Original Article

Predicting Chronic Spontaneous Urticaria Symptom Return After Omalizumab Treatment Discontinuation: Exploratory Analysis

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What is already known about this topic? Omalizumab treatment can control symptoms in a high percentage of patients with chronic spontaneous urticaria (CSU), but symptoms can return, either fast or slow, after stopping treatment.

What does this article add to our knowledge? The results of this study suggest that it is possible to selectively identify patients with CSU who are at risk of rapid symptom return after omalizumab treatment discontinuation.

How does this study impact current management guidelines? Based on our findings, a simple digital tool could be developed and used to estimate the probability of rapid symptom return after CSU treatment discontinuation, which could improve the management of patients with CSU in the clinic.

BACKGROUND: Omalizumab is highly effective in controlling chronic spontaneous urticaria (CSU) symptoms; however, patients can experience symptom return on treatment discontinuation. Pivotal clinical trials have identified 2 categories of patients who experience symptom return: rapid and slow.
OBJECTIVE: The objective of this study was to identify potential predictors of the speed of symptom return after stopping omalizumab treatment.
METHODS: Phase III randomized controlled trial (RCT) data from ASTERIA I (n = 319; 6 × 4 weekly injections of omalizumab 75, 150, 300 mg or placebo; NCT01287117) and ASTERIA II (n = 323; 3 × 4 weekly injections of omalizumab 75, 150, 300 mg, or placebo; NCT01292473) were pooled to identify predictors of symptom return after stopping omalizumab treatment (16-week follow-up). The least absolute shrinkage and selection operator regularization regression model was used to select predictive variables, and relapse probability was represented using heatmap visualizations. Model accuracy was tested using data from the GLACIAL phase III RCT (n = 336; 6 × 4 weekly injections of omalizumab 300 mg or placebo; NCT0126493).
RESULTS: Of 746 variables assessed, 2 were selected by the model as predictors of symptom return: baseline urticaria activity score over 7 days (UAS7) and early area above the curve (AAC; determined by plotting the UAS7 scores across time points). Results suggest that high baseline UAS7 and low UAS7 AAC (slow decrease of symptoms) indicate a higher probability of rapid symptom return than low baseline UAS7 and high UAS7 AAC.
CONCLUSIONS: These results suggest that the probability of rapid symptom return in patients with CSU who discontinue treatment with omalizumab can be estimated based on baseline UAS7 and early treatment response. **(J Allergy Clin Immunol Pract 2018;6:1191-7)**

Key words: *Chronic spontaneous urticaria; LASSO model; Urticaria activity score; Chronic urticaria; Symptom return; Omalizumab; Treatment discontinuation*

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Abbreviations used
AAC- Area above the curve
AUC- Area under the curve
BOCF- Baseline observation carried forward
CSU- Chronic spontaneous urticaria
CU- Chronic urticaria
LASSO- Least absolute shrinkage and selection operator
LOCF- Last observation carried forward
RCT- Randomized controlled trial
UAS- Urticaria activity score
UAS7- Urticaria activity score over 7 days

Chronic spontaneous urticaria (CSU) is a common skin disorder that occurs in 0.5% to 1% of the population at any one time.[1,2] It is characterized by the reoccurrence of itchy hives, angioedema, or both for more than 6 weeks with no external trigger.[3] CSU is associated with significant health-related quality of life impairment and socioeconomic burden.[3-10] Epidemiologic data in chronic urticaria (CU) are scarce, but a Spanish cohort suggests that 52% of patients will experience remission (with or without treatment) within 3 months of symptom onset, and 80% will experience it within 12 months; however, 11% still suffer from CU after 5 years.[1] Therefore, the majority of patients require effective and safe continuous pharmacological treatment for prolonged periods (weeks, months, or years) to control the signs and symptoms of urticaria.

Urticaria guidelines recommend that treatment should aim for complete symptom control.[3] Second-generation H1-antihistamines are recommended as the first-line treatment (approved dose) and second-line treatment (high dose; up to 4 times the approved dose) and achieve control at high doses in 60% of patients.[3,11] Omalizumab is recommended as third-line treatment and ciclosporin is recommended fourth-line.[3] In the absence of adequate biomarkers to assess the complete remission of CSU episodes in patients who have achieved complete symptom control,[12] treatment interruption is required to assess potential remission. Being able to predict which patients will experience rapid symptom return after treatment discontinuation would enable health care providers to optimize treatment schedules and facilitate a more informed discussion with patients on their long-term outcome expectations.

Omalizumab, a humanized anti-IgE antibody, is the only approved third-line treatment for patients with antihistamine-refractory CSU.[3] The efficacy and safety of omalizumab 300 mg in patients with antihistamine-refractory CSU has been reported in 3 pivotal phase III randomized controlled trials (RCTs),[13-15] in which 52.4% to 58.8% of patients achieved well-controlled urticaria (urticaria activity score over 7 days [UAS7] $\leq$ 6) and 33.7% to 40.0% achieved complete symptom control (UAS7 = 0) after 12 weeks of treatment.[16] Furthermore, 2 types of omalizumab responders were described based on these RCTs: early responders, who achieve UAS7 $\leq$ 6 before week 4 (ie, after a single dose), and late responders, who require more than 3 monthly doses to achieve UAS7 $\leq$ 6.[17] The early responder rates for these RCTs were 37% for ASTERIA I, 51% for ASTERIA II, and 36% for GLACIAL.[17] Baseline demographic and disease characteristics were reported not to influence how patients responded to omalizumab treatment.[18]

As expected based on CSU treatment in regular clinical practice, urticaria symptoms returned for the majority of patients after discontinuing omalizumab treatment in the pivotal phase III clinical trials; however, the rate and severity of symptom return varied between patients (Figure E1 in this article's Online Repository at www.jaci-inpractice.org).[17] Until now, it was unknown whether baseline patient characteristics or the speed of response to omalizumab treatment may be useful predictors of rapid symptom return after omalizumab discontinuation. The objective of this *post hoc* analysis was to identify potential predictors of rapid symptom relapse after stopping omalizumab treatment. To achieve this objective we aimed to (1) define a set of early treatment or patient characteristics that stratifies patients into 2 categories: rapid symptom return and slow symptom return; and (2) assess the predictive accuracy of the selected variables.

