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JAS and KLK developed the model. JAS wrote the manuscript. JAS, RWI, SAW, and AJ performed the experiments and analyzed the data.

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CONFLICTS OF INTEREST

All authors declare that they have no relevant conflicts of interest.

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How to discontinue omalizumab in chronic spontaneous urticaria?

To the Editor,

The clinical efficacy and safety of omalizumab in chronic spontaneous urticaria (CSU) has been demonstrated in several clinical trials and real-life studies.^{1,2} The EAACI/GA²LEN/EDF/WAO urticaria guideline recommends omalizumab as an add-on third-line treatment option for patients with CSU.³ As of now, there is no consensus on when and how to discontinue omalizumab treatment in CSU patients who show complete response.

Chronic spontaneous urticaria, in most patients, is a self-limited disease. The duration of CSU is usually longer than 1 year, and

the 5-year remission rate is 34-86%.^{4,5} Because of this, omalizumab discontinuation should be tried periodically in patients with completely controlled disease in order to understand whether the disease is in remission or not.⁶ In many patients, this is done by simply stopping omalizumab treatment after 6 months or 1 year. Alternatively, discontinuation of omalizumab has been suggested to be done by prolonging treatment intervals.⁶⁻⁹ As of now, there is very little information on how well this works in real-life clinical practice.

Here, we assessed the response of CSU patients to treatment discontinuation by interval prolongation. We included 19 of 86 patients with CSU who received omalizumab treatment at the Erciyes University Allergy Clinic between 2017 and 2018. These 19 patients: (a) had been treated with omalizumab (300 mg/4 wk)

Abbreviations: AH, anti-histamines; CSU, chronic spontaneous urticaria; EAACI/GA²LEN/EDF/WAO, European Academy of Allergology and Clinical Immunology, Global Allergy and Asthma European Network, European Dermatology Forum, World Allergy Organization; IgE, immunoglobulin E; IQR, interquartile range; UCT, urticaria control test.

for at least 6 months and (b) had controlled disease as defined by urticaria control test (UCT) scores of ≥ 12 and minimal intake of anti-histamines (≤ 2 times/wk). We prolonged the treatment interval by one week and then assessed disease activity by UCT and anti-histamine (AH) intake. In patients who continued to show controlled disease, we continued to increase the treatment intervals by one week per application. If their CSU remained controlled after prolongation of treatment intervals to 8 or 9 weeks, we discontinued omalizumab treatment and monitored patients for relapse for 3 months. In patients who showed uncontrolled disease after interval prolongation, we shortened the interval by 1 week per application until the disease was under control again. We assessed the rate of patients who successfully discontinued omalizumab treatment by interval prolongation and compared it to that of patients who did not. Statistical analyses were done with SPSS (SPSS, Inc, Chicago, IL, v17). Continuous parameters were expressed as median (25-75 interquartile range; IQR) unless stated otherwise. Chi-square and Mann-Whitney U tests were used for comparing variables.

Of the 19 patients who tried, nine successfully discontinued omalizumab treatment by interval prolongation, and they did not show relapse of their CSU for at least 3 months after their last omalizumab treatment. Ten patients were unable to prolong treatment intervals without losing control of their CSU. They were not discontinued, and received their next omalizumab application using the last interval duration (during which their CSU was controlled) (Table 1). There was no difference between the two groups with regard to

age, gender, urticaria phenotypes, or the duration of omalizumab treatment (Table 2).

While it is clear that the need for further applications of omalizumab in complete responder CSU patients should be tested by stopping the treatment, it is unclear how best to do this.^{1,2} In the pivotal clinical trials on omalizumab in CSU, treatment intervals were always 4 weeks and omalizumab was discontinued abruptly [10-12*]. In our study, 58% of patients showed reoccurrence of urticaria symptoms when interval prolongation was tried, whereas in 42% of patients, the disease remained completely controlled for at least 3 months. Previous studies, where omalizumab was stopped abruptly, reported relapse rates ranging from 17 to 67% [13-16*]. To test whether relapse rates are different in patients who stop omalizumab treatment by interval prolongation as compared to those who stop treatment abruptly, controlled trials are needed.

The EAACI/GA²LEN/EDF/WAO guideline recommends that treatment of CSU should aim at complete symptom control "treat the disease until it is gone" using as much pharmacotherapy as needed and as little as possible.³ Periodic efforts to prolong the treatment interval of omalizumab application and to attempt discontinuation, in complete responders, meet this recommendation. Patients who can tolerate interval prolonging get less pharmacotherapy and may be ready for discontinuation. If a patient cannot tolerate interval prolonging, he/she will also not tolerate abrupt discontinuation.

The concept of individualizing omalizumab treatment intervals in CSU patients and to use this approach to discontinue treatment is

TABLE 1 Showing the patients that attempts for prolonging the treatment interval resulted in omalizumab discontinuation and the patients who showed uncontrolled disease after interval prolongation.

