RESEARCH LETTER

Omalizumab serum levels predict treatment outcomes in patients with chronic spontaneous urticaria: A three-month prospective study

To the editor,

The recommended treatment of antihistamine refractory chronic spontaneous urticaria (CSU) is omalizumab.[1] However, little is known about the association between serum-omalizumab drug concentrations and response to treatment in patients with CSU, and about the association between various patient characteristics and serum-omalizumab concentrations.

To examine this, a total of 23 patients (19 women and 4 men), who initiated treatment with 300 mg omalizumab every 4th week, were included in a 12-week prospective study from a dermatological university department (Department of Dermatology, Bispebjerg Hospital, Copenhagen, Denmark). From each patient, two blood samples were collected; one before (trough level) and at Day seven (peak level[2]) after each injection. Each blood sample was centrifugated, and serum samples were stored in the freezer at –20°C. Each sample was analysed at Laboratory of Medical Allergology, Gentofte Hospital, Hellerup, Denmark, using a newly developed method for detection of omalizumab in the serum samples.

The method to detect serum omalizumab was based on IgE (Calbiochem) coupled to magnetic, colour-coded microspheres (Luminex) using the xMAP® Antibody Coupling Kit (Luminex). Serum-omalizumab samples were thawed and diluted 1:300 in an assay buffer consisting of DPBS (Sigma), Tween 20 (Sigma) and FCS (Sigma). Standard curve consisted of twofold dilutions of omalizumab with concentration range from 10 to 640 ng/ml. The IgE-coated microspheres were transferred to a Bio-Plex Pro™ Flat Bottom Plate and followed by addition of diluted omalizumab serum samples. The plate was incubated for 90 min (on an orbital shaker while protected from light) and followed by a washing step and addition of biotinylated anti-IgG (Sigma). The plate was hereafter incubated for 60 min and followed by a washing step and addition of Streptavidin-R-Phycoerythrin (Agilent). After 30 min of incubation, the samples were analysed using the Bio-Plex 200 system.

Treatment was evaluated with patient-reported outcomes (PROs) every 4th week during 12 weeks of treatment with urticaria activity score in the past week (UAS7) as primary outcome and urticaria control test (UCT), Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) and dermatology life quality index (DLQI) as secondary outcomes.

After a treatment period of 12 weeks with omalizumab, an improvement in UAS7 of 16.8 points (95% CI 10.8–22.8), $p < .001$ was seen. Minimal disease activity (UAS7 score ≤6) was achieved in 9 patients (39.1%), whereas 6 patients (26.1%) achieved a UAS7 score of 0. The minimal clinically important difference (MCID) of 10 points in UAS7 was reached in 17 patients (73.9%). UCT, CU-Q2oL and DLQI also improved significantly from baseline to 12-week follow-up: 7.4 points (4.7–10.1), 22.8 points (13.4–31.8) and 7.8 points (4.0–11.8), $p < .001$ for all comparisons respectively. The MCID in UCT and DLQI was reached in 15 patients (65.2%) and 14 patients (60.9%) respectively. During the 12-week treatment period, a total of five patients (21.7%) reported at least one suspected side effect of omalizumab; headache (2 patients), fatigue (2 patients), weight gain (2 patients) and dry mouth (2 patients). No severe side effects were reported.

The serum-omalizumab drug concentrations at each visit throughout the treatment period for each patient are presented in Figure 1. The range of serum-omalizumab concentrations at trough and peak level was 7.0–33.1 µg/ml and 11.4–54.0 µg/ml respectively. The mean serum-omalizumab concentration (peak or trough level) appeared to reach a plateau (steady-state) at 8–12 weeks of treatment. A significant increase was seen from trough serum-omalizumab concentration to peak serum-omalizumab concentration at all three visits, although the greatest difference was seen at Week 8 (difference: Week 4, 15.6 µg/ml; Week 8, 19.8 µg/ml; Week 12, 12.6 µg/ml, $p < .001$). Furthermore, a significant increase was seen in trough serum-omalizumab concentrations from Week 4 to Week 8 (difference: 2.9 µg/ml, $p = .04$) and from Week 4 to Week 12 (5.0 µg/ml, $p = .01$). No significant difference was observed between Weeks 8 and 12. Peak serum-omalizumab concentrations increased significantly from baseline to each follow-up visit; however, the greatest difference in peak serum-omalizumab concentration was seen from baseline to Week 8 (difference: Week 4, 7.7 µg/ml; Week 8, 12.3 µg/ml; Week 12, 8.3 µg/ml, $p < .01$). No significant difference was seen between peak serum-omalizumab concentrations from Weeks 4 to 8 or Weeks 8 to 12. The mean half-life ($T_{½}$) of omalizumab was found to be 35.7 days (25.7–45.7).

