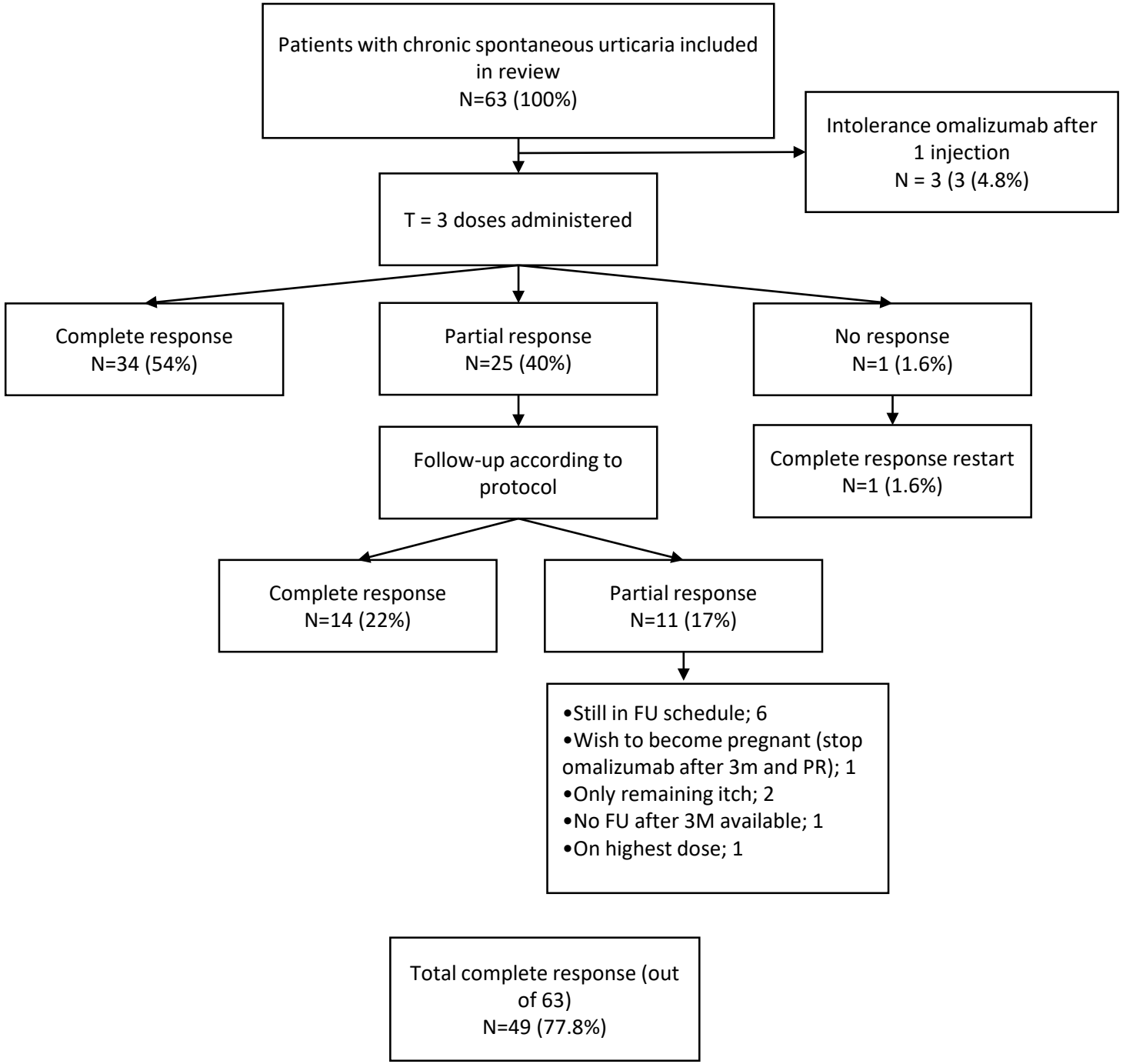
Patients with chronic spontaneous urticaria included in review
N=63 (100%)
Intolerance omalizumab after 1 injection
N = 3 (3 (4.8%)
T = 3 doses administered
Complete response
N=34 (54%)
Partial response
N=25 (40%)
No response
N=1 (1.6%)
Follow-up according to protocol
Complete response restart
N=1 (1.6%)
Complete response
N=14 (22%)
Partial response
N=11 (17%)
•Still in FU schedule; 6
•Wish to become pregnant (stop omalizumab after 3m and PR); 1
•Only remaining itch; 2
•No FU after 3M available; 1
•On highest dose; 1
Total complete response (out of 63)
N=49 (77.8%)

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

Short title: Personalized treatment with omalizumab in CSU

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Capsule summary

Dose optimization of omalizumab in patients with chronic spontaneous urticaria demonstrates better clinical effectiveness and down dosing can be performed without loss of efficacy in many patients.

