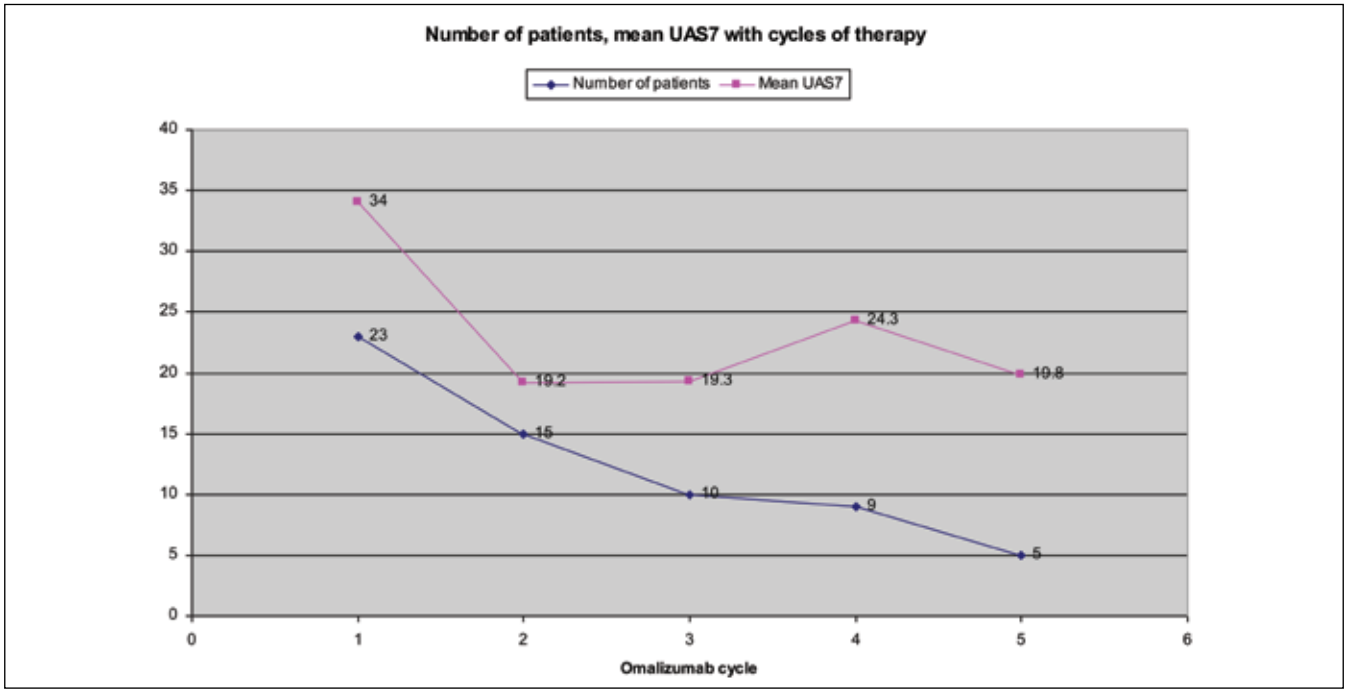
Twenty three patients (18 women, mean age 39.6 years, range 18-76 years) were reviewed. Mean UAS7 at baseline was 34(±SD 5.2) with range 20-42. A total of 396 doses of omalizumab was used (mean of 17 doses). Mean UAS7 post 1st cycle was 19 (±SD 15.1) with range 0-42 (difference in means extremely significant, $p<0.0001$). 6 patients achieved CR after 1st cycle (26%) and 4 in sustained remission (7 months follow up). 13 patients had PR (48%), 6 classed NR (26%). 15 patients required 2nd cycle, with good responses after each dose. 13% patients had sustained effect after 2nd cycle for 4-5 months, while 53% relapsed in 3-4 weeks. 10 patients required 3rd cycle again with excellent responses after each dose, but 9 patients required 4th cycle and 5 patients are on 5th cycle. Overall, 14 patients remain indefinitely on therapy (**figure 1**).

Thirteen of 23 patients had significant angioedema, only 15% attained CR after 1st cycle. Median baseline IgE was 250 U/ml (n=13, IQR25-75 25-470), tryptase 4.9 ng/ml (n=16, IQR25-75 range 3.8-6.5). Antinuclear antibody was negative in all patients tested and two patients were positive for anti-thyroid peroxidase antibodies. There was no difference between baseline IgE level and tryptase with response to omalizumab. A total of 396 doses of omalizumab were given and no serious adverse events such as anaphylaxis were seen. The commonest side effects were injection-site reactions (pain, erythema and itching), headache, slightly raised body temperature and fatigue after a median of 2 weeks of receiving the dose. Omalizumab appeared to be resistant in a third of patients and relapses of urticaria were common following interruption of therapy. No patient-specific factors to predict response to omalizumab were identified, apart from the presence of angioedema that appeared to have a negative outcome.