The following patient-specific factors measured at baseline were examined for an association with serum-omalizumab peak

concentrations: age, sex, body mass index (BMI), angioedema, positive basophil HR test, blood basophils and eosinophils, angioedema, and serum total IgE. Of these, BMI was the only statistically significant predictor of omalizumab peak concentrations during the study (standardized difference −2.75, p < .05), that is higher BMI was associated with lower omalizumab peak concentrations (Figure 2A). The same patient-specific factors and serum-omalizumab trough concentrations were examined for a possible association with changes in PROs during the study. Of these factors, omalizumab trough concentrations were associated with UAS7 score (difference −0.82, p < .001), that is higher omalizumab trough concentrations were associated with lower UAS7 scores (better response). The same was observed for UCT (difference 0.28, p < .001), CU-Q2oL (−1.52, p < .001) and DLQI (−0.35, p < .001) (Figure 2B).

In this prospective study, we observed that low serum trough concentrations of omalizumab during treatment were associated with a poorer response on urticaria activity, urticaria control and health-related quality of life. Furthermore, we observed that a higher BMI was a significant predictor of lower omalizumab peak concentrations during treatment. All patients included in this prospective study had significant disease activity, low disease control and significantly impaired quality of life before initiating treatment with omalizumab every fourth week. After 12 weeks of treatment, a significant improvement of disease activity was seen in almost 75% of the patients. Also, a significant improvement of disease control and quality of life was seen in 65% and 60% of the patients after 12 weeks of treatment respectively. These findings are congruent with previously reported effectiveness of omalizumab[3,4]

We observed substantial variation in omalizumab concentrations between patients and time points; however, patients with a high BMI obtained lower omalizumab peak concentrations during treatment. This may be of clinical importance as omalizumab is administrated as a fixed dose to patients with CSU, unlike in patients with severe allergic asthma, where the dose of omalizumab is determined by pre-treatment serum total IgE levels and body weight.[5] Therefore,

> ### Key Messages
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> - Omalizumab (anti-IgE) is effective and safe for treating antihistaminerefractory chronic spontaneous urticaria.
> - Chronic spontaneous urticaria patients with higher BMI had lower peak omalizumab concentration during treatment.
> - Lower trough (minimum) omalizumab concentrations were associated with poorer patient-reported effectiveness outcomes.

