Maoz-Segal et al. World Allergy Organization Journal (2024) 17:100905
http://doi.org/10.1016/j.waojou.2024.100905

WORLD ALLERGY ORGANIZATION JOURNAL

Open Access

Omalizumab withdrawal outcomes in chronic spontaneous urticaria are linked with baseline IgE and eosinophil levels

Ramit Maoz-Segal, MD[a]*, Guy Levenberg, B.MED.SC[b], Tanya Levy, MD[a,1], Soad Haj-Yahia, MD[a], Ronen Shavit, MD[a], Diti Machnes-Maayan, MD[a,b], Yulia Lifshitz -Tunitsky, MD[a,b], Stanely Niznik, MD[a], Irena Offengenden, MD[a], Mona Iancovich-Kidon, MD[a,b] and Nancy Agmon-Levin, MD[a,b]

ABSTRACT

Background: Chronic Spontaneous Urticaria (CSU) is an immune-mediated skin disease that may require prolonged treatments. Currently, there are no recommendations for treatment discontinuation once CSU symptoms are controlled, particularly among patients primarily diagnosed with severe CSU.

Objective: In this real-life study we aimed to describe our experience of omalizumab (Oma) treatment withdrawal in CSU and define biomarkers related to these outcomes.

Methods: CSU patients followed at our allergy clinic from January 2016 to December 2022 were included. Response to Oma therapy, and Oma-withdrawal outcomes among patients who reached complete remission for >6 months were analyzed.

Results: During the study period 192/335(%) CSU patients were categorized as severe-CSU and entitled to receive Oma according to our country's regulations. Of them, 131/192(68%) were considered "Oma-responders", and 95/131(72.5%) patients underwent gradual treatment withdrawal. Successful Oma-withdrawal was documented in 47/95(49.5%) whereas 48/95(50.5%) patients experienced flare and were defined as unsuccessful OMA-withdrawal. The first was associated with shorter disease duration 7.1 $\pm$ 7.4 years vs. 10.7 $\pm$ 9.4 ($P = 0.042$), lower baseline-IgE 81.6 $\pm$ 84.1IU/ml vs. 324.7 $\pm$ 555.9 ($P = 0.005$), and lower baseline-eosinophils count 131.4 $\pm$ 110.5 vs. 195.6 $\pm$ 98.4 ($P = 0.043$) in comparison to failure of Oma-withdrawal group.

Conclusion: OMA may be successfully withdrawn in up to 50% of severe CSU patients following complete remission of disease symptoms, utilizing a gradual withdrawal protocol. Oma-withdrawal failure was linked with longer duration of disease as well as high IgE and eosinophil counts prior to initiation of Oma therapy. These parameters may enable the design of a treatment withdrawal algorithm.

Keywords: Omalizumab, Chronic spontaneous urticaria, IgE, Eosinophil, Treatment withdrawal

[a]The Clinical Immunology, Angioedema and Allergy Unit, Center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer, Ramat Gan 52621, Israel
*Corresponding author. The Clinical Immunology, Angioedema and Allergy Unit, Center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer, Ramat Gan 52621, Israel. E-mail: Ramit.maozsegal@sheba.health.gov.il
[1] This study was conducted as part of the student arrow project at the Sheba medical center.

Full list of author information is available at the end of the article

http://doi.org/10.1016/j.waojou.2024.100905
Received 25 December 2023; Received in revised from 1 April 2024; Accepted 9 April 2024
Online publication date xxx

INTRODUCTION

Chronic spontaneous urticaria (CSU) is an autoimmune/immune-mediated disease characterized by the presence of pruritic wheals, angioedema, or both for at least 6 weeks,[1] and is associated with comorbidities as well as a substantial impact on patient's quality of life.[2-4] The prevalence of CSU is estimated as 1% in most western countries, CSU is more prevalent in young women.[4,5]

The known underlying mechanisms have been described namely "autoallergy" and "type II autoimmunity". The former is characterized by the presence of specific IgE to autoantigens (eg, Thyro-peroxidase [TPO], IL-24, dsDNA, and others) while the latter is defined by the presence of IgG autoantibodies directed at membrane-bound IgE or FcεRI high-affinity receptors.[6,7] Both mechanisms elicit mast cell degranulation through direct activation of mast cells. A strong link exists between CSU and other autoimmune conditions as well as the presence of different autoantibodies.[8]

In the last decade, several treatment guidelines for CSU have been published.[1,9,10] These guidelines are based on a stepwise approach beginning with a standard dose of H1-antihistamine, followed by up-dosing of 2nd generation anti-histamine up to four-fold with or without leukotriene inhibitors by which remission is achieved in about 50% of patients.[11] Thereafter add on treatment with Oma, a humanized monoclonal anti-IgE antibody, improves CSU control in up to 85% of patients.[12-14] For the remaining 15% of patients with resistant disease higher doses of Oma and/or other immunosuppressant (eg, cyclosporine and others as azathioprine, methotrexate etc) may be used to achieve remission.[15] Having said that, it is important to point that since the publication of international guidelines 2018,[1] leukotriene inhibitors and immunosuppressants other than cyclosporin A are not recommended, at least for routine use.