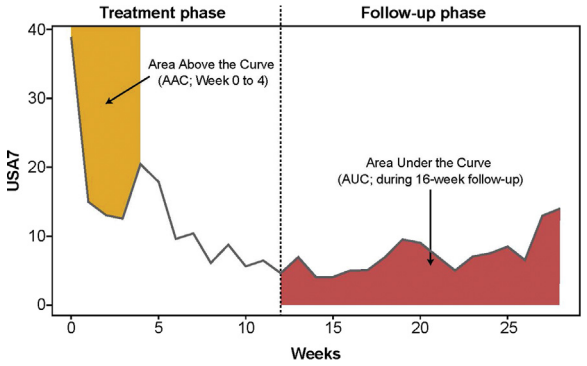

FIGURE 1. Example UAS7 curve during the omalizumab treatment phase (12 weeks) and follow-up phase (16 weeks) in ASTERIA II. UAS7 area above the curve (AAC) and area under the curve (AUC) were used as quantitative measures of the speed of response to treatment (yellow area) and speed and severity of symptom return (outcome variable; red area), respectively. *UAS7*, urticaria activity score over 7 days.

METHODS

Patient population

Patient level data from the 4 treatment arms of 2 RCTs, ASTERIA I[15] (n = 319; 6 injections of omalizumab 75, 150, 300 mg or placebo every 4 weeks; 16-week follow-up) and ASTERIA II[13] (n = 323; 3 injections of omalizumab 75, 150, 300 mg or placebo every 4 weeks; 16-week follow-up), were pooled (training data set) to evaluate potential predictors of rapid symptom relapse after stopping omalizumab treatment. Individual patient-level data from the GLACIAL RCT[14] (n = 335; 6 injections of omalizumab 300 mg or placebo every 4 weeks; 16-week follow-up) were used as a validation set to test the predictive accuracy of the variables selected using ASTERIA I and II.

All patients randomized to treatment were included in this analysis. Inclusion criteria for the studies were similar across the 3 included RCTs[13-15]: age 12 to 75 years (18 to 75 years in Germany), diagnosis more than 6 months before study, moderate-to-severe CSU (UAS7 score $\geq$16 during the 7 days before randomization), and hives and itch for more than 6 (GLACIAL) or 8 weeks (ASTERIA I and II) despite approved doses of H1-antihistamine treatment (ASTERIA I and II) or H2-antihistamines, leukotriene receptor antagonists, or both (GLACIAL). ASTERIA I, ASTERIA II, and GLACIAL study protocols were approved by the institutional review board or ethics committee at each center. They were conducted in accordance with US FDA regulations, the International Conference on Harmonization

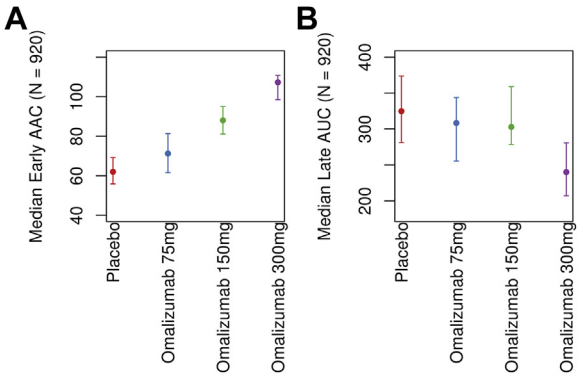

FIGURE 2. Median UAS7 AAC and AUC in each treatment group (ASTERIA I, ASTERIA II, and GLACIAL). (**A**) Median UAS7 AAC (weeks 0-4) and (**B**) median UAS7 AUC (16-week follow-up phase) for each treatment group. Error bars indicate 95% confidence intervals. Missing data are imputed using LOCF. *AAC*, Area above the curve; *AUC*, area under the curve; *LOCF*, last observation carried forward; *UAS7*, urticaria activity score over 7 days.

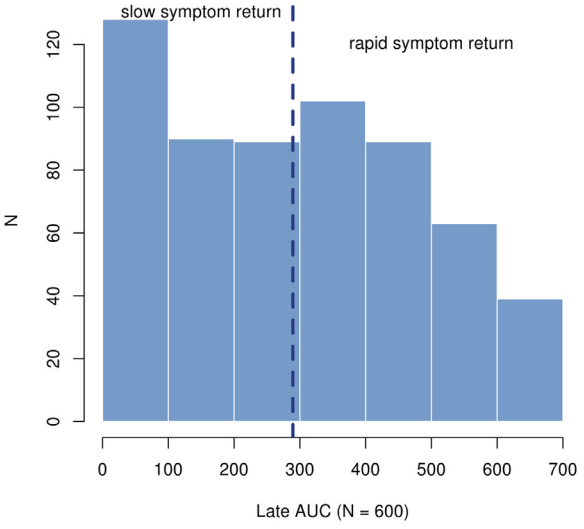

FIGURE 3. Distribution of UAS7 AUC during the follow-up phase (outcome variable; ASTERIA I and ASTERIA II). The dotted line represents the threshold selected using k-means to stratify patients; patients on the left are stratified as having "slow symptom return" and patients on the right of the line have "rapid symptom return." Missing data are imputed using LOCF. *AUC*, Area under the curve; *LOCF*, last observation carried forward; *UAS7*, urticaria activity score over 7 days.