a lower peak concentration of omalizumab in CSU patients with a higher BMI may suggest a poorer response to omalizumab. Similar observations were reported in a retrospective study, where CSU patients with a BMI >30 kg/m^2 were linked to non-response to omalizumab treatment,[6] while an observational study linked severe CSU and high BMI to a poor response to omalizumab treatment.[7] In another study of patients with severe allergic asthma, it was also seen that non-responders to omalizumab had a significantly higher BMI (>30 kg/m^2) compared with responders.[8] The impaired circulation of omalizumab in patients with high BMI could be linked to a slow distribution due to the subcutaneous administration of the drug as the subcutaneous layer is thicker in patients with high BMI. Furthermore, a doubling of body weight increases the clearance rate of omalizumab twofold.[5] Hence, patients with a high BMI may appear to have a lower peak concentration due to a higher elimination of omalizumab at the injection site or a delayed lymphatic absorption of the drug leading to a delay in peak concentrations.[9] Lower trough concentrations were associated with poorer response on UAS7, UCT, CU-Q2oL and DLQI. This could indicate a faster elimination of omalizumab in some patients, which could lead to a poorer response to treatment, as urticaria symptoms relapse during the interval between injections. A higher dose of omalizumab or shorter interval between injections could be considered in these patients.[1]
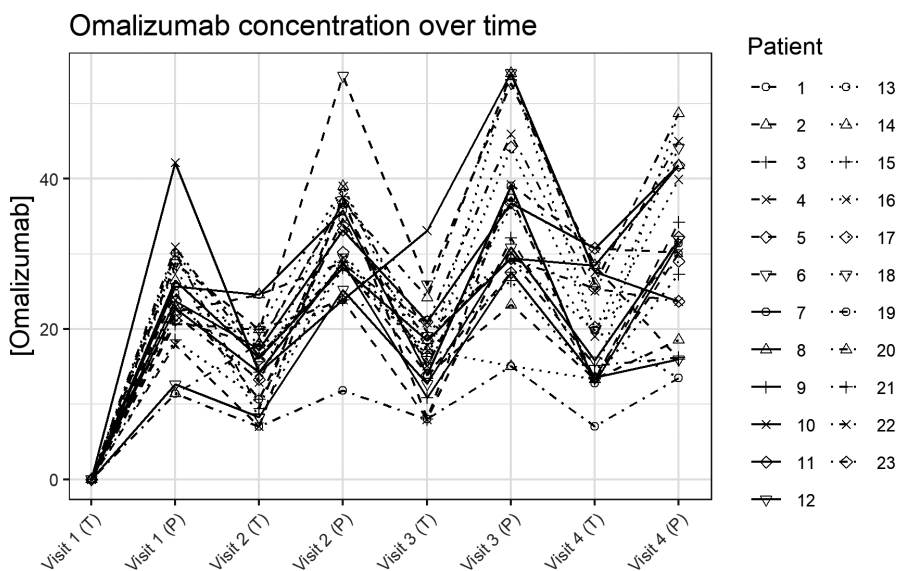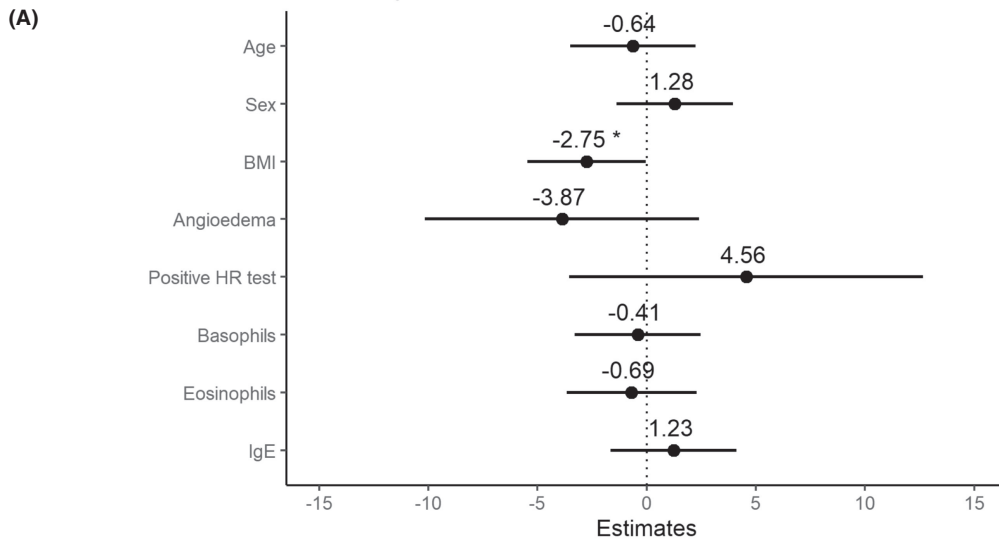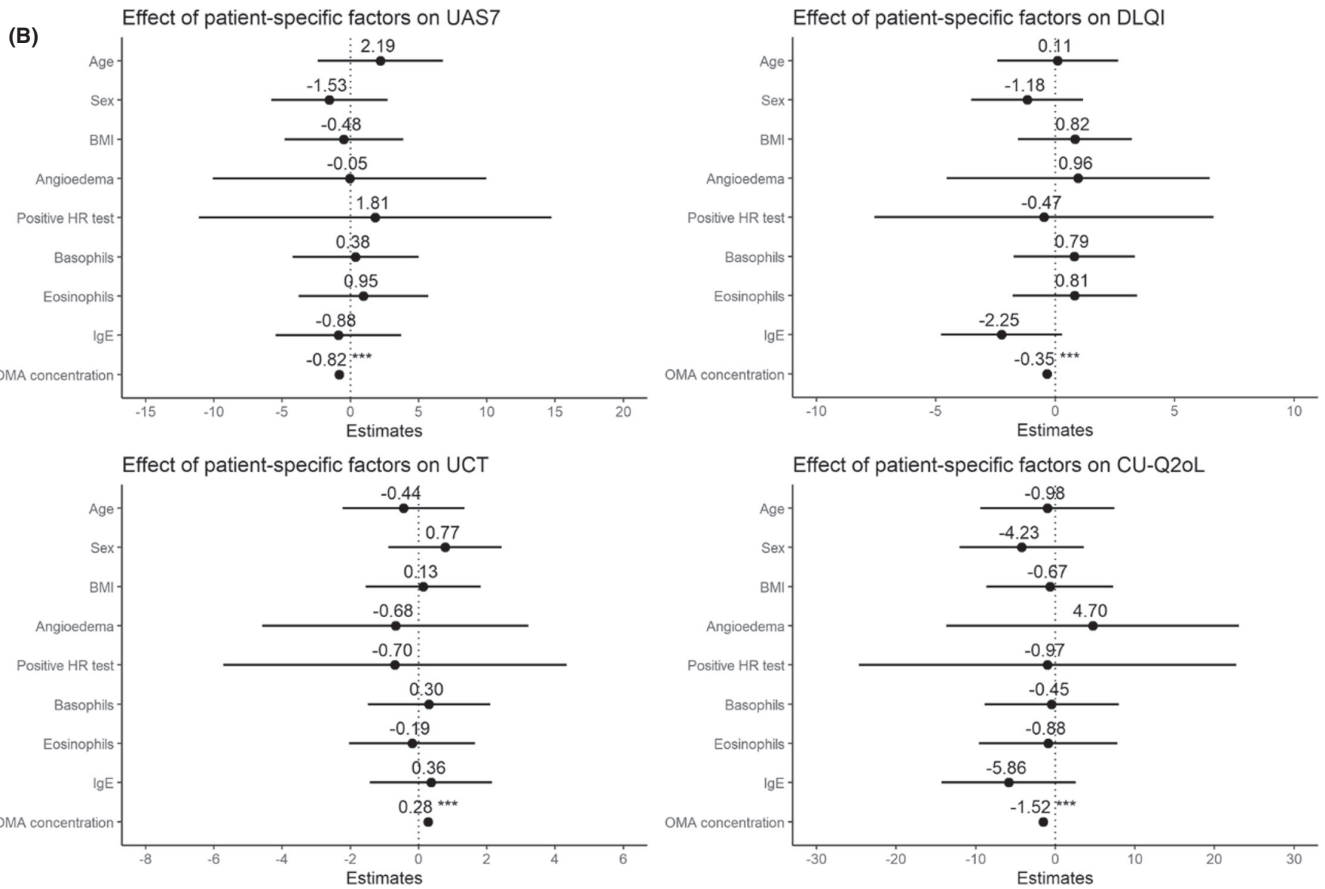

FIGURE 1 Serum-omalizumab drug concentrations measured immediately before (T, trough level) and at Day 7 after each injection (P, peak level)

FIGURE 2 (A) Association between patient-specific factors and serum-omalizumab peak concentrations presented with estimates and their 95% confidence intervals. *p < .05. (B) Association between patient-reported outcomes and serum-omalizumab trough concentrations presented with estimates and their 95% confidence interval. ***p < .001

Furthermore, studies with a larger sample size are needed to understand the variation in serum-omalizumab concentration and its association with treatment efficacy and patient-specific factors in CSU.

KEYWORDS

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

MNG and SFT conceived and planned the experiments. MNG, JGH and SFT carried out the experiments. MNG and JGH collected the data. MNG, EAB, LKP, BMJ and JGH contributed to sample preparation. EAB, LKP, BMJ and CE developed and analysed the blood sample method (serum omalizumab). NSA, AW, NØ, MNG and SFT made the data analyses of the results and contributed to the interpretation of the results and models. MNG took the lead in writing the manuscript supervised by SFT. All authors discussed the results and contributed to the final manuscript.

DATA AVAILABILITY STATEMENT

Additional information about study methods and findings are available in the following repository: https://figshare.com/articles/figure/Supplementary_material/19213101.

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