#	Treatment intervals before the discontinuation of omalizumab (weeks)	Outcome	#	Treatment interval (weeks)	Outcome	Final status
1	○ 4 ○ 4 ● 5 ● 6 ● 8 ● 9	Remission	1	○ 4 ○ 4 ● 4 ● 5 ● 6 ● 5 ● 5	Relapsed	Well controlled
2	○ 4 ○ 4 ● 4 ● 4 ● 4 ● 5 ● 7 ● 8	Remission	2	○ 4 ○ 4 ● 4 ● 4 ● 4 ● 5 ● 6 ● 7 ● 6 ● 6	Relapsed	Well controlled
3	○ 4 ○ 4 ● 5 ● 5 ● 6 ● 7 ● 8 ● 9	Remission	3	○ 4 ○ 4 ● 4 ● 4 ● 5 ● 6 ● 6 ● 5	Relapsed	Well controlled
4	○ 4 ○ 4 ● 4 ● 5 ● 5 ● 6 ● 7 ● 8 ● 9	Remission	4	○ 4 ○ 4 ● 4 ● 4 ● 4 ● 5 ● 6 ● 5 ● 4 ● 4 ● 4 ● 5 ● 6 ● 5	Relapsed	Uncontrolled, interval shortened
5	○ 4 ○ 4 ● 5 ● 6 ● 6 ● 7 ● 8	Remission	5	○ 4 ○ 4 ● 4 ● 5 ● 6 ● 5 ● 4 ● 4 ● 4 ● 5	Relapsed	Well controlled
6	○ 4 ○ 4 ● 4 ● 4 ● 4 ● 5 ● 5 ● 6 ● 7 ● 8	Remission*	6	○ 4 ○ 4 ● 4 ● 5 ● 4 ● 5	Relapsed	Well controlled
7	○ 4 ○ 4 ● 4 ● 5 ● 6 ● 7 ● 8	Remission	7	○ 4 ○ 4 ● 4 ● 4 ● 4 ● 5 ● 4	Relapsed	Uncontrolled, interval shortened
8	○ 4 ○ 4 ● 4 ● 5 ● 5 ● 6 ● 8	Remission	8	○ 4 ○ 4 ● 4 ● 4 ● 5 ● 6 ● 5 ● 5 ● 5 ● 4 ● 4	Relapsed	Well controlled
9	○ 4 ○ 4 ● 5 ● 6 ● 7 ● 8 ● 9	Remission	9	○ 4 ○ 4 ● 4 ● 4 ● 4 ● 4 ● 4 ● 4 ● 5 ● 4 ● 4 ● 4 ● 5 ● 6	Relapsed	Well controlled
			10	○ 4 ○ 4 ● 4 ● 4 ● 4 ● 4 ● 4 ● 4 ● 4 ● 5 ● 6 ● 7 ● 8 ● 9 ● 8	Relapsed	Uncontrolled, interval shortened

UCT: urticaria control test, AH: anti-histamines

○ Build-up doses (300 mg/4 weeks, independent from the symptom scores).

● Omalizumab application visit with UCT < 12 and/or high AH need.

● Omalizumab application visit with UCT ≥ 12 and low AH need.

| Omalizumab discontinuation visit. (After 8 or 9 weeks from the last application visit, all patients had UCT ≥ 12 , did not need high AH. Omalizumab was discontinued and not applied at that visit).

* Symptoms showed up 15 weeks after discontinuation but were tolerable only with AH. Omalizumab was not reinitiated.

TABLE 2 Baseline characteristics of CSU patients

	Interval prolongation and discontinuation were possible (n = 9)	Interval prolongation and discontinuation were not possible (n = 10)	P-value
Female gender; n (%)	8 (89)	8 (80)	1
Age; y (range)	40 (28-51)	33.5 (23-40)	0.24
CSU phenotypes; n (%)			
Wheals, no angioedema	5 (56)	6 (60)	1
Angioedema, no wheals	-	-	
Wheals and angioedema	4 (44)	4 (40)	
Duration of CSU before omalizumab treatment; y (range)	7 (3-10)	3 (2-4)	0.034
Duration of omalizumab therapy (from first to last application); wk (range)	33 (28-41)	47.5 (29-55)	0.1

not new. Previous expert opinions also advised prolonging the treatment interval instead of an abrupt stop.⁶⁻⁹ Uysal et al proposed the first algorithm with individualized dose intervals [17*]. They showed that prolonging the treatment interval up to 8 weeks was efficient, well tolerated, and cost-effective. Another study showed that prolonging the omalizumab dosing intervals did not lower its maintenance effectiveness, and authors advised prolonging the intervals up to 12 weeks [18*].

Discontinuation of omalizumab treatment by prolongation may also have benefits for those patients who do not tolerate this. With abrupt discontinuation, patients who show relapse are at risk of suffering extended periods of increasing CSU disease activity before omalizumab treatment is reinitiated. In contrast, with interval prolongation, it is possible to schedule and evaluate patients after periods which are only 1 week longer than the last interval, and if CSU recurs, the last largest time interval needed to achieve full control can be maintained.