The long term safety of Oma has been established and this therapy may be continued for years.[12,13] On the other hand, CSU is considered a self-limiting condition and treatment withdrawal may be targeted once complete remission is achieved.[16] In general, withdrawal protocol can be gradual *via* dose tapering down or prolonging treatment intervals while assessing patient's response, or by abrupt discontinuation. The latter approach may pose a greater risk of severe relapse in comparison to the gradual approach.[17,18] However, currently there are no recommendations for Oma treatment withdrawal, and such protocols are backed by little evidence to guide clinical decision-making. In particular, data on how to choose candidates for withdrawal, clinical parameters, or biomarkers to predict protocol success are lacking. Moreover, treatment withdrawal requires close monitoring and may be cumbersome. Lastly, physician and patients may be reluctant to stop Oma, particularly if disease was primarily severe and/or prolonged and concerns of relapse are substantial. Thus, further data and particularly clinical and biomarkers to predict outcomes of Oma withdrawal are needed. In this real-life study, we present a gradual protocol for Oma withdrawal in a cohort of relatively severe CSU patients. We further analyze clinical and laboratory parameters that may predict withdrawal outcomes.

METHODS

Study design and population

In this single-center observational real-life study, we retrospectively evaluated CSU patients treated with Oma who were considered for treatment discontinuation following disease remission. Patients were followed at our tertiary allergy center from January 2016 to December 2022. Demographic characteristics, disease features (eg, duration, co-presence of inducible urticaria, angioedema), comorbidities, concomitant type 2 inflammation (eg, atopic dermatitis, allergic rhinitis and asthma), laboratory parameters prior to initiation of Oma (eg, CRP; autoantibodies, baseline-IgE levels etc.), treatment used and treatment outcomes were collected and analyzed. Blood analysis performed prior to initiation of Oma were analyzed. CSU was considered to be "associated with autoimmunity" (AiCSU) if concomitant overt autoimmune disease and/or high titers of autoantibodies were documented. The data of demographics and disease characteristics was collected for all patients treated with Oma.

This study received approval by the institutional ethics committee and fulfilled the ethical guidelines of the Declaration of Helsinki (Edinburgh 2000).

Treatment protocol

Our treatment protocol is based on the Israeli recommendations for CSU treatment[10] and the Israeli ministry of health regulation. Briefly, in order to receive therapy with Oma all patients received high dose (ie, 3-4-fold) of anti-histamines for at least 6 and at least 2 courses of oral glucocorticoids and at least 4 weeks of montelukast within the 6 months prior to initiation of Oma. Thereafter, Oma 300 mg/month was initiated as add on therapy. If remission was not achieved within 6 months of Oma use, we aimed at up-dosing of Oma if possible (as this required special approval of the patient's Ministry of Health instructions). Alternatively, an immunosuppressive agent was added if partial improvement was noted with Oma or replace Oma if no response was noted (eg, cyclosporine 1–3 mg/kg/day, azathioprine 1–2.5 mg/kg/day, methotrexate up to 20 mg/week). Doses were tailored individually and were raised gradually according to disease severity and drug tolerability.

Once CSU control was achieved for 12 weeks, gradual tapering down of medications other than Oma was commenced (eg, anti-histamines and anti-leukotrienes). At any point during tapering of treatments if flare occurred therapy was re-augmented to achieve stable control of disease. Patients were considered for Oma withdrawal if CSU control was maintained while treated with regular doses of anti-histamine (ie,1 tab/day) and Oma (ie, 300 mg/month) for at least 12 weeks.

The withdrawal protocol

Patients eligible for Oma withdrawal were instructed to gradually taper Oma therapy while continuing treatment with a single tablet of anti-histamine daily, according to our protocol (Fig. 2). "*Oma withdrawal failure*" was defined if disease flare was observed requiring re-augmentation of Oma dose or re-treatment with Oma during 6 months following Oma discontinuation. For some patients several attempts of withdrawal were performed.

"*Oma withdrawal success*" was defined if no flare was observed for 6 months following complete abrogation of Oma therapy. During the protocol, patients were followed every 4–8 weeks and 12–24 weeks following Oma discontinuation.

Statistics

The data was collected in tabular format in Microsoft Excel. Statistical analysis was performed using Microsoft Excel 2023 and IBM SPSS Statistics, Version 28.0. Armonk, NY: IBM Corp. Continuous variables were described as mean SD, and categorical variables as percentages. To evaluate categorical variables, Chi-square or Fisher's exact test were used accordingly. To compare continuous data, student's *t*-test or Mann-Whitney's *U* test were used accordingly. For all tests, a p-value of less than 0.05 was considered statistically significant.

RESULTS

In the study period from January 2016 to December 2022, 355 patients with chronic spontaneous urticaria (CSU) were treated in the allergy clinic. Of them, 199/355 (56%) were defined as severe CSU and treated with Oma according to the Israeli guidelines, their characteristics delineated in Table 1. Data regarding demographics and disease characteristics are available for 199 patients (including the 7 patients that were lost of follow up before evaluated their compatibility for withdrawal; Table 1).

