

Omalizumab for the Treatment of Solar Urticaria: Case Series and Systematic Review of the Literature



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What is already known about this topic? Solar urticaria (SU) is a rare type of inducible urticaria appearing within minutes of sunlight exposure. Although most patients can control the disease with antihistamines and leukotriene antagonists, a minority of patients require third-line therapies.

What does this article add to our knowledge? Treatment with omalizumab resulted in clinical improvement for 80% of patients with antihistamine refractory SU, and 50% of patients became symptom free. Patients who fail to improve on standard omalizumab dose may benefit from higher monthly dosages.

How does this study impact current management guidelines? This study highlights the efficacy and safety of omalizumab in the treatment of antihistamine refractory SU.

BACKGROUND: Solar urticaria (SU) is a rare photodermatosis causing a significant impact on patients' quality of life. Although the condition can be controlled with phototherapy and/or a combination therapy of antihistamines and leukotriene antagonist in most patients, a subset of patients require additional therapy with omalizumab; however, efficacy data are sparse.

OBJECTIVE: The objective of this study was to determine the efficacy and safety of omalizumab for treating SU.

METHODS: A case series of 5 patients with SU refractory to antihistamine and leukotriene antagonist combination who were treated with omalizumab is described. In addition, a systematic review of studies evaluating patients with SU treated with omalizumab was conducted. The primary outcome was partial/complete clinical response. Secondary outcomes were 10-fold

decreases in the baseline minimal urticarial dose and adverse events.

RESULTS: Our case series included 5 patients with SU. Monthly omalizumab doses of 150 to 600 mg resulted in clinical improvement in all patients and complete remission in 4. No adverse effects were reported. The systematic review included 22 studies (48 patients). All patients failed to control disease with antihistamines before omalizumab treatment. Patients received omalizumab at monthly doses of 150 to 750 mg over a follow-up period of 4 to 200 weeks. Thirty-eight patients (79%) experienced clinical improvement. Four patients (11%) had mild adverse effects.

CONCLUSIONS: Omalizumab provided clinical benefits in approximately 80% of patients with SU. Patients failing to improve on standard omalizumab doses may benefit from higher monthly dosages. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:1198-204)

Key words: Light; Omalizumab; Photoprovocation; Solar urticaria

Solar urticaria (SU) is a rare type of inducible urticaria characterized by an abrupt onset of transient erythema, wheals, and pruritus in light-exposed areas, appearing within minutes of exposure to light.¹ Although the pathogenesis has not been clearly elucidated, an unidentified, photo-induced, endogenous antigen is likely the triggering factor. Mechanism wise, SU is classified into 2 subtypes: in type I, IgE antibodies are targeted against abnormal chromophore, whereas in type II, IgE antibodies are targeted against normal chromophore.¹ The light waves (ie, action spectra) that trigger SU are usually within the range of 400 to 700 nm (visible light [VL]) and 320 to 400 nm (ultraviolet [UV] A), and infrequently 280 to 320 nm (UVB).²

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Abbreviations used

BID- Twice daily
CSU- Chronic spontaneous urticaria
MUD- Minimal urticaria dose
QD- Once daily
SU- Solar urticaria
UVA- Ultraviolet A
UVB- Ultraviolet B
VL- Visible light

Patients often have to completely avoid outdoor activities, which severely impacts their quality of life. Although for most patients treatment regimens consisting of antihistamines and a leukotriene antagonist may adequately control the disease, a minority of patients with severe refractory disease require third-line therapies including omalizumab, phototherapy (hardening), azathioprine, cyclosporine, or intravenous immunoglobulins.^{3,4} Omalizumab is a recombinant humanized anti-IgE antibody that binds to the Cε3 domain of IgE, forming trimers or hexamers that prevent it from binding to FcεRI on the surface of mast cells and basophils. Eventually, it downregulates cell surface IgE receptors, thereby preventing IgE-mediated histamine release.⁵ Omalizumab was approved in the United States, Europe, and several other countries including Israel as a third-line treatment for refractory chronic spontaneous urticaria (CSU). However, data regarding its efficacy in SU are scarce and limited to small case series and case reports.⁶

We herein present our clinical experience with 5 patients with severe antihistamine-refractory SU treated with omalizumab. A systematic literature review regarding the efficacy of omalizumab in patients with SU is also provided.