E6 Guideline for Good Clinical Practice, Declaration of Helsinki, and any other applicable country laws.

Urticaria activity assessment

Daily disease activity was assessed using the twice-daily Urticaria Activity Score (UAS),[19] which captures severity of itch and number of hives. UAS values are reported over 7 days (UAS7) and range from 0 (no symptoms) to 42 (highest urticaria activity). In the current analysis, missing values were replaced using the last observation carried forward (LOCF) and baseline observation carried forward (BOCF; results available in this article's Online Repository at www.jaci-inpractice.org) methods.

TABLE I. Nonstandardized regression coefficients for baseline UAS7 and UAS7 AAC (ASTERIA I and ASTERIA II)

		Confidence intervals	
	Coefficient	2.5%	97.5%
Intercept	236.41	142.57	330.25
Baseline UAS7	5.91	3.56	8.26
UAS7 AAC*	−1.55	−1.95	−1.15

AAC, Area above the curve; *LOCF*, last observation carried forward; *UAS7*, urticaria activity score over 7 days.
*UAS7 AAC by week 4. Missing data are imputed using LOCF.

Definition of the predictor and outcome variables

Overall, 746 possible baseline or early treatment (up to 4 weeks) variables were identified and tested as potential predictors of the outcome variable (ie, rapid symptom return): UAS7 area above the curve (AAC) at week 4 (calculated as quantitative measure of the speed of response to omalizumab treatment, up to a maximum UAS7 value of 42 [Figure 1]), angioedema, age, sex, race (7 possible predictors—white, black, Native American/Alaskan Native, Asian, Multiracial, not available, Native Hawaiian, or other Pacific Islander), weight, duration of CSU, itch severity score, omalizumab dose, number of doses, CU index test (Viracor-IBT Laboratories, Lee's Summit, MO; evaluates the ability of CSU sera to activate normal donor basophils inducing histamine release, reflecting an autoimmune phenotype[20]), IgE levels, UAS7 score, pre- and post-baseline medications (Table E1 in this article's Online Repository at www.jaci-inpractice.org).

The UAS7 area under the curve (AUC) during the 16-week follow-up phase was calculated, using the flux package for R (R Foundation for Statistical Computing, Vienna, Austria), as a quantitative measure of the speed and severity of symptom return (outcome variable; Figure 1). Patient level AUC data for placebo were plotted as a histogram, and a one-dimensional k-means was used to obtain 2 separate patient strata: "slow symptom return" and "rapid symptom return."

The LASSO model: variable selection and analysis of predictive accuracy

Least absolute shrinkage and selection operator (LASSO) is a regularized regression algorithm, commonly used to select variables (ie, baseline characteristics, demographics, etc.) that have the strongest effects on the outcome of interest (ie, the late AUC); the algorithm has been previously described by Tibshirani.[21] For the optimization of the LASSO model to the ASTERIA I/II data, the glmnet package for R was used.[22] The one-standard error rule[22] penalization method was used with the LASSO method to reduce the risk of false discoveries. The covariance test, previously described by Lockhart et al,[23] was used to examine the significance of gain in predictive performance as a result of the addition of each predictor. The covariance test statistics were calculated using the covTest package for R.[23]

Data visualization

Median UAS7 AAC and AUC data were plotted individually for the placebo, omalizumab 75, 150, and 300 mg groups (missing data were imputed using LOCF). The predictive models were then trained on pooled data with all doses together, regardless of the response to treatment at week 12, using UAS7 AAC and baseline

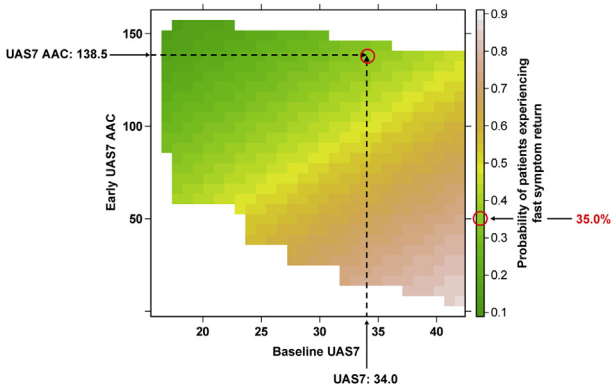

FIGURE 4. Heatmap representing the probability of symptom return with the predictive variables, early UAS7 AAC and baseline UAS7 (pooled data from ASTERIA I and II). Lower UAS7 AAC and higher baseline UAS7 (red/pink) indicates a higher probability of fast symptom return; higher UAS7 AAC and lower baseline UAS7 (green) indicate lower probability. For example, Patient A (UAS7 AAC = 138.5; UAS7 = 34.0) has 35.0% probability of fast symptom return. Missing data were imputed using LOCF. *AAC*, Area above the curve; *LOCF*, last observation carried forward; *UAS7*, urticaria activity score over 7 days.

UAS7 as input variables. Heatmaps were generated using the lattice package for R. Variables that are predictive of symptom return (according to the LASSO regularization regression model) were used to generate heatmaps representing the probability of rapid symptom return. Linear regression analysis was used to estimate the probability of a patient from the GLACIAL study having rapid symptom return based on the selected variables.