Data regarding response to Oma was available for 192 patients (Fig. 1). In our cohort, 131/192 (68%) were defined as "OMA responders", while 61/192 (32%) were considered "OMA non-responders" most of which 45/61 (73%) required additional (on top of Oma) immunosuppressive agents mostly Cyclosporine. To note, 10/16 patients refused treatment with immunosuppressive agents. No differences between Oma-responders and Oma-non-responders were noted, except for the requirement of additional treatments (Table 2).

Among "OMA-responders" 95/131 (72.5%) patients met our criteria for Oma withdrawal namely no symptoms while treated with regular doses of antihistamines (1 tab/day) and Oma (300 mg/month) for 12 weeks. The other 36/131 (27.5%)

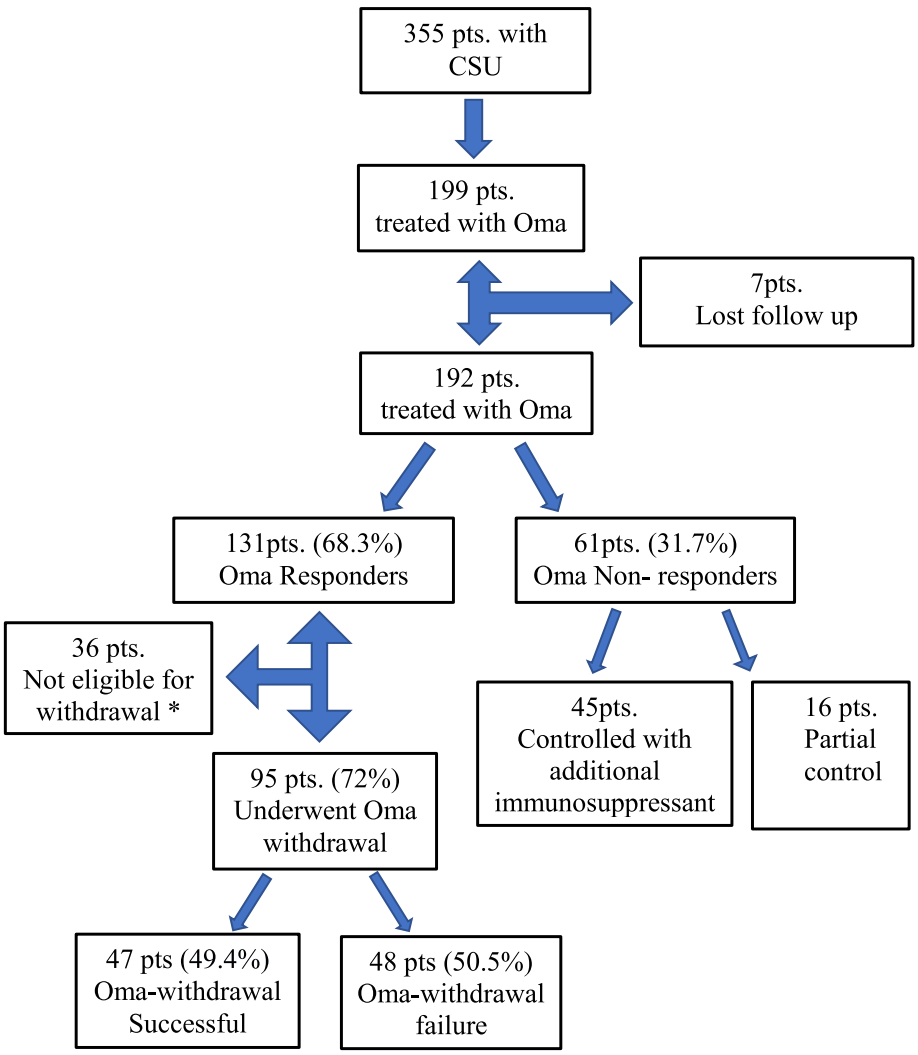
Age (years)	49.4 ± 18
Gender – female (%)	72.9%
Duration of disease (years)	7.7 ± 8
Concomitant Angioedema (%)	70.3%
Recurrent disease (%)	29.6%
Concomitant inducible urticaria	28.1%
Concomitant Autoimmune disease	33.1%
History of Atopy[a]	25.1%
Laboratory values	
Elevated CRP (%)	25.6%
TSH – abnormal (<0.3 > 5 mU/L)	9.04%
Lymphocytes × 10^9/L (mean ± SD)	2.3 ± 1
Neutrophils × 10^9/L (mean ± SD)	4.9 ± 2
Eosinophils × 10^9/L (mean ± SD)	0.2 ± 0.2
Platelets × 10^9/L (mean ± SD)	265.6 ± 76.1
MPV fL (mean ± SD)	10.4 ± 1.7
Immunologic laboratory values	
anti TPO ab's	22.1%
anti TG ab's	5.5%
Rheumatoid factor (%)	4.5%
ANA (%)	21.1%
IgE IU/ml (mean ± SD) (normal≤90IU/ml)	241.4 ± 430.2
IgG IU/ml (mean ± SD)	1094.2 ± 278.5
IgM IU/ml (mean ± SD)	121.3 ± 63
IgA IU/ml (mean ± SD)	201.3 ± 120.4
Low complement C3 or C4 (%)	2.5%
Medical treatment	
Glucorticoids cumulative dose (mg)[b]	1315.1 ± 1500.7
Oma mean dose (mg/month)	369.5 ± 119.3
Oma Duration (months)	31.1 ± 24.8
Immunosuppressive treatment (%)	17.6%
Cyclosporine	27(13.5%)
Methotrexate	5 (2.5%)
Azathioprine	3 (1.5%)