METHODS

Case series

All patients with refractory SU were eligible for the study. Refractory SU was defined as unsuccessful usage of broad-spectrum sunscreens and combination treatment with high-dose H1-antihistamines and a leukotriene antagonist. All patients developed transient urticaria within 1 hour of daylight exposure and underwent a controlled photoprovocation test to verify diagnosis.^{7,8} Photoprovocations were performed as previously described.⁹ Briefly, 2 × 2 cm² skin areas of the exposed skin on the patient's back underwent a single exposure to 50 J/cm² of VL, 20 J/cm² of UVA, and 0.03 J/cm² of broadband UVB. The minimal urticaria dose (MUD) was determined by stepwise decreasing dose until no urticaria was provoked. All patients underwent baseline laboratory workup, including complete blood count, erythrocyte sedimentation rate, C-reactive protein, kidney and liver function tests, thyroid function tests, antinuclear antibodies, anti-RO, anti-LA, and porphyrins levels in blood, stool, and 24-hour urine collection.

Systematic literature review

The systematic literature review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement¹⁰ and registered with the PROSPERO international prospective register (CRD42017080691). We searched without date limits on November 2017 using PubMed, Google Scholar, and the ongoing trials registry of the U.S. National Institutes of Health (<http://www.clinicaltrials.gov>). Reference lists from key trials and a previous systematic review were manually scanned for additional results.⁶ The following search criteria were used:

"urticaria"[MeSH Terms] OR "urticaria"[All Fields] OR "solar"[-MeSH Terms] OR "solar"[All Fields] AND "omalizumab"[MeSH Terms] OR "omalizumab"[All Fields] OR "anti-IgE"[MeSH Terms] OR "anti-IgE"[All Fields] OR "anti IgE"[MeSH Terms] OR "anti IgE"[All Fields].

Study selection and data extraction

We included studies of all designs, without language restriction, evaluating patients with a physician diagnosis of SU treated with omalizumab. Because of an expected low number of studies using validated severity scores (eg, urticaria activity score),¹¹ our primary outcome was a clinical response defined as follows:

1. Complete response was defined by the use of the following terms: "total relief," "complete control," "symptom free," and so on.
2. Partial response was defined by the use of the following terms: "partial improvement," "improved," "clinical improvement," and so on.
3. No response was defined by the use of the following terms: "no improvement," "no response," and so on.

Secondary outcomes were 10-fold decreases in the baseline MUD10 and adverse events.¹² Two reviewers (IS and NK) independently screened titles and abstracts followed by the full text of studies considered potentially eligible. The first author (IS) extracted data onto an electronic form and the second author (NK) checked data, including first author name, year of publication, number of participants, age, sex, atopic background, baseline IgE level, previous treatments, omalizumab dose and duration, baseline and follow-up photoprovocation results, clinical response, and adverse effects. Studies were graded according to their level of evidence: (A) prospective study; (B) retrospective study; and (C) case report or case series.¹³

Statistical analysis

Data were analyzed using descriptive statistics. Categorical variables are presented as number and percent, and continuous variables as mean and standard deviation or median and range.

RESULTS

Case series

Between 2013 and 2017, 5 patients suffering from SU refractory to high-dose antihistamines and leukotriene receptor antagonist combination were evaluated at the photodermatosis clinic in Beilinson Hospital, Petah-Tikva, Israel. Their clinical histories and omalizumab treatments are detailed below. [Table 1](#) summarizes the main characteristics of these patients.