RESULTS

ASTERIA I and ASTERIA II patient characteristics

Data from 600 patients (ASTERIA I, n = 301; and ASTERIA II, n = 299) with H1-antihistamine-refractory CSU were pooled together and used to train and optimize the model, whereas data from 320 patients (GLACIAL) was used to test the predictive accuracy of the model. Overall, 57 patients were excluded from this exploratory analysis as they were missing baseline variables (n = 32 missing baseline IgE; n = 17 missing baseline duration of CSU; n = 3 missing CU index; and n = 5 missing >1 variable).

Patients treated with omalizumab 300 mg had the highest median UAS7 AAC (4-week) and lowest median UAS7 AUC (outcome variable; 16-week follow-up) versus the 3 other treatment arms (placebo, omalizumab 75 mg, and omalizumab 150 mg), indicating earlier response to omalizumab treatment and slower symptom return after treatment discontinuation, respectively (Figure 2). The threshold value between "slow symptom return" and "rapid symptom return" strata was found to be at AUC = 289.375 using one-dimensional k-means analysis and calculating the midpoint separating the 2 resulting clusters (Figure 3).

Variables selected using the LASSO model

Using the one-standard error rule, the LASSO model identified 2 parameters that can jointly estimate the probability of rapid symptom return after omalizumab treatment discontinuation: speed of treatment response (UAS7 AAC at week 4) and baseline UAS7 score (Table I). Both UAS7 AAC and baseline UAS7 (week 0-4) were selected irrespective of whether BOCF (Figures E2-E5 in this article's Online Repository at www.jaci-inpractice.org) or LOCF imputation was used. The other variables analyzed were not predictive of symptom return (angioedema, age, sex, weight, duration of CSU, itch severity score, omalizumab dose, number of doses, CU index test IgE levels, or pre- and post-baseline medications).

Probability and predictive accuracy of the model

UAS7 AAC and baseline UAS7, the 2 variables selected by the LASSO model, were used to build a probability heatmap based on ASTERIA I and II (Figure 4). The probability heatmap represents the probability of a patient falling into the "rapid symptom return" category given the values of their "baseline UAS7" and "UAS7 AAC" weeks 0-4. Separate probability heatmaps were generated for the individual omalizumab doses and placebo (Figure E6 in this article's Online Repository at www.jaci-inpractice.org). In general, the pattern revealed that both baseline UAS7 and early UAS7 AAC are predictors for relapse after omalizumab discontinuation; however, for placebo, the early UAS7 AAC is more predictive of the late AUC. As the dose of omalizumab increases, the baseline UAS7 becomes a more important predictor.

The model can be used to selectively make predictions for patients whose outcomes are more likely to be correctly predicted, and the accuracy can vary from 0.628 at week 0 to 0.688 at week 11 if no selectivity is applied, and from 0.857 at week 1 to 0.868 at week 11 when selecting patients for which a correct prediction is more likely, as shown in Table II. When the model is refitted using UAS7 AACs spanning different numbers of weeks (weeks 0-11; Table II), the predictive accuracy of the variables increases as the number of weeks of UAS7 data increases. These tighter prediction intervals indicate more certainty in the predictions (Figure E5 in this article's Online Repository at www.jaci-inpractice.org).

Three GLACIAL patients, with varying UAS7 AAC and baseline UAS7 values, were selected as examples to test the predictive accuracy of the model (Figure 5; patient A, patient B, and patient C). Using the 2 variables selected by the model and the probability heatmap (Figure 4), we can predict that patient A (baseline UAS7, 34.0; UAS7 AAC, 138.5) has a probability of 0.35 (or 35%; see example in Figure 4) of rapid symptom return, whereas patient B (baseline UAS7, 33.5; UAS7 AAC, 75.0) has a probability of 0.57 (or 57%), and patient C (baseline UAS7, 23.5; UAS7 AAC, 154.25) has a probability of 0.19 (or 19%).

DISCUSSION

There is a great need for markers to monitor treatment response in patients with CSU. A recent review examining potential clinical and laboratory biomarkers of CSU[24] identified 3 publications investigating predictive biomarkers of omalizumab effectiveness. These publications reported that both basophil histamine release assay and autologous serum skin test were correlated with the time to symptom relief,[25] whereas lack of basophil CD203c-upregulating activity in the serum[26] and D-dimer plasma levels[27] were biomarkers of clinical response. In contrast to these studies, we focused on identifying predictive markers of time to relapse rather than clinical response.

TABLE II. Predictive accuracy of baseline UAS7 and UAS7 area under the curve at predicting the outcome variable in the test population (GLACIAL)

Week of prediction	Accuracy*	AUROC	RMS†	Patients with ≥80% probability of a correct prediction‡	Accuracy in patients with ≥80% probability§	AUROC in patients with ≥80% probability
0	0.628	0.707	186.6	0.0%	NA	NA
1	0.653	0.719	181.7	6.6%	0.857	0.877
2	0.675	0.725	180.3	7.5%	0.875	0.843
3	0.669	0.728	179.2	9.7%	0.871	0.865
4	0.675	0.733	177.7	11.6%	0.838	0.882
5	0.684	0.740	175.6	13.4%	0.837	0.882
6	0.678	0.743	174.0	15.0%	0.854	0.869
7	0.675	0.745	172.7	17.8%	0.842	0.872
8	0.684	0.745	171.7	18.4%	0.847	0.891
9	0.688	0.749	170.6	20.0%	0.859	0.890
10	0.688	0.752	169.5	22.2%	0.887	0.894
11	0.688	0.755	168.5	23.8%	0.868	0.895

AUC, Area under the curve; *AUROC*, area under the receiver operating characteristic curve; *RMS*, root mean square; *UAS7*, urticaria activity score over 7 days.
*Number of correct predictions divided by the total number of predictions.
†RMS error on the outcome variable (AUC during the follow-up phase).
‡Percentage of patients in the GLACIAL study for which there is ≥80% probability that the model will return a correct prediction (ie, these patients are predicted to be located away from the threshold of rapid or slow symptom return according to the ASTERIA I/II data).
§Accuracy observed in the subset of the patients from GLACIAL with ≥80% probability of a correct prediction.