Table 1. Demographics and disease characteristics of 199 CSU patients treated with Oma. *MPO, mean platelet volume, Anti-TPO ab's-anti-thyroid peroxidase antibodies, Anti-TG ab's-anti-thyroid peroxidase antibodies, ANA – anti nuclear antibodies, IgE-immunoglobulin E, Oma-omalizumab, NR-non-relevant.* [a]*History of atopy-related diseases as allergic rhinitis, asthma, atopic dermatitis, food allergy or eosinophilic esophagitis etc.* [b]*Glucorticoids cumulative dose was calculated after exclusion of one patient who took prednisone 20 mg a day for 20 years. The value before the exclusion of this patient was 4562.6 ± 20,330.8 mg*

"Oma-responders" were not candidates for withdrawal as they didn't fulfill the criteria for instance they could not reduce concomitant medications due to disease flares.

Oma withdrawal according to our gradual protocol (Fig. 2) was successful in 47/95 (49.5%) *versus* 48/95 (50.5%) patients in which Oma withdrawal failed. The latter suffered disease flare during Oma tapering down all of which regain disease control once therapy was resumed. Notably, 11/48 (23%) patients required only low dose Oma 150 mg/month to reclaim complete remission, the others 37/48 (77%) needed re-treatment with regular dose 300 mg/month Oma to achieve symptoms control. Numerically multiple withdrawal attempts were documented in 28.2% and 42.5% of "Oma-withdrawal successful" and "Oma withdrawal failure" groups respectively ($p = 0.15$).

Several markers were found to be related to Oma withdrawal outcomes. Successful withdrawal was linked with a relatively shorter duration of disease 7.1(±7.4) *vs*.1 0.7(±9.4) years = P) 0.042), lower baseline IgE level 81.6(±84.1) vs.



**Not eligible for withdrawal (i.e. controlled while treatment with > Omalizumab 300 mg/month and/or high dose anti-Histamine;*

Oma-Omalizumab, pts.=patients.

Fig. 1 Study design.

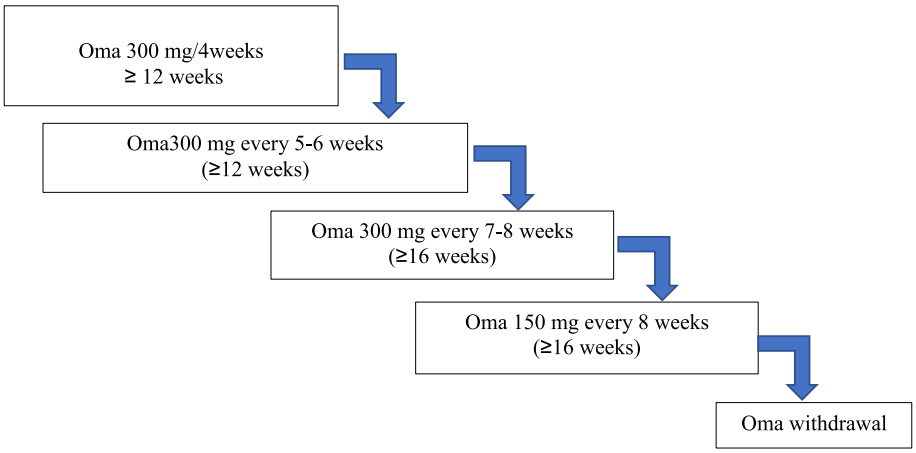


Fig. 2 Omalizmab gradual withdrawal protocol *. *Oma- omalizumab; *The withdrawal protocol was initiated only once complete control of disease was achieved while treated with regular doses of omalizumab (300 mg/month) and anti-histamine (1 tab/day). Treatment with anti-histamine was maintained at least until Oma withdrawal was completed.*

324.7(±555.9) IU/ml (P = 0.005) and lower baseline number of blood eosinophils 131.4(±110.5) vs. 195.6(±98.4) (P = 0.043). Oma withdrawal failure was almost doubled if baseline IgE was >90 IU/ml and/or blood eosinophils >0.15 × 10^9/L (Table 3).

DISCUSSION

Omalizumab (Oma) changed the treatment paradigm of CSU in the last decade and enabled complete control of disease in the majority of patients. However, on the one hand CSU is considered a self-limiting disease while on the other Oma therapy is costly. As for many novel biologics long-term safety data on Oma are still relatively limited, although data regarding safety among asthma patients for more than 15 years with no serious AE is available. Hence, Oma withdrawal can and should be aimed for patients that experience complete remission.