What is the ideal interval duration before discontinuation is attempted? As seen in Table 1, most of the patients in our study developed loss of control after extending their treatment interval to 5 or 6 weeks. Therefore, we propose that the minimum interval length before treatment discontinuation should be 8 weeks. The limitations of our study are the low number of patients, its retrospective design, and single-center nature. Further larger studies comparing the effects of interval prolonging and abrupt stop on disease control, quality of life, and economic burden are needed.

In conclusion, in CSU patients with well-controlled disease and low AH intake, discontinuation of omalizumab treatment by prolonging the treatment interval may reduce relapse rates and limit the duration of relapse before re-initiation of treatment.

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*Additional references 10 – 18 are provided as online supplement.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Association between asthma, rhinitis, and conjunctivitis multimorbidities with molecular IgE sensitization in adults

To the Editor,

Allergic multimorbidity is well established for rhinitis and asthma. However, the role of conjunctivitis in the allergic multimorbidity is not clear. A large number of pollen-allergic patients suffer from both rhinitis and conjunctivitis. Rhinitis is often ascribed to rhinoconjunctivitis and it is thought that ocular symptoms occur during high allergenic exposure. In fact, ocular symptoms are among the most bothering symptoms of allergic rhinoconjunctivitis.^{1,2} However, the links between nasal and ocular symptoms are unclear.

In a novel approach examining daily symptoms with mobile technology (MASK: mobile airways sentinel network), we found previously unrecognized patterns of multimorbidity. Days with eye and nasal symptoms were associated with impaired work productivity by comparison to days with nasal symptoms alone, suggesting the importance of conjunctivitis in allergic multimorbidities.³ In accordance with this hypothesis, a study in a random sample of school aged children showed that rhinoconjunctivitis was associated with multiple allergic sensitization as compared to rhinitis.⁴ However, in the MeDALL study the cluster analysis identified eye symptoms in the multimorbid phenotype but was not considered independently.⁵ There is a need to confirm whether conjunctivitis should be considered separately in allergic multimorbidity.

A cross-sectional study (EGEA, France and BAMSE, Sweden) investigated allergen sensitization using an enhanced micro-array technique and found that patients with multimorbid rhinitis and asthma had significantly more IgE sensitizations to allergen molecules than those with rhinitis alone or asthma alone.⁶ However, the impact of conjunctivitis was not tested as the data of the MASK study were not available when analyses were performed.³

The objective of the current study is to assess whether allergic sensitization profiles differed between allergic multimorbidity patterns including asthma, rhinitis, and conjunctivitis starting from the recently published EGEA study considering only asthma and rhinitis.⁶ We hypothesized that more allergic multimorbidity is associated with increased IgE recognition frequencies and that considering

conjunctivitis in addition to rhinitis and asthma in allergic multimorbidities changes the IgE recognition frequencies.

The analysis is based on IgE reactivity to 64 clinically relevant respiratory allergenic molecules determined with the MeDALL-chip in samples from the French EGEA cohort (n = 840, mean [SD] age = 40.7 ± 17.1 years) (Table S1). For the analysis of the number of allergen-specific IgE reactivities, results are given by medians and 25-75 percentiles. The age- and sex-adjusted associations between the number of IgE reactivities (≥ 0.3 ISU) and the different asthma-rhinitis-conjunctivitis phenotypes were assessed using a negative binomial model, which estimates the incidence rate ratio (IRR), that is the ratio of the mean number of positive allergen-specific IgE (and its 95% confidence interval) between phenotypes. These methods are published elsewhere^{6,7} and presented in the Data S1. Some differences exist between this study and the recently published study⁶: (a) A more sensitive definition of rhinitis was used by considering either the report of allergic rhinitis or hay fever or a positive answer to the question on rhinitis symptoms: "Have you ever had a problem with sneezing, or a runny or blocked nose when you did not have a cold or the flu?"; (b) we further consider allergic conjunctivitis defined using a positive answer to the question: "Have you ever had allergic conjunctivitis?"

Among the 840 adult participants tested, 463 had asthma, 629 had rhinitis, and 347 had conjunctivitis. There were 143, 187, 278, and 232 participants with 0, 1, 2, and 3 allergic diseases, respectively. The median number of IgE-reactive allergens varied from 0 to 1, 2 to 5, and increased up to 8 in groups with 1, 2, and 3 allergic morbidities, respectively (Table 1). The number and levels of IgE reactivities were statistically significantly increased in each allergic multimorbidity phenotype as compared to the controls (R-C-A-), except for conjunctivitis only (Table 1). The rhinoconjunctivitis multimorbidity was associated with an increased number of IgE reactivities as compared to subjects with rhinitis only ($P < 0.001$) or conjunctivitis only ($P < 0.001$). This pattern was observed whatever the asthma status, and the rhinoconjunctivitis multimorbidity was the only phenotype associated with an increased number of IgE

Additional references for online supplementary

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