

However, only the 6-month-old had increased fur Fel d 1 levels (61.44 $\mu\text{g/g}$). Therefore the data do not confirm or refute previous reports that intact male cats have greater fur Fel d 1 levels.

It is a common belief that certain cat breeds are hypoallergenic. Hair length as a surrogate for breed did not explain differences in Fel d 1 levels. Siebers et al⁹ also found that sex, fur color, and fur length were not related to Fel d 1 levels in reservoir dust from homes. Although 23% of cats had fur Fel d 1 levels of greater than 30 $\mu\text{g/g}$ in this study, it is possible that other factors, such as day-to-day variation or lack of grooming, might have led to these higher levels.

In conclusion, we observed cat-to-cat variability of Fel d 1 levels in fur of domestic cats unrelated to breed, sex, or age. This is contrary to other observations for Fel d 1.³ The data suggest that hormonal status can affect salivary Fel d 4 levels in female cats and urinary Fel d 1 levels in male cats. These findings deserve further investigation. In addition, it would be of interest to compare levels of Fel d 4 and Fel d 1 in homes with cats. Given the low levels of Fel d 4 in cat fur, it is likely that levels in houses will also be low but might be still be sufficient to induce levels of specific IgE in patients with cat allergy.

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Personalized omalizumab treatment improves clinical benefit in patients with chronic spontaneous urticaria



To the Editor:

Omalizumab is a humanized anti-IgE mAb that was found to be highly efficacious in several randomized clinical trials, which led to licensing for chronic spontaneous urticaria (CSU) by the US Food and Drug Administration in 2014.¹⁻³ Omalizumab targets free IgE at the site of the Fc region of IgE (FcεRI), which prevents free IgE from binding to the high-affinity receptor FcεRI on mast cells and basophils. Possible mechanisms of action in patients with CSU include neutralization of IgE autoantibodies in so-called “autoallergic” patients and the gradual downregulation of the FcεRI receptor in so-called “autoimmune” patients who have IgG antibodies directed against the high-affinity receptor FcεRI.^{4,5}

A major limitation of treatment with omalizumab in patients with CSU concerns the per-label fixed dosing schedule, without any options to adapt or tailor the therapy to the needs of the individual patient. Moreover, treatment duration in the registration studies was limited to a maximum of 6 months, and the next steps (ie, dose maintenance, downdosing, or discontinuation) remain unclear and are not discussed in international guidelines.

The objective of this study was to retrospectively evaluate the effectiveness of omalizumab in patients who were treated according to a predefined algorithm. In this personalized approach, we explored (1) the potential of up dosing in patients who did not achieve complete remission (CR) with the standard treatment regimen, (2) a gradual down dosing schedule for patients who achieved CR, and (3) relapse rates after gradual down dosing. Patients initially received 300 mg of omalizumab every 4 weeks for 12 weeks per label. Four weeks after the third dose, the effect was evaluated with the validated Urticaria Activity Score (UAS-7) questionnaire. In case of CR (UAS-7 = 0), a down dosing schedule was initiated that entailed progressively increasing the dosing interval by 1 week every visit up to 8 weeks, as long as the patient remained in CR. Treatment was then discontinued if the patient remained in CR after these 4 additional administrations.

Patients were advised to continue treatment with up dosed H1 antihistamines for at least 12 weeks after stopping omalizumab. If symptoms reoccurred before the next scheduled administration, the dose interval was shortened so that the length of the next dosing interval equaled the previous symptom-free period. The dose interval of patients who relapsed during the first down dosing attempt was extended again as soon as they stayed symptom free for 4 weeks.

Patients with a partial response (PR; minimum decrease of 9.5 points) initially continued with the same dose of 300 mg every 4 weeks for 1 to 3 doses depending on the severity of symptoms. For those with CR, after this extended period of per-label treatment, tapering was started in the same way as for patients who achieved CR after 3 doses. For patients with a persistent PR, either the dose was increased to 450 mg every 4 weeks or the interval was decreased to 3 weeks if symptoms worsened during the fourth week. Doses were increased up to 600 mg every 3 to 4 weeks when needed to reach CR. When CR was reached, first the dose was down titrated stepwise to the per-label dose of 300 mg every 4 weeks, if possible, before starting the tapering schedule.