In our cohort, 68% of patients were categorized as "OMA responders". This is consistent with former reports such as the *Asteria* and other pivotal studies..[13,14,16,19] Notably, in our study, Oma was used only for severe and resistant disease, following failure of daily treatment with four-fold antihistamines and anti-leukotrienes and at least 2 courses of systemic corticosteroids in the six-month prior to Oma initiation as this was the indication in Israel at that time. In contrast, in other studies patients were included following failure of only regular dose of H1 antihistamines. The good response to Oma in our cohort may be partially attributed to the stringent monthly monitoring of our patients.

It appears that our cohort consisted patients with more severe disease, as the concomitant angioedema was higher than expected (70%) and few patients with low complement level indicates a concomitant autoimmunity. *One might claim that it might indicate the diagnosis of urticarial vasculitis, but it was excluded* mostly clinically (a classic appearance of the urticarial rash) and a good response to treatment according to the guidelines.

Complete remission of CSU is a major criterion for initiating Oma withdrawal as defined herein and in other studies such as *OPTIMA*.[16] To mention, categorization of patients treated with only 1 antihistamine while receiving Oma and with clinical remission permitted ∼50% of controlled patients for stepping down Oma. It may be plausible to consider the possibility that if the most recommended management (maintaining 4 tab/day anti-H1) more patients could have achieved Oma withdrawal.

In our "real-life" study we used the same clinical definition of complete remission (ie, no symptoms while treated with regular doses of Oma and anti-histamine) but in regard to timing we used a more rigorous determination of 12 weeks opposed to 8 weeks in the *OPTIMA* study, as our patients had a more severe and prolonged disease. Nevertheless, 72.5% of our Oma-responders were categorized as

variable	Oma responders n = 131	Oma non-responders n = 61	P value
Age (years)	48.5 ± 18.3	50.9 ± 17.4	0.42
Gender – female (%)	73.2%	73.7%	0.54
Duration of disease (years)	7.9 ± 7.8	7.6 ± 9	0.36
Concomitant Angioedema (%)	71.5%	67.2%	0.68
Recurrent disease (%)	30.7%	27.8%	0.18
Concomitant inducible urticaria	32.3%	22.9%	0.18
Concomitant Autoimmunity	35.3%	27.8%	0.3
History of Atopy[a]	23%	31.1%	0.23
Laboratory values			
Elevated CRP (%)	24.7%	30.7%	0.467
TSH – abnormal (<0.3 > 5)	8.7%	9.3%	0.91
Lymphocytes × 109/L (mean ± SD)	2.3 ± 1	2.2 ± 0.8	0.81
Neutrophils × 109/L (mean ± SD)	4.7 ± 1.8	5.6 ± 2.3	0.13
Eosinophils × 109/L (mean ± SD)	0.1 ± 0.1	0.3 ± 0.4	0.97
Platelets × 109/L (mean ± SD)	262.7 ± 80.4	278.7 ± 62.8	0.43
MPV fL (mean ± SD)	10.5 ± 1.6	9.9 ± 2.2	0.29
Immunologic laboratory values			
anti TPO ab's	23.3%	17.1%	0.45
anti TG ab's	5.1%	7.1%	0.78
Rheumatoid factor (%)	4.9%	4.7%	0.97
ANA (%)	18%	27.2%	0.2
Baseline IgE IU/ml (mean ± SD)	241 ± 444.1	246.5 ± 438.8	0.42
IgG IU/ml (mean ± SD)	1122.8 ± 260.2	1048.6 ± 314.1	0.24
IgM IU/ml (mean ± SD)	115.4 ± 57	127 ± 72.6	0.87
IgA IU/ml (mean ± SD)	200.2 ± 88.2	206 ± 172.5	0.25
Low C3 or C4 (%)	1.1%	5.2%	0.16
Medical treatment			
Glucocorticoids cumulative dose (mg)[a]	953.4 ± 1170.8	1767.5 ± 1744.9	**0.006**
Oma mean highest dose (mg/month)	334.6 ± 86.6	452.5 ± 143.3	**<0.001**
Oma Duration (months)	33.1 ± 25.4	26.7 ± 23.1	**0.072**

(continued)

variable	Oma responders n = 131	Oma non-responders n = 61	P value
Immunosuppressive treatment Cyclosporine Methotrexate Azathioprine	0	73.8% (35) 77.1% (27) 14.2% (5) 8% (3)	NR

Table 2. (Continued) Comparison between Oma responders and Oma non-responders (total 192 patients). *History of atopy-a former background of atopy related diseases as allergic rhinitis, asthma, atopic dermatitis, food allergy or eosinophilic esophagitis.MPO, mean platelets volume, Anti TPO ab's-anti-thyroid peroxidase antibodies, Anti TG ab's-anti-thyroid peroxidase antibodies, ANA- anti nuclear antibodies, IgE-immunoglobulin E, NR-non-relevant. Oma-omalizumab.* [a]*Glucorticoids cumulative dose was calculated after the exclusion of one patient who took prednisone 20 mg a day for 20 years. The values before the exclusion of this patient were 7010.3 ± 27654 (for Oma responders) and 1767.5 ± 1744.9 (for Oma non-responders), respectively*

complete responders and underwent treatment withdrawal using a gradual protocol.