Case 1. A 29-year-old female patient presented to our clinic with an 8-month history of SU appearing within 5 minutes of sun exposure outdoors or indoors through a window glass. Broad-spectrum sunscreens were inefficient. Her medical history included atopic dermatitis, asthma, and recurrent sinusitis with nasal polyps. No extracutaneous symptoms (including angioedema, shortness of breath, and wheezing) were reported. Avoidance of sun exposure had a major impact on her quality of life. Laboratory workup was unremarkable except for peripheral eosinophilia (absolute eosinophil count of 1600/μL). Photoprovocation was positive for VL (MUD = 30 J/cm²) and UVA light (MUD = 10 J/cm²). She was unresponsive to a combination of 3 H1-antihistamines (desloratadine 5 mg twice daily [BID], fexofenadine 180 mg BID, and cetirizine HCl 10 mg

TABLE 1. Characteristics of case series patients treated with omalizumab

Case	Sex/age	Atopic background	Previous treatments	Treatment duration and dosage	Baseline IgE level (IU/mL)	Baseline photoprovocation	Follow-up photoprovocation	Clinical response	Ten-fold baseline MUD decrease	Adverse events	Comment
1	F/29	AD, asthma, sinusitis	AH, AL, CS	300 mg once every 4 wk over 24 wk	NA	10 J/cm ² (UVA) 30 J/cm ² (VL) NR (UVB)	NR (VL)	1/1	1/1	None	Complete response
2*	F/10	Asthma, food allergy	AH, AL	150 mg once every 4 wk over 68 wk	243	NR (UVA) 50 J/cm ² (VL) NR (UVB)	NR (VL)	1/1	1/1	None	Complete response
3*	M/40	Allergic rhinitis, sinusitis	AH, AL	300 mg once every 4 wk over 28 wk	NA	NR (UVA) 50 J/cm ² (VL) NR (UVB)	Only asymptomatic erythema (VL)	1/1	1/1	None	Complete response
4	F/30	None	AH, AL	300-450 mg once every 3-4 wk over 16 wk	684	2 J/cm ² (UVA) 1 J/cm ² (VL) NR (UVB)	NA	1/1	NA	None	Partial response
5	M/6	AD, allergic rhinitis, ADHD	AH, AL	300 mg once every 2-4 wk over 144 wk	2004	NR (UVA) 30 J/cm ² (VL) NR (UVB)	NR (VL)	1/1	1/1	None	Almost complete response

AD, Atopic dermatitis; ADHD, attention deficit hyperactivity disorder; AH, antihistamines; AL, leukotriene antagonist; CS, corticosteroids; MUD, minimal urticaria dose; NA, not available; NR, no response; UVA, ultraviolet A; UVB, ultraviolet B; VL, visible light.

*Patients underwent photoprovocation while being treated with AH.

BID) and leukotriene receptor antagonist (montelukast 10 mg QD). A short course of prednisone (40 mg daily over 7 days) and a single dose of intramuscular betamethasone (5 mg betamethasone dipropionate; 2 mg betamethasone sodium phosphate), both administered before evaluation in our clinic, failed to improve symptoms. She reported significant relief from symptoms after the first dosage of 300 mg of omalizumab, with complete resolution of symptoms after the second administration, enabling her to return to normal outdoor activity. No additional usage of either antihistamines or leukotriene receptor antagonist was required. After 6 months of omalizumab treatment (300 mg every 4 weeks), the patient is asymptomatic and without any treatment-related adverse effects. However, attempts to prolong the intervals between omalizumab administrations resulted in mild urticaria. Repeated photoprovocation performed 2 weeks after the fifth administration of omalizumab was negative for VL.

Case 2. A 10-year-old female patient presented with an 8-month history of SU, which appeared within a few minutes of sun exposure outdoors or indoors through a window glass. Broad-spectrum sunscreens were inefficient. Her medical history included asthma, and peanut, pollen, and dust mite allergy. No type I extracutaneous symptoms (such as angioedema or shortness of breath) were reported. Laboratory workup was unremarkable except for mild elevation of serum IgE (243 IU/mL). At baseline, photoprovocation was positive for VL (MUD = 50 J/cm²). Treatment was initiated with desloratadine 5 mg BID, fexofenadine 120 mg BID, and montelukast 10 mg QD. Because no improvement was seen, the fexofenadine was increased to 180 mg BID, which brought a mild subjective and short-lived improvement. Because of the patient's young age, a low dose of 150 mg omalizumab dose was administered that brought a dramatic resolution of cutaneous symptoms as well as improvement in asthma control, without any side effects. Treatment with antihistamine and leukotriene receptor antagonist was gradually decreased until complete cessation. Repeated photoprovocation after 5 treatments with omalizumab was negative for VL. An attempt of extending the treatment intervals to once every 5 weeks resulted in mild erythema and pruritus a few days before the next injection; thus the 4-week interval regimen was reinstated. Over the past 17 months, with a 150 mg monthly dosage, the patient remains asymptomatic and without side effects.