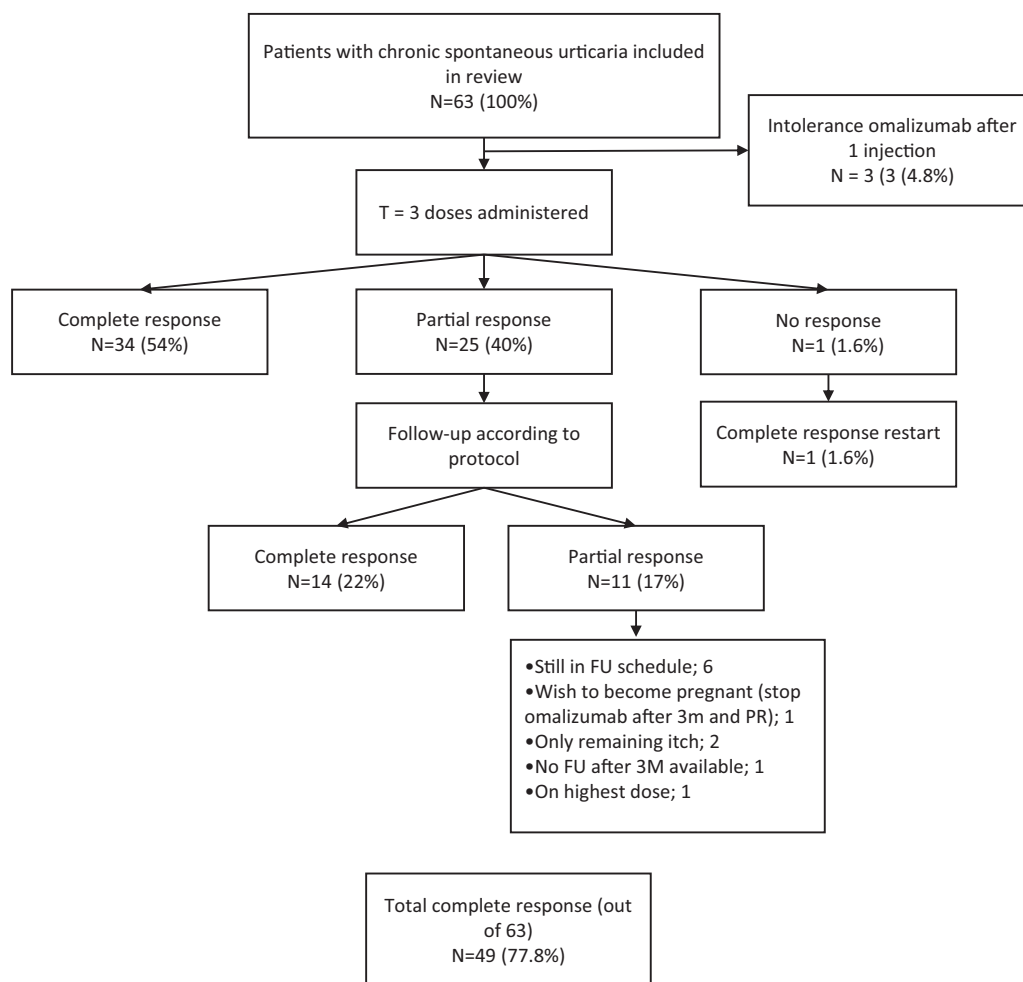


FIG 1. Flow chart of patients with CSU treated with omalizumab using a personalized approach.

In patients who were nonresponders after 3 doses, the dose was directly increased to 450 mg. If the patients remained nonresponders despite adjustment of the dose and/or interval, treatment with omalizumab was discontinued, and patients were switched to another treatment. In patients who relapsed after omalizumab discontinuation, treatment was immediately restarted.

During the treatment period, all patients completed UAS-7 questionnaires. After 3 administrations of omalizumab (300 mg/4 weeks), 34 (54%) patients reached CR. Twenty-five (40.3%) patients had a PR, and 1 patient had no response (1.6%; Fig 1). Three patients had an adverse reaction to omalizumab after the first administration of omalizumab and discontinued treatment. All patients with PRs entered the personalized treatment schedule to optimize dosing with the goal of achieving CR. This was achieved in 14 (56%) of 25 patients. Of these 14 patients, 6 reached CR with a continued dose of 300 mg, 3 patients needed a higher dose, and another 4 patients needed both a higher dose and a shorter interval to reach CR. It has been hypothesized that this subset of patients has IgG antibodies that are directed at FcεRI on mast cells, leading to mast cell degranulation and inflammatory mediator release.

Omalizumab does not target IgG directly, and therefore it is agreed that no immediate effect will occur. However, because

omalizumab will induce a strong reduction in levels of free serum IgE, a secondary effect will be downregulation of the FcεRI receptor. This can lead to inactivation of mast cells that are rendered not or less responsive to stimuli. Downregulation is a slow process and therefore can coincide with a slower response, as was observed in these patients.^{4,5} Therefore we believe that treatment should not be stopped too early, which was also concluded by Maurer et al.⁶ However, in the absence of IgE level measurements in this study, it must be noted that this mechanism remains speculative and that more research is needed to corroborate this concept.

