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Editorial

Omalizumab: new addition to dermatologic therapy for chronic spontaneous/idiopathic urticaria

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Chronic spontaneous urticaria (CSU)/ chronic idiopathic urticaria (CIU) remains a therapeutic challenge for treating dermatologists, allergologists and general physicians. The recent updated European Academy of Allergology and Clinical Immunology (EAACI) / Global Allergy and Asthma European Network (GA(2) LEN) / European Dermatology Forum (EDF) and World Allergy Organization (WAO) guidelines[1] recommend second-generation non-sedating antihistamines as the first-line treatment of CSU/CIU and in non-responding cases 4-fold increased dose can be used. However, a certain proportion of patients still remains symptomatic and discontinues these drugs because of side effects. Third-line treatment options for patients who do not achieve complete control of their symptoms with increased dosages of H1-antihistamines have included short-term corticosteroids, add-on therapy with cyclosporin, a leukotriene receptor antagonist, or omalizumab.

Omalizumab is a humanized monoclonal antibody of IgG1 subclass which binds free IgE antibody, the main trigger of mast cell degranulation and release of histamine, leukotrienes, tryptase, chymase, prostaglandin D2 and other cytokines involved in the pathogenesis of CSU/CIU. It also downregulates the expression of the high-affinity receptor for the Fc region of IgE (FcεRI) on basophils. Omalizumab is already approved for the treatment of moderate to severe persistent asthma and recently has been licensed by European Medicines Agency and the U.S. Food and Drug Administration as 150mg or 300mg subcutaneously every 4 weeks in ≥12 year old patients for the treatment of CSU/CIU.

Recently published an in-depth GRADE assessment by Urgert *et al*.[2] indicates high quality evidence for the effectiveness and safety of omalizumab 300mg per month for up to six months. Five double-blind, placebo-controlled, multicenter, randomized clinical trials, 3 phase III studies (ASTERIA I,[3] ASTERIA II[4] and GLACIAL[5]) and two phase II studies (MYSTIQUE[6] and X-QUISITE[7]) evaluated the role of omalizumab in CSU. In GLACIAL study, the primary objective was to assess the safety of drug, whereas other studies focused mainly on the effectiveness of omalizumab. The main outcome measures used for effectiveness in these studies were: *Urticaria Activity Score* (UAS-7), the strongly recommended parameter by EAACI/ GA(2) LEN/ EDF/ WAO to assess the disease severity, calculates the sum of the individual scores of daily urticaria activity in the last 7 days, the score range from 0 to 42 points per week; *Weekly Itch Severity Scale* (ISS) consisting of average daily sum (morning and evening) of pruritus scores in the last 7 days,

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range from 0 to 21; *The Dermatology Life Quality Index*, includes 10 items in 6 domains: symptoms and feelings, daily activities, leisure, work/school, personal relationships and treatment, the overall score of DLQI ranges from 0 to 30, the higher score indicates the bigger impact on quality of life; *Chronic Urticaria Quality of Life Questionnaire* (Cu-Q2oL) which includes 23 items in six domains i.e. pruritus, swelling, impact on life activities, sleep problem, limits and looks (range 0-115); and *Angioedema-Free Days*. Safety of drug was measured by frequency of adverse events; serious adverse events; and adverse events suspected to be caused by the study drug.

Pooled data from 749 participants showed high effectiveness and safety with omalizumab than placebo. Treatment response was dose-dependent and was highest with 300mg omalizumab given 4-weekly.[8] After 12 weeks of treatment, the mean difference in UAS7 was 11.58 points lower after treatment with omalizumab compared with placebo (P<0.001). Complete clearance i.e. UAS=0 was achieved in 38% of patients treated with omalizumab compared with 5.6% of patients treated with placebo (*P*<0.001) whereas partial response (UAS≤6) was achieved in 55.1% in the active group compared with 13.7% of patients in the placebo group (*P*<0.001). The proportion of angioedema-free days was assessed in 576 patients. The mean proportion of angioedema-free days was 5.66% higher after treatment with oral when compared with placebo (*P*<0.001).[2] The median time to achieve minimum important difference response (≥ 5 point decrease) in weekly itch severity score (range 0-21) ranged from 1.0 to 2.0 week. Clinical response to treatment with omalizumab was unrelated to concomitant medicines for CSU/CIU.

Similarly quality of life assessed using the DLQI and CU-Q2oL, revealed significant improvement in the treatment group (*P*<0.001).

Adverse events occurred in 73.7% (342 of 464) patients treated with omalizumab and in 64.2% (188 of 285) of controls with no significant difference between the groups (*P*>0.05). However, the majorities of adverse events were mild to moderate and did not warrant discontinuation of treatment. 6.2% patients in placebo group, 1.7% in 150mg- and 5.3% in omalizumab 300 mg group had severe adverse effects. Injection-site reactions such as pain, swelling, erythema and pruritus were also reported 2-7% omalizumab 300mg vs (0.8% placebo). Anaphylaxis, a well-known adverse event associated with omalizumab, was not observed in the given studies. Overall omalizumab had good safety profile.

The median time to loss of response, after discontinuation of therapy was 3 and 5 weeks with 150mg- and 300mg omalizumab treatment groups in ASTERIA I and II studies and 7 weeks with 300 mg treatment in GLACIAL study.

No doubt the high quality evidence supports the effectiveness and safety of omalizumab in CSU/CIU, still there remain unmet needs in the management of disease. The loss of response after discontinuation of therapy suggests that omalizumab is not disease modifying drug for CIU, hence it has to be continued for longer durations until the disease itself burns out.[9] So the benefits of long-term treatment with omalizumab in CSU/CIU need to be studied further. Similarly in the settings of clinical trials, a drug is used in the selected population of patients and it is difficult to generalize its results in the real-world population. Additional information on the effectiveness and safety of omalizumab will become available once it is used in patients with other comorbidities e.g.

autoimmune diseases, or pre-existing renal or hepatic impairment etc. and other concomitant drugs. Thirdly, one dose of 300mg omalizumab costs US$ 600 which is likely to restrict its use in many resource poor Asian and African countries. Furthermore, drug has to be given subcutaneously, albeit rare (<1 in 1000 in asthma patients) chances of anaphylactic reaction do exist, hence drug has to be given in the hospital settings.[10]

In spite of its limitations, omalizumab offers an alternative modality with a different mechanism of action for fast relief from symptoms for patients with difficult-to-manage CSU/CIU.

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