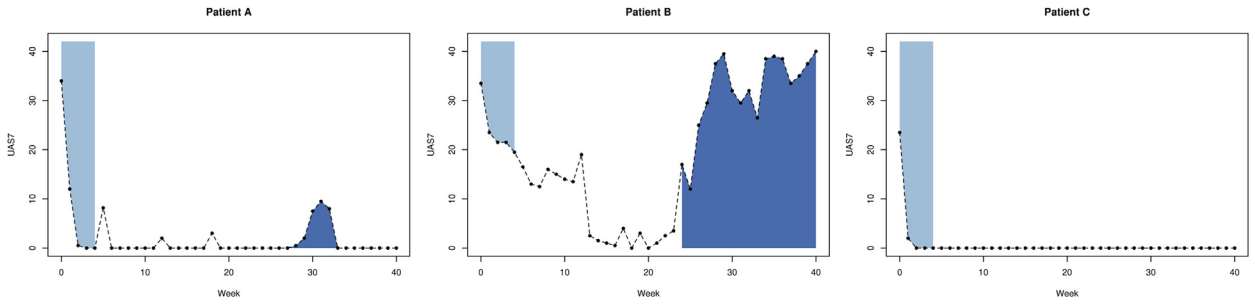

FIGURE 5. Examples of individual UAS7 profiles of 3 patients from the GLACIAL study. Patients were treated with omalizumab 300 mg for 24 weeks. Patients A and C responded quickly and remained in remission after treatment discontinuation (Patient A: AAC = 138.5, AUC = 27.5; Patient C: AAC = 154.25, AUC = 0); Patient B responded slower and symptoms returned soon after treatment discontinuation (AAC = 75.0, AUC = 514.0). *AAC*, Area above the curve; *AUC*, area under the curve; *UAS7*, urticaria activity score over 7 days.

Previously, it was shown that patient-level data from ASTERIA I/II and GLACIAL revealed differences in individual patient response to omalizumab treatment and to the speed of urticaria symptom return after omalizumab treatment discontinuation.[17] In this exploratory analysis, we investigated whether baseline patient characteristics or speed of response to omalizumab treatment could predict patients who are at risk of rapid symptom return after omalizumab treatment discontinuation.

After subcutaneous administration, peak serum concentrations are reached after 7 to 8 days and the mean terminal half-life of omalizumab is 19 to 22 days[28]; after multiple doses, accumulation occurs and steady-state serum concentrations are reached by 14 to 28 days.[29] In our analysis, the LASSO model selected 2 variables that are predictive of symptom return: baseline UAS7 and UAS7 AAC (from week 0 to week 4). According to our analysis, patients with lower baseline UAS7 and rapid treatment response (ie, high UAS7 AAC) have a lower probability of rapid symptom return and patients with high baseline UAS7 and slower initial response to treatment (ie, low UAS7 AAC) had a higher probability of rapid return after treatment discontinuation. Furthermore, the speed of symptom return was independent of other baseline characteristics assessed, including duration of CSU, angioedema, previous treatments received, or patient demographics. Additional statistical analysis demonstrated the predictive accuracy of the model significantly improves if the UAS7 AAC is calculated at >7 weeks. However, in the real-world treatment of CSU, the 4-week time point is likely to be more practical and, therefore, developing a prediction tool may be more useful if it was based on 4-week data. Clinically, these results are important as they suggest that physicians could predict those patients with CSU who are at high risk of rapid symptom return after treatment discontinuation. This information could be used to counsel patients, after the first 4 weeks of treatment, on the duration of treatment or to inform them about the risk of symptom return after omalizumab treatment discontinuation.

Our results also support the use of 300 mg as the initial dose, because a faster and prolonged effect was achieved compared with patients who received lower doses (Figure 2). These data agree with previous publications, whereby, the proportion of patients who achieved a sustained response through the observational period was higher with the 300 mg dose versus lower doses.[17] Although similar initial control was achieved with the 150 mg dose, an earlier and more severe relapse was seen thereafter.

The fact that higher baseline UAS7 is associated with faster and more severe symptom return could be explained by the mechanism by which omalizumab inhibits basophil[30-32] and mast cell[33] activation.[34,35] Omalizumab sequesters free or FcεRI receptor-bound IgE, thus inhibiting both mast cell and basophil activation.[30,33] Omalizumab reduces surface expression of FcεRI in CSU; however, the reduction in skin mast cells is slower than that in basophils (10 weeks vs 1 week).[35-39]

It could also be explained in conditions where the roles of mast cells and basophils are reduced after the involvement of endothelial cells and the recruitment of inflammatory cells to the lesioned skin. In this situation, the effect of omalizumab would be reduced, thus making it more difficult to provide symptom relief.[40,41] Another explanation might be due to variations in the amounts of bound IgE or free FcεRI receptors on mast cell and/or basophils, or differences in autoantibodies or IgE isotypes targeted by omalizumab. Furthermore, although we did not identify any parameter that could differentiate the groups, these different patterns of response to treatment may not only be related to different patients, but may be due to different stages of the disease among episodes within the same patient. These findings can only be confirmed by gathering data from a large sample of patients who are retreated on symptom recurrence and assessing their pattern of response.

