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Omalizumab's efficacy and safety against chronic spontaneous urticaria

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ABSTRACT

I have read the article titled, "Efficacy and safety of omalizumab against chronic spontaneous urticaria: Real-world study from China", by Wang et al with great interest. Nevertheless, there are a couple of questions raised in my mind. And clarification of some aspects of the study will help the reader benefit and have a better understanding of the study.

Keywords: Omalizumab, Chronic spontaneous urticaria, Immunoglobulin E

DEAR EDITOR

I have read the article titled, "**Efficacy and safety of omalizumab against chronic spontaneous urticaria: Real-world study from China**", by Wang et al[1] with great interest. Nevertheless, there are a couple of questions raised in my mind during my reading. And clarification of some aspects of the study will help the reader benefit and have a better understanding of the study.

All patients in the study received at most 3 injections of omalizumab, and the mean duration of therapy was 3.4 ± 1.0 months. This study included the management of too-young children over a shorter period than usual. However, the use of omalizumab is not still approved by the US Food and Drug Association (FDA) for less than 6 years of age in asthma and not approved for less than 12 years of age in chronic spontaneous urticaria (CSU).[2,3] According to the European Medicines Agency (EMA) of European Union, omalizumab is approved as add-on therapy in adults, adolescents, and children (6–12 years of age) with severe/persistent allergic asthma.[4] I think that 150 or 300 mg/month, just 3 injections in 3 months may not be an adequate dose and time to take care of these patients. Despite the controversy, in the Europe and United States guidelines,[5] treatment duration of CSU generally varies from 6 to 12 months.

The mean follow-up time was 5.7 ± 2.0 months, as well. And follow-up time also did not seem to be enough to observe real effectiveness and disease relapse rate in these children. Therefore, I do not agree with the authors' suggestion that a dose of 150 mg for 3 months in those patients under 12 years of age may be successful for the treatment of the disease.

In Table 2,[1] around week 12, the outcome looks almost perfect as expected, because we see the maximum effect of omalizumab around the third month of omalizumab use, since the half-life of omalizumab is 26 days.[6] Correspondingly, serum free IgE quickly may decline after omalizumab is given, by way of unceasing therapy, there is resulting downregulation of the FcεR1 expression

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on the inflammatory immune (dendritic) and allergy (basophils and mast) cells happening over the next 4–6 months.[7] However, this satisfying outcome most of the time does not continue/persist in the real world and CSU frequently recurs especially after 6–12 months of treatment discontinuation.

Again, it is emphasized in the international guide[2] that omalizumab used in the third step should be used for 6 months and that unresponsiveness to the treatment should be decided accordingly, and consequently, switching to the add-on fourth step immunosuppressive cyclosporine.[5] However, the total treatment period in this study[1] did not exceed 3 months and the observation period did not exceed 6 months most of the time.

In this study, omalizumab treatment was also tried in CSU patients with the presence of mild to moderate urticaria (represented by the mean scores UAS7 24,8 $\pm$ 8.6 and CDLQI score 9.5 $\pm$ 4.8) in the clinic of the patients, and also the antihistamine treatment was not observed to be increased up to 4 times the dose as stated in the guidelines (EAACI/GA^{2}LEN/EDF/WAO International Guideline).[5] (The authors said that the CSU patients received at least double doses of antihistamines). In addition, our observation of the higher baseline scores of those CSU patients who did not respond to treatment, as shown in Table 3 of the results of this study,[1] is compatible with our opinion and confirms it.

As a summary of above points, this is a study in which the efficacy and safety of omalizumab treatment were evaluated in a very short period of 3 months, including children as young as 4 years of age, with mild to moderate CSU. Thus the efficacy of omalizumab is tested in very selected groups, which does not fit real-life data.

Although this study[1] is a safety and efficacy study of a drug, there is no evaluation of how and when the omalizumab treatment will be terminated, although there are many who dropped out of the study and discontinued the drug. In Figure 1,[1] what is the difference between groups between "not followed up" and "dropped out"? Moreover, although this study was conducted during the COVID-19 pandemic, the safety of omalizumab use in COVID-19 patients has not been discussed.[8]

There was no good standardization in the study[1] and it did not seem to be a well-planned study. The fact that there is no difference between the relapsed and non-relapsed groups, and the responders and non-responders groups on any parameter reported to make a difference in the literature also raises suspicion about the study design.[9] In Figure 2A,[1] a patient above 12 years of age was followed up to week 28. Patients under 12 years of age were followed up to week 24. Why are the weeks different? Indeed the study period is very short and during follow-up, after week 16 the overall enrolled patient number was decreased to 1 patient and they were also only able to follow up at the most 87/235 patients in this study. Lastly, in Figure 3,[1] scores of the twelfth week and entire treatment are the same. The entire treatment period is not the same in most of the patients. They should not have the same score during evaluation.

Minor point: Were there any CSU patients having inducible urticaria together? It will be helpful for the reader to know this. At the same time, this is an issue that may affect the treatment response.

In conclusion, by clarifying and revealing the issues of the above-mentioned study the authors will make the study more useful and understandable for the reader.

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