To notice, in this study, patients were kept with 1x/d of anti-H1 while on Oma and only if control not lost Oma was withdrawn. The main reasons for that was safety (the relatively lake of data regarding long -term treatment with Oma) and cost effectiveness.

In our study, Oma withdrawal was successful in approximately 50% of our patients, like the *Optima study*[16] in which withdrawal was initiated abruptly. Although outcomes were similar for both the abrupt and gradual protocols our cohort included patients with severe and resistant disease most of which suffered from CSU for many years and in a real-life scenario using a gradual protocol was well accepted by patients and physician and seems to be a practical approach. Such gradual withdrawal approach was supported by other studies,[17,18,20,21] as well as studies that implied using a gradually extended dosing intervals protocols which might provide a long duration of remission in CSU.[22,23]

Furthermore, similarly to the *Optima study,* in our cohort, CSU relapse during the withdrawal protocol was easily controlled by re-augmentation or re-initiation of Oma therapy in all patients.

This study present plausible markers to predict Oma withdrawal outcomes. In our hands, a relatively shorter duration of disease, probably with less evidence of recurrence, as well as baseline low IgE and eosinophils levels were associated with success of Oma withdrawal. In other words, baseline IgE of >90 IU/ml and/or blood eosinophils $>0.15 \times 10^9$/L were linked with almost doubling the risk for withdrawal failure. To mention, most recently, different biomarkers were proposed to predict a successful lengthened interval, as higher median pre-omalizumab D-dimer and C-reactive protein values than those with a standard dose.[24]

Notably, a link between IgE and response to Oma was noted previously as low baseline IgE level was linked with a slower response to Oma,[25,26] which support the notion that low IgE may be a marker of a subgroup of CSU patient. This subgroup differs as on the one hand the mechanisms of initial response to Oma required a longer time to achieve response while on the other hand once remission is achieved, as seen in this study, their chances for successful withdrawal is higher.

Eosinophils are increased in CSU and were demonstrated in lesions as well as non-lesioned skin biopsies, and somewhat like low IgE, also low blood eosinophils counts were found to be linked to poor or slower response to Oma in former studies.[27] Interestingly, like IgE levels, low number of eosinophils was associated with successful Oma withdrawal. In this regard, our withdrawal protocol is prolonged and it may be suggested that once successful withdrawal may be predicted shortening of the protocol can be aimed.

Our study has several limitations derived from its retrospective, single-centered and observational nature. Laboratory-specific parameters of autoimmunity (such as IgG-anti-IgE receptor antibodies) were not measured due to unavailability and limits our ability to diagnose autoimmune CSU. However, we believe that our meticulous follow-up and examination by a specialist using the same treatment algorithm for all patients enabled us to present

Variable	Successful Oma-Withdrawal n = 47	Failure of Oma -Withdrawal n = 48.	P value
Age (years)	48.3 ± 19.8	51.2 ± 16.8	0.44
Gender – female (%)	76.6%	68.7%	0.39
Duration of disease (years)	**7 ± 7.4**	**10.6 ± 9.3**	**0.04**
Concomitant Angioedema (%)	78.2%	68.7%	0.29
Recurrent disease (%)	**21.7%**	**37.5%**	**0.09**
Concomitant inducible urticaria	23.9%	33.3%	0.31
Concomitant Autoimmune disease	39.1%	29.1%	0.3
History of Atopy[a]	13%	10.4%	0.69
Laboratory values			
Elevated CRP (%)	28.1%	18.9%	0.36
TSH – abnormal (<0.3 > 5)	8.1%	7.5%	0.92
Lymphocytes × 10^9/L (mean ± SD)	2.1 ± 1	2.2 ± 7.2	0.73
Neutrophils × 10^9/L (mean ± SD)	4.7 ± 1.4	4.4 ± 1.3	0.6
Baseline Eosinophils > 0.15 × 10^9/L	**28.6%**	**68%**	**0.008**
Platelets × 10^9/L (mean ± SD)	269.2 ± 102.3	263.4 ± 57	0.82
MPV fL (mean ± SD)	10.2 ± 2.1	10.3 ± 1.4	0.87
Immunologic laboratory values			
anti TPO ab's	34.7%	16.6%	0.12
anti TG ab's	0%	20%	0.08
Rheumatoid factor (%)	4.7%	5.5%	0.91
ANA (%)	13.8%	16.6%	0.74
Baseline IgE IU/ml (mean ± SD)	**81.6 ± 84**	**324.6 ± 555.9**	**0.005**
IgE > 90 IU/ml	**33.3%**	**68.2%**	**0.028**
IgG IU/ml (mean ± SD)	998.9 ± 283.5	1147.11 ± 192	0.07
IgM IU/ml (mean ± SD)	98.52 ± 31.67	119.8 ± 56.3	0.17
IgA IU/ml (mean ± SD)	202.7 ± 96.9	225.1 ± 83.3	0.44
Medical treatment (before withdrawal)			
Glucorticoids cumulative dose (mg)	684 ± 495.1	1472.7 ± 1285.8	0.11
Oma highest dose (mg/4weeks)	326.0 ± 96.4	340.6 ± 80.32	0.332

Table 3. Successful vs. failure of Oma withdrawal. *MPV, mean platelets volume, Anti-TPO ab's-anti-thyroid peroxidase antibodies, Anti-TG ab's-anti-thyroid peroxidase antibodies, ANA- anti nuclear antibodies, IgE-immunoglobulin E, Oma -Omalizumab, NR-non-relevant. [a]History of atopy-a former background of atopy-related diseases (such as allergic rhinitis, asthma, atopic dermatitis, food allergy or eosinophilic esophagitis)*

valuable real-life data that can be reproducible and enable physicians to better tailor CSU therapy.