This study was limited by the use of data from a restrictive clinical trial (ie, GLACIAL) to test the model instead of real-world clinical data; however, we do not have sufficient real-world data to test the model at present, but plan to do so in a future analysis. Here, we offer an innovative approach that could be further developed for clinical practice to predict relapse after omalizumab treatment discontinuation. This approach could facilitate personalized medicine in the absence of validated biomarkers for CSU.

CONCLUSIONS

The results of this analysis suggest that it is possible to accurately predict patients who are at risk of rapid symptom return after omalizumab treatment discontinuation. These results open the possibility of developing a simple digital tool to estimate the probability of rapid symptom return to improve the management of patients with CSU in the clinic.

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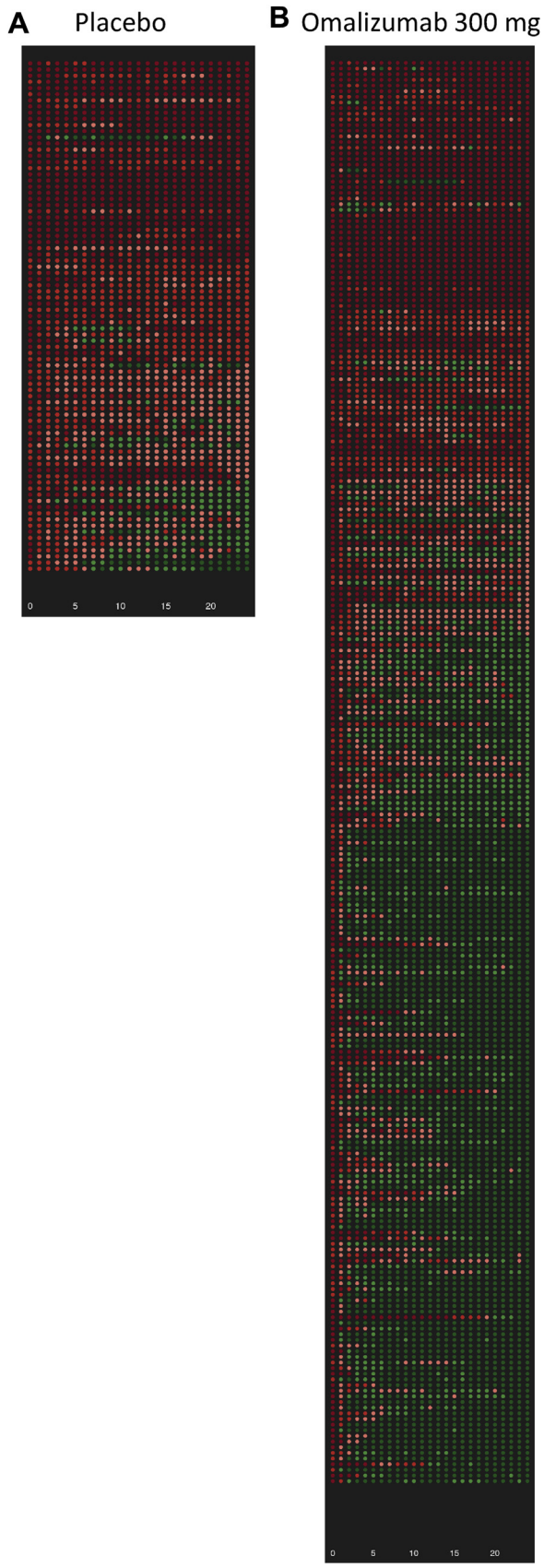

FIGURE E1. (**A**) Placebo and (**B**) omalizumab 300 mg patient heatmap images from the GLACIAL study.

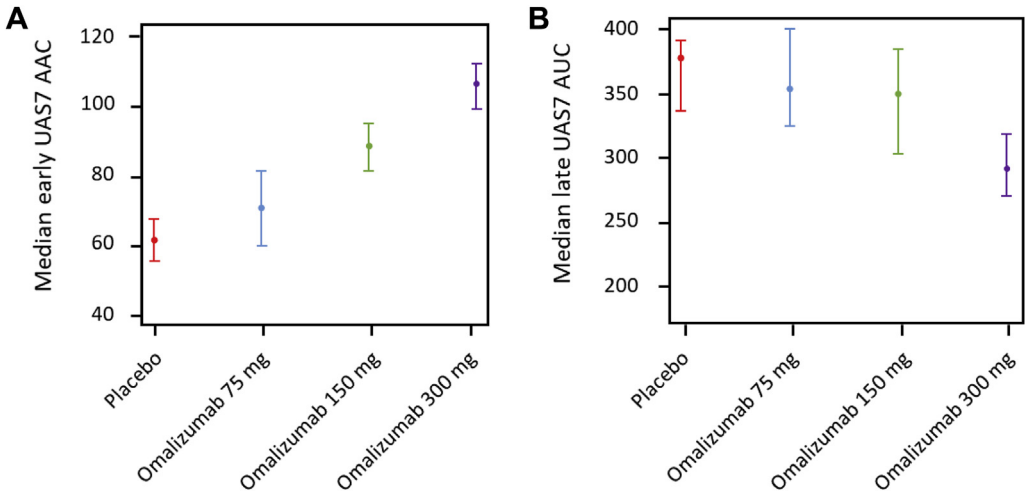

FIGURE E2. Median UAS7 AAC and AUC in each treatment group. (**A**) Median UAS7 AAC (weeks 0-4) and (**B**) median UAS7 AUC (16-week follow-up phase) for each treatment group. Patients in the omalizumab 300 mg group had the fastest response to treatment (highest early AAC score) and slowest symptom return (smallest AUC during the follow-up phase). Error bars indicate 95% confidence intervals. Missing data are imputed using BOCF. *AAC*, Area above the curve; *AUC*, area under the curve; *BOCF*, baseline observation carried forward; *UAS7*, urticaria activity score over 7 days.