Of the remaining 11 patients with a PR, 6 are currently still in the follow-up schedule, 1 was lost to follow-up after 3 doses, 1 stopped treatment because of the wish to become pregnant, 2 have only remaining itch symptoms, and 1 is receiving the highest dose of 600 mg/3 weeks and continues to have only a PR. Although a complete response was not reached in this patient (UAS-7 varying between 5 and 10), quality of life improved remarkably, and treatment was continued. The initial nonresponder restarted with omalizumab treatment when his disease was more stable after a course of oral prednisone and ultimately became a CR.

Of the 63 included patients treated with omalizumab, in 24 (38%) patients the dosing interval was successfully extended to 8 weeks and then discontinued. The remaining 39 patients are

still in the initial treatment phase or did not yet complete the tapering schedule. Therefore these data cannot be analyzed at this time. Of these 24 patients, 14 (58%) remained symptom free until the present (mean relapse-free period, 208 weeks). Ten patients experienced a relapse after treatment with omalizumab was discontinued (42%). In 7 of the patients with relapses, symptoms returned after approximately 12 weeks. In these patients omalizumab was restarted with different intervals but eventually similar outcomes, namely a continued symptom-free dosing interval of 12 weeks. Three patients had a relapse that was most likely related to exposure of a known trigger for urticaria. Patients restarted omalizumab treatment with a 4-week dosing interval, which was prolonged directly after the first dose until the interval of 8 weeks was reached before stopping treatment again. All patients who restarted treatment reached CR within 4 weeks after a single 300-mg omalizumab administration.

To summarize, the overall efficacy rates in this study (77.8% CR and 17% PR) are considerably higher than the previously reported combined efficacy rates of 5 randomized controlled trials (38.1% CR and 55.1% PR).⁷ CR rates after our tapering schedule (58%) were greater than reported before; only 12% of the patients in a retrospective analysis by Metz et al⁸ remained in CR in the 4- to 16-month follow-up period. Another retrospective analysis by Turk et al⁹ reported 39% of the patients remained symptom free.

In conclusion, this study demonstrates the clinical benefit of dose optimization of omalizumab with our therapeutic algorithm in patients with refractory CSU. Larger studies are warranted to confirm our findings and to formally evaluate the cost-effectiveness of this personalized approach.

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A novel allergen-specific therapy with CD40-silenced B cells and dendritic cells



To the Editor:

Recently, regulatory B (Breg) cells were shown to contribute to inhibition of allergic responses.^{1,2} However, the Breg cells in these studies were not antigen specific. Although IgE is generated from B cells, CD40 is required for germinal center formation, IgE production, and memory B-cell development.³⁻⁵ Blockade of the CD40-CD40 ligand interaction also induces generation of regulatory T (Treg) cells.⁶ Considering the above, CD40-silenced B cells would seem to be attractive for use in therapeutic approaches to allergic diseases.

RNA interference using small interfering RNA (siRNA) is a potent, selective, and easy method for specific blocking of gene expression. We previously reported that CD40-silenced antigen-specific dendritic cells (DCs), which were induced by siRNA, inhibited allergic responses and symptoms.⁶ However, to our knowledge, there has been no prior study examining allergen-specific therapy with Breg cells induced by siRNA. In this study we investigated the effect of CD40-silenced allergen-specific B cells on allergic responses and examined the similarities and differences of CD40-silenced DCs and CD40-silenced B cells.

As shown in Fig E1 in this article's Online Repository at www.jacionline.org, siRNA-specific CD40 (CD40 siRNA) suppressed CD40 expression on B cells, the proliferative response of B cells, and IgE synthesis by B cells. Next, the effect of CD40-silenced ovalbumin (OVA) B cells, which were transfected with CD40 siRNA and pulsed with OVA, on T-cell response was examined. CD40-silenced OVA B cells significantly inhibited OVA-specific T-cell proliferation (Fig 1, A). However, these cells did not inhibit keyhole limpet hemocyanin (KLH)-specific T-cell responses (Fig 1, B).

CD40-silenced B cells significantly upregulated the rate of forkhead box protein 3 (Foxp3)⁺ cells in CD4⁺CD25⁺ cells and *Foxp3* gene expression (Fig 1, C and D). CD4⁺CD25⁺ cells generated by CD40-silenced OVA B cells significantly suppressed the ongoing OVA-specific T-cell response (Fig 1, E). However, these CD4⁺CD25⁺ cells did not significantly inhibit the KLH-specific T-cell response (Fig 1, F). On the other hand, CD4⁺CD25⁺ cells induced by CD40-silenced B cells pulsed with KLH did not significantly inhibit OVA-specific T-cell responses, although these cells significantly inhibited KLH-specific T-cell responses (see Fig E2 in this article's Online Repository at www.jacionline.org).

The effect of CD40-silenced B cells *in vivo* was also investigated (see this article's Methods section in the Online Repository at www.jacionline.org). Mice that had received