CONCLUSIONS

Gradual protocol for Oma withdrawal is safe and feasible in a real-life scenario also for severe resistant CSU once completer remission is achieved. Utilizing such protocol approximately 50% of patients could stop therapy while the other 50% regain remission once therapy was resumed. To the best of our knowledge, this is the first study to report markers that predict success of Oma withdrawal protocol, namely shorter duration of disease, low baseline IgE levels (<90 IU/ml) and low baseline eosinophils count ($<0.15 \times 10^9$/L). The latter may enable physician to better tailor Oma therapy discontinuation.

Abbreviations
Oma, omalizumab; CSU, chronic spontaneous urticaria

Funding
None.

Availability of data and materials
All data and materials are available and will be presented by demand.

Authors' contributions
The authors confirm contribution to the paper as follows:
Study conception and design: Ramit Maoz Segal, Nancy Agmon Levin.
Data collection: Ronen Shavit, Diti Machnes-Maayan, Irena Offengenden, Tanya Levy.
Analysis and interpretation of results: Guy Levenberg, Stanely Niznik
Draft manuscript preparation: Ramit Maoz-Segal, Mona Iancovich-Kidon, Soad Haj-Yahia. All authors reviewed the results and approved the final version of the manuscript.

Ethics approval
This study was approved by the hospital ethics committee, Sheba Medical Center.

Consent for publication
All authors gave their consent for publication.

Financial and non-financial competing interests
None.

Declaration of competing interest
None.

Author details
[a]The Clinical Immunology, Angioedema and Allergy Unit, Center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer, Ramat Gan 52621, Israel. [b]Faculty of Medicine, Tel Aviv University, Tel Aviv 6329302, Israel.

REFERENCES

1. Zuberbier T, Abdul Latiff AH, Abuzakouk M, et al. The International EAACI/GA^{2}LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. *Allergy*. 2022;77(3):734–766. https://doi.org/10.1111/all.15090.
2. Shalom G, Magen E, Dreiher J, et al. Chronic urticaria and atopic disorders: a cross-sectional study of 11 271 patients. *Br J Dermatol*. 2017;177(4):e96–e97. https://doi.org/10.1111/bjd.15347.
3. Shalom G, Linder D, Comaneshter D, et al. Healthcare services utilization and drug use in patients with chronic urticaria. *J Invest Dermatol*. 2015;135(12):3187–3189. https://doi.org/10.1038/jid.2015.330.
4. Zuberbier T, Balke M, Worm M, Edenharter G, Maurer M. Epidemiology of urticaria: a representative cross-sectional population survey. *Clin Exp Dermatol*. 2010;35(8):869–873. https://doi.org/10.1111/j.1365-2230.2010.03840.x.
5. Wertenteil S, Strunk A, Garg A. Prevalence estimates for chronic urticaria in the United States: a sex- and age-adjusted population analysis. *J Am Acad Dermatol*. 2019;81(1):152–156. https://doi.org/10.1016/j.jaad.2019.02.064.
6. Schmetzer O, Lakin E, Topal FA, et al. IL-24 is a common and specific autoantigen of IgE in patients with chronic spontaneous urticaria. *J Allergy Clin Immunol*. 2018;142(3):876–882. https://doi.org/10.1016/j.jaci.2017.10.035.
7. Kolkhir P, Church MK, Weller K, Metz M, Schmetzer O, Maurer M. Autoimmune chronic spontaneous urticaria: what we know and what we do not know. *J Allergy Clin Immunol*. 2017;139(6):1772–1781.e1. https://doi.org/10.1016/j.jaci.2016.08.050.
8. Confino-Cohen R, Chodick G, Shalev V, Leshno M, Kimhi O, Goldberg A. Chronic urticaria and autoimmunity: associations found in a large population study. *J Allergy Clin Immunol*. 2012;129(5):1307–1313. https://doi.org/10.1016/j.jaci.2012.01.043.
9. Bernstein JA, Lang DM, Khan DA, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. *J Allergy Clin Immunol*. 2014;133(5):1270–1277. https://doi.org/10.1016/j.jaci.2014.02.036.
10. Levin Agmon N, Kessel A, Maoz Segal R, et al. [Recommendation for evaluation and treatment of chronic urticaria – the Israeli association for allergy and clinical immunology]. *Harefuah*. 2017;156(6):385–389.
11. Maurer M, Church MK, Gonçalo M, Sussman G, Sánchez-Borges M. Management and treatment of chronic urticaria

(CU). *J Eur Acad Dermatol Venereol JEADV*. 2015;29(Suppl 3): 16–32. https://doi.org/10.1111/jdv.13198.