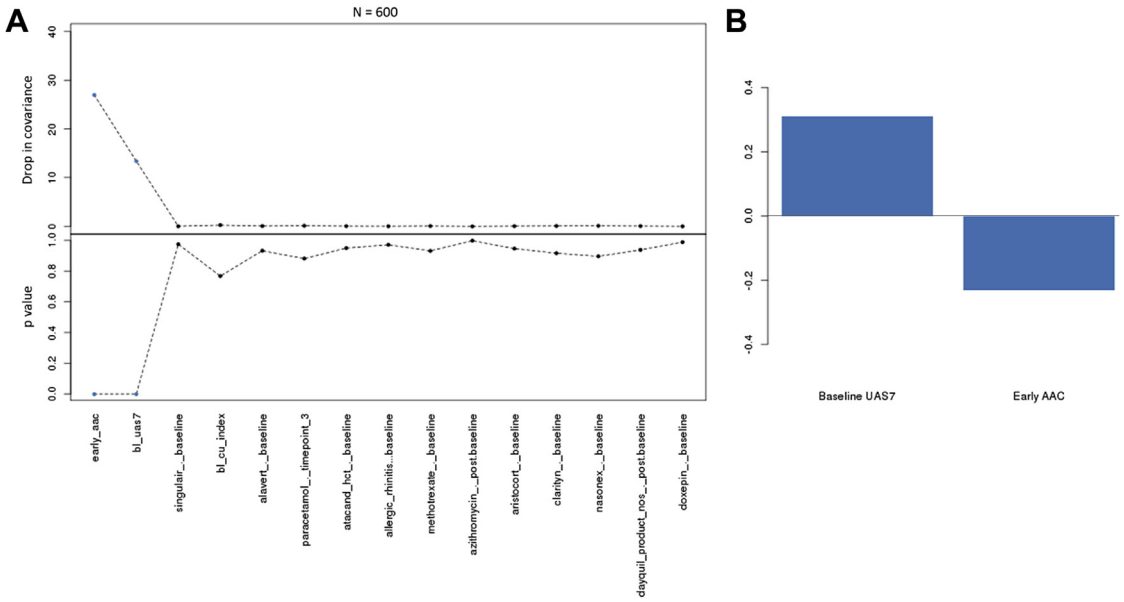

FIGURE E3. Baseline UAS7 scores and early response to omalizumab treatment (early AAC) were selected as predictive variables using the LASSO method with (**A**) minimum error rule ("aggressive" method) or (**B**) one standard error rule ("conservative" method). Missing data are imputed using BOCF. *AAC*, Area above the curve; *bl*, baseline; *CSU*, chronic spontaneous urticaria; *CU*, chronic urticaria; *BOCF*, baseline observation carried forward; *LASSO*, least absolute shrinkage and selection operator; *UAS7*, urticaria activity score over 7 days.

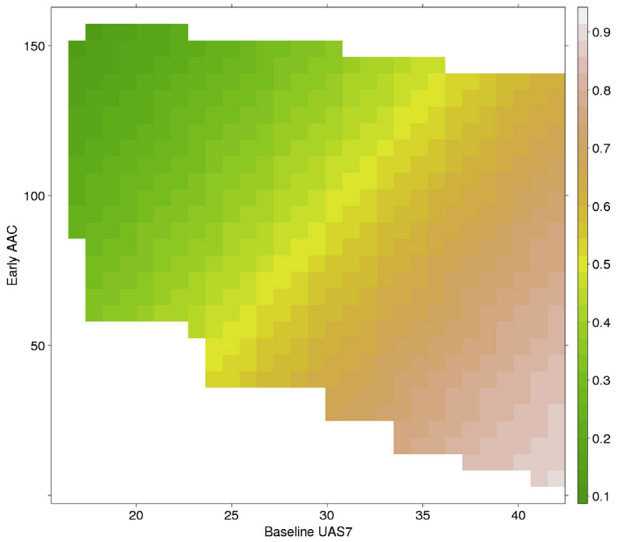

FIGURE E4. Heatmap representing the probability of fast symptom return with the predictive variables, early UAS7 AAC and baseline UAS7. Lower UAS7 AAC and higher baseline UAS7 (red/pink) indicates a higher probability of fast symptom return; higher UAS7 AAC and lower baseline UAS7 (green) indicate lower probability. Missing data were imputed using BOCF. *AAC*, Area above the curve; *BOCF*, baseline observation carried forward; *UAS7*, urticaria activity score over 7 days.