Keywords: chronic spontaneous urticaria, omalizumab, personalized treatment, dose optimization, up dosing, down dosing

Abbreviations: CSU (chronic spontaneous urticaria), QoL (quality of life), AH (antihistamines), UAS-7 (urticaria activity score)

TO THE EDITOR

Omalizumab is a humanized anti-IgE monoclonal antibody that was found highly efficacious in several randomized clinical trials, with led to licensing for CSU by the FDA (U.S. 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 basophiles. Possible mechanisms of action in CSU include neutralization of IgE auto-antibodies in so-called 'auto-allergic' patients and the gradual downregulation of the FcεRI receptor in so-called 'auto-immune' patients who have IgG antibodies directed against the high affinity receptor FcεRI (4, 5). A major limitation of treatment with omalizumab in patients with chronic spontaneous urticaria (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 six months, the next steps (i.e. dose maintenance, down dosing or discontinuation) remain unclear and are not discussed in the 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; I) the potential of up dosing in patients who did not achieve complete remission (CR) with standard the standard treatment regimen, II) a gradual down dosing schedule for patients who achieved complete remission and III) the relapse rates after gradual down dosing. Patients initially received omalizumab 300 mg every four weeks for twelve weeks per label. Four weeks after the third dose, the effect was evaluated with the validated UAS-7 questionnaire. In case of CR (UAS-7=0), a down dosing schedule was initiated which entailed progressively increasing the dosing interval by one week every visit, up to eight weeks, as long as the patient remained in complete remission. Treatment was then discontinued if the patient

remained in CR after these 4 additional administrations. Patients were advised to continue treatment with updosed 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 four weeks. Patients who partially responded (PR; minimum decrease of 9.5 points) initially continued with the same dose of 300 mg every four weeks for one to three doses depending on the severity of symptoms. For CR, after this extended period of per label treatment, tapering was started in the same way as the CR after three doses. For the persistent PR, either the dose was increased to 450 mg every four weeks or the interval was decreased to three 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 four weeks if possible, before starting the tapering schedule. In patients who were non-responders (NR) after three doses, the dose was directly increased to 450 mg. If they still remained NR 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 three administrations of omalizumab (300mg/4weeks), 34 patients (54%) reached CR. 25 (40.3%) patients showed PR and one patient had NR (1.6%), Figure 1. Three patients had an adverse reaction to omalizumab after the first administration of omalizumab and discontinued treatment. All PR entered the personalized treatment schedule to optimize dosing with the goal to achieve CR. This was achieved in 14 of 25 patients (56%). Of these 14 patients, six reached CR with a

continued dose of 300mg, four patients needed a higher dose, and another four patients needed both a higher dose and shorter interval to reach CR. It has been hypothesized that this subset of patients has IgG antibodies, which are directed at the high affinity IgE receptor (FcεRI) on mast cells leading to mast cell degranulation and the release of inflammatory mediators. Omalizumab does not target IgG directly, so it is agreeable that no immediate effect will occur. However, since omalizumab will induce a strong reduction of free serum IgE, a secondary effect will be the downregulation of the FcεRI receptor. This may lead to inactivation of mast cells that are rendered not or less responsive to stimuli. Downregulation is a slow process and therefore may coincide with a slower response as was observed in these patients (4, 5). Therefore, we believe that treatment should not be stopped to early, which was also concluded by *Maurer et al.* (6). However, in absence of IgE level measurements in this study it must be noted that this mechanism remains speculative and more research is needed to corroborate this concept. Of the remaining 11 patients with a PR, six patients are currently still in the follow-up schedule, one patient was lost to follow-up after three doses, one patient stopped treatment due to the wish to become pregnant, two patients have only remaining itch symptoms and one patient is on the highest dose of 600mg/3 weeks and continues to be a PR. Although a complete response was not reached in this patient (UAS7 varying between 5 and 10), QoL improved remarkably and treatment was continued. The initial NR 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 eight 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 patients (58%) remained symptom free until present (mean relapse free period 208

weeks). Ten patients experienced a relapse after treatment with omalizumab was discontinued (42%). In seven of the relapse patients, 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 four-week dosing interval, which was prolonged directly after the first dose, until the interval of eight weeks was reached before stopping treatment again. All patients who restarted treatment, reached CR within four weeks after a single 300mg 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 five RCTs (38.1% CR and 55.1% PR) (7), Complete remission rates after our tapering schedule (58%) were higher than reported before; only 12% of the patients in a retrospective analysis by Metz *et al*. remained in complete remission in the 4-16 months follow-up period (8). Another retrospective analysis by Turk *et al*. reported 39% of the patients to remain symptom free (9). In conclusion, this study demonstrates the clinical benefit of dose optimization of omalizumab with our therapeutic algorithm in refractory CSU patients. Larger studies are warranted to confirm our findings and to formally evaluate the cost-effectiveness of this personalized approach.

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FIGURE LEGEND

Figure 1. Flowchart of chronic spontaneous urticaria patients treated with omalizumab using a personalized approach.