Our study had limitations with the retrospective nature and with low patient numbers we were unable to use log-transformed IgE to account for atopic status and perhaps why we were unable to find any relationship with total IgE level and response to omalizumab. This contradicts previous published studies where IgE level was a predictor of response. Marzano et al study (n=470) showed a lower mean IgE level (42 kU/L) was associated with resistance (2), similar to Asero et al (n=76) where they showed fast omalizumab responders had higher mean total IgE levels (404 kU/L) than slow responders (112 kU/L) (3), but the authors concluded that much higher numbers are required to make any meaningful comparison. Most studies show a wide range of IgE values between omalizumab responders versus non-responders and as suggested, it is therefore possible that those CSU patients who have a kind of 'auto-allergy' or self-reactive IgE to thyroid antigens or IL-24 have an excellent response to omalizumab (4, 5).

Since omalizumab has been approved by National Institute for Health and Care Excellence (NICE) in the United Kingdom for use in patients with CSU unresponsive to standard treatments, it has proved to be a game-changer in the treatment pathway. It is undoubtedly extremely safe when compared to ciclosporin or dapsone, with no requirement for routine monitoring of bloods. However, a significant number of patients relapse after the first cycle of omalizumab, but respond very well to continuous therapy. Achieving complete remission in CSU with anti-IgE therapy seems a difficult goal, and therefore combining immunosuppressive agents such as ciclosporin or dapsone in lower doses with omalizumab may be the way forward in some patients resistant after the first few doses of omalizumab therapy (6-8). This combined strategy may also reveal additional mechanisms that are at play in CSU and how we can explore further therapeutic options.

Figure 1 - *Patient numbers with cycle of treatment (each with 6 doses) with mean UAS7 scores.*



Note: All patients were selected from initiation of therapy, but were at various phases of treatment in the time period mentioned. UAS7 score was taken for the last week before the injection was due and not an overall mean for 4 weeks between doses.

Conflict of interests

The author declare that they have no conflict of interests.

References

1. Tonacci A, Nettis E, Asero R, Rossi O, Tontini C, Gangemi S. Omalizumab retreatment in patients with chronic spontaneous urticaria: a systematic review of published evidence. Eur Ann Allergy Clin Immunol. 2020 Feb 28. [Epub ahead of print].
2. Marzano AV, Genovese G, Casazza G, Fierro MT, Dapavo P, Crimi N et al. Predictors of response to omalizumab and relapse in chronic spontaneous urticaria: a study of 470 patients. J Eur Acad Dermatol Venereol. 2019;33:918-924.
3. Asero R, Ferrucci S, Casazza G, Marzano AV, Cugno M. Total IgE and atopic status in patients with severe chronic spontaneous urticaria unresponsive to omalizumab treatment. Allergy. 2019;74:1561-1563.
4. Schmetzer O, Lakin E, Topal FA, Preusse P, Freier D, Church MK, Maurer M. IL-24 is a common and specific autoantigen of IgE in patients with chronic spontaneous urticaria. J Allergy Clin Immunol. 2018;142:876-882.
5. Altrichter S, Peter HJ, Pisarevskaja D, Metz M, Martus P, Maurer M. IgE mediated autoallergy against thyroid peroxidase--a novel pathomechanism of chronic spontaneous urticaria? PLoS One. 2011 Apr 12;6(4):e14794.
6. Sánchez J, Alvarez L, Cardona R. Cyclosporine and omalizumab together: A new option for chronic refractory urticaria. J Allergy Clin Immunol Pract. 2020 Feb 26. [Epub ahead of print].
7. McIntyre AP, Viswanathan RK, Moss MH, Mathur SK. Real-world dosing of omalizumab for chronic spontaneous urticaria. Ann Allergy Asthma Immunol. 2020;124:211-212.
8. Kavati A, Zhdanava M, Ortiz B, LeCocq J, Schiffman B, Pilon D, Ching Cheung H, Lefebvre P, Stone BD. Long-term omalizumab outcomes in chronic idiopathic urticaria: a real-world study. Allergy Asthma Proc. 2019;40:321-328.