12. Zhao ZT, Ji CM, Yu WJ, et al. Omalizumab for the treatment of chronic spontaneous urticaria: a meta-analysis of randomized clinical trials. *J Allergy Clin Immunol*. 2016;137(6):1742–1750. e4. https://doi.org/10.1016/j.jaci.2015.12.1342.
13. Maurer M, Rosén K, Hsieh HJ, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med*. 2013;368(10):924–935. https://doi.org/10.1056/NEJMoa1215372.
14. Vadasz Z, Tal Y, Rotem M, et al. Omalizumab for severe chronic spontaneous urticaria: real-life experiences of 280 patients. *J Allergy Clin Immunol Pract*. 2017;5(6):1743–1745. https://doi.org/10.1016/j.jaip.2017.08.035.
15. Maoz-Segal R, Levy T, Haj-Yahia S, Offengenden I, Iancovich-Kidon M, Agmon-Levin N. Combination therapy with omalizumab and an immune-suppressive agent for resistant chronic spontaneous rrticaria – a real-life experience. *World Allergy Organ J*. 2020;13(8), 100448. https://doi.org/10.1016/j.waojou.2020.100448.
16. Sussman G, Hébert J, Gulliver W, et al. Omalizumab re-treatment and step-up in patients with chronic spontaneous urticaria: OPTIMA trial. *J Allergy Clin Immunol Pract*. 2020;8(7): 2372–2378.e5. https://doi.org/10.1016/j.jaip.2020.03.022.
17. Türk M, Maurer M, Yılmaz İ. How to discontinue omalizumab in chronic spontaneous urticaria? *Allergy*. 2019;74(4):821–824. https://doi.org/10.1111/all.13675.
18. Alizadeh Aghdam M, Pieterse RH, Kentie PA, Rijken F, Knulst AC, Röckmann H. Effective omalizumab interval prolongation in the treatment of chronic urticaria. *J Allergy Clin Immunol Pract*. 2020;8(10):3667–3668.e1. https://doi.org/10.1016/j.jaip.2020.06.056.
19. Saini SS, Bindslev-Jensen C, Maurer M, et al. Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on H1 antihistamines: a randomized, placebo-controlled study. *J Invest Dermatol*. 2015;135(1):67–75. https://doi.org/10.1038/jid.2014.306.
20. Terhorst-Molawi D, Fox L, Siebenhaar F, Metz M, Maurer M. Stepping down treatment in chronic spontaneous urticaria: what we know and what we don't know. *Am J Clin Dermatol*. 2023. https://doi.org/10.1007/s40257-023-00761-z. Published online February 22.
21. Niemeyer-van der Kolk T, van Maaren MS, van Doorn MBA. Personalized omalizumab treatment improves clinical benefit in patients with chronic spontaneous urticaria. *J Allergy Clin Immunol*. 2018;142(6):1992–1994. https://doi.org/10.1016/j.jaci.2018.07.032.
22. Salman A, Aktas M, Apti Sengun O. Remission of chronic spontaneous urticaria following omalizumab with gradually extended dosing intervals: real-life data. *Australas J Dermatol*. 2021;62(3):398–402. https://doi.org/10.1111/ajd.13656.
23. Tontini C, Marinangeli L, Cognigni M, Bilò MB, Antonicelli L. Omalizumab in chronic spontaneous urticaria: patient-tailored tapering or planned discontinuation? *Ann Allergy Asthma Immunol Off Publ Am Coll Allergy Asthma Immunol*. 2015;115(2): 147–148. https://doi.org/10.1016/j.anai.2015.05.005.
24. Brás R, Costa C, Limão R, Caldeira LE, Paulino M, Pedro E. Omalizumab in chronic spontaneous urticaria (CSU): real-life experience in dose/interval adjustments and treatment discontinuation. *J Allergy Clin Immunol Pract*. 2023;11(8): 2392–2402. https://doi.org/10.1016/j.jaip.2023.01.022.
25. Pedersen NH, Sørensen JA, Ghazanfar MN, Zhang DG, Vestergaard C, Thomsen SF. Biomarkers for monitoring treatment response of omalizumab in patients with chronic urticaria. *Int J Mol Sci*. 2023;24(14), 11328. https://doi.org/10.3390/ijms241411328.
26. Ertas R, Ozyurt K, Atasoy M, Hawro T, Maurer M. The clinical response to omalizumab in chronic spontaneous urticaria patients is linked to and predicted by IgE levels and their change. *Allergy*. 2018;73(3):705–712. https://doi.org/10.1111/all.13345.
27. Kolkhir P, Church MK, Altrichter S, et al. Eosinopenia, in chronic spontaneous urticaria, is associated with high disease activity, autoimmunity, and poor response to treatment. *J Allergy Clin Immunol Pract*. 2020;8(1):318–325.e5. https://doi.org/10.1016/j.jaip.2019.08.025.