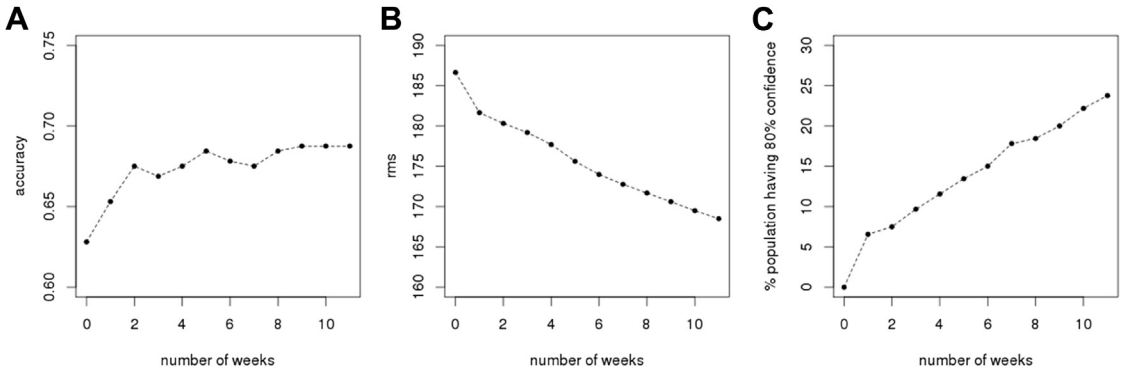

FIGURE E5. Adaptive prediction (BOCF imputation). (**A**) Improvement in the accuracy, (**B**) reduction in error, and (**C**) increase in the percentage population having 80% confidence is evident as increasing weeks of UAS7 data are used to fit the model. *BOCF*, Baseline observation carried forward; *rms*, root mean square; *UAS7*, urticaria activity score over 7 days.

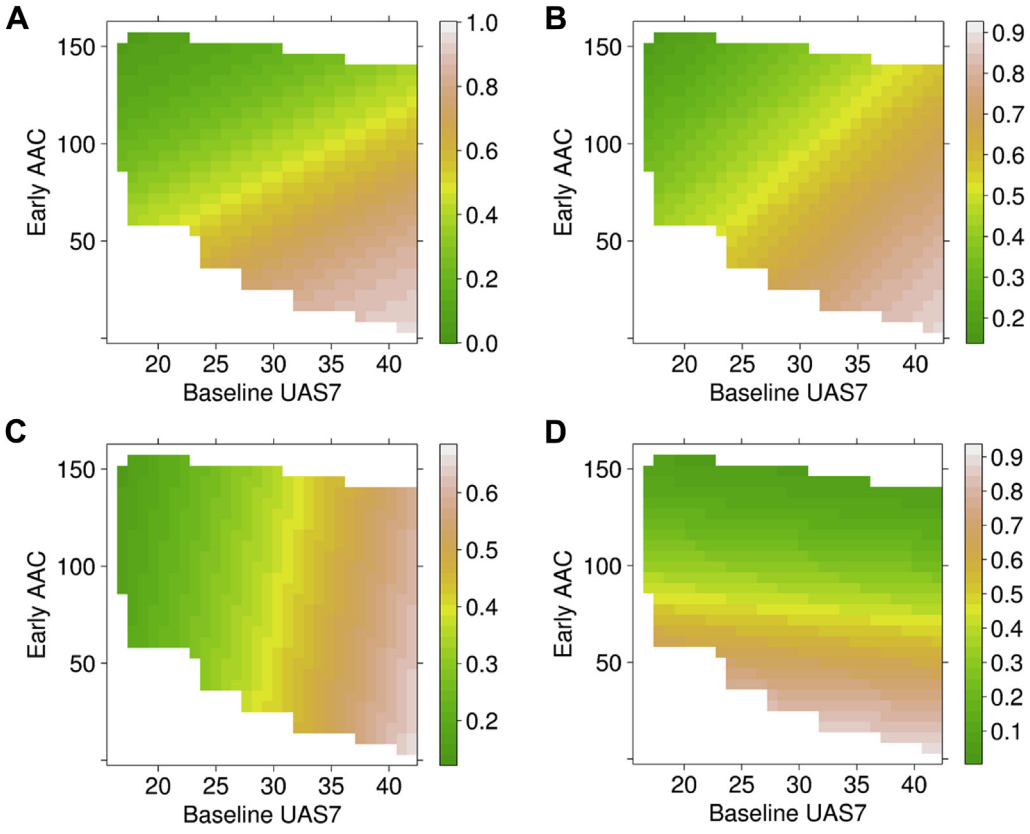

FIGURE E6. Omalizumab (**A**) 75 mg, (**B**) 150 mg, (**C**) 300 mg, and (**D**) placebo heatmaps representing the probability of symptom return with the predictive variables, early UAS7 AAC and baseline UAS7 (pooled data from ASTERIA I and II). *AAC*, Area above the curve; *UAS7*, urticaria activity score over 7 days.

TABLE E1. Summary of potential predictors of the outcome variable

Category	No. of variables	Description of variables
Baseline	20	Age; Race (white, black, American Indian/Alaska, Asian, not available, multiracial, Hawaiian/Other Pacific); Weight; Angioedema; CSU duration; Itch score; IgE; H1-antihistamines; H2-antihistamines; LTRA, UAS7; CU index; Female; Number of doses
Medication	713	Composed of all concomitant medications recorded at 5 time points (ie, baseline and weeks 1, 2, 3, 4)
Diagnosis at baseline	9	Allergic rhinitis; Angioedema; Asthma; Coronary artery disease; Diabetes mellitus; Hypercholesterolemia; Hypertension; Myocardial infarction; Serum sickness
Diagnosis postbaseline	1	Allergic rhinitis
area	2	Early; Late
Treatment arm	1	Omalizumab

CSU, Chronic spontaneous urticaria; *CU*, chronic urticaria; *LTRA*, leukotreine receptor antagonist; *UAS7*, urticaria activity score over 7 days.