Case 3. A 40-year-old male patient presented with a 7-year history of SU occurring outdoors and indoors through a window glass. Broad-spectrum sunscreens were inefficient. Medical history included past childhood allergic rhinitis with recurrent sinusitis. He denied systemic symptoms but reported fatigue after resolution of urticaria. Although evaluated in our clinic, he was being treated with a combination of 2 H₁-antihistamines (fexofenadine 180 mg BID; cetirizine HCl 10 mg BID) and a leukotriene receptor antagonist. This therapeutic regimen provided only partial relief, enabling the patient to sustain outdoor activities in the shade, for approximately 20 minutes. Laboratory workup was unremarkable. Under this regimen, photoprovocation was positive for VL (MUD = 50 J/cm²). An omalizumab dose of 150 mg was not beneficial; a monthly 300 mg dosage brought a complete resolution of symptoms. After 4 months of treatment, repeated photoprovocation with VL (50 J/cm²) induced only asymptomatic erythema without urticaria, which resolved after 20 minutes. After 6 months, treatment

intervals were gradually prolonged to 6 weeks without affecting efficacy. The patient has been treated with omalizumab for the past 7 months and is symptoms free without any side effects from treatment.

Case 4. A 30-year-old female patient presented with a 6-week history of gradually worsening SU, which appeared within a few seconds after light exposure outdoors, or indoors after exposure to regular or artificial light. Broad-spectrum sunscreens were inefficient. Cutaneous manifestations were accompanied with dizziness, abdominal pain, and burning sensation of eyes with an obvious impact on quality of life. Medical history was unremarkable. Laboratory workup was unremarkable except for elevated serum IgE (684 IU/mL). Photoprovocation was positive (with very low MUDs) for VL (1 J/cm²) and UVA light (2 J/cm²). Broadband UVB (0.03 J/cm²) induced erythema and pruritus without urticaria. She was unresponsive to a combination of 3 H₁-antihistamines (desloratadine 5 mg BID; fexofenadine 180 mg BID; cetirizine HCl 10 mg BID) and a leukotriene receptor antagonist (montelukast 10 mg QD). Treatment with a 300 mg monthly dosage of omalizumab was applied over the past 3 months with only a partial improvement. The dosage was increased to 450 mg once every 3 weeks, enabling her to remain free of symptoms indoors and for several minutes outdoors.

Case 5. This patient was previously described after his initial successful response to omalizumab treatment.¹⁴ A 6-year-old male patient presented with an 18-month history of recurrent and slowly worsening symptoms of urticaria and angioedema appearing within a few minutes of light exposure. Medical history included attention deficit hyperactivity disorder, allergic rhinitis, and atopic dermatitis. Laboratory tests showed elevated IgE (2004 IU/mL). Photoprovocation was positive for VL (MUD = 30 J/cm²). He was treated with a combination of 3 antihistamines (desloratadine 5 mg BID, fexofenadine 120 mg BID, cetirizine HCl 10 mg BID) and leukotriene receptor antagonist (montelukast 4 mg QD) with only a mild, subjective, and short-lived improvement. Despite being treated with this regimen, he experienced 1 episode of anaphylaxis after sunlight exposure, which required treatment with intramuscular epinephrine. Because of the patient's young age, a gradual dose increment of omalizumab was initiated; 75 mg followed by a 150 mg dose failed to significantly improve symptoms. However, a 300 mg bimonthly dose resulted in the symptoms vanishing without any adverse effect. Increasing the dosing interval to once every 4 weeks maintained remission. Antihistamines and montelukast were gradually decreased. Repeated photoprovocation performed 2 weeks after treatment was negative. After 3 months of treatment, the patient reported symptoms a few days before the next intended omalizumab administration; consequently, the dose was increased to 300 mg every 3 weeks. Over the past 36 months, the patient continued treatment with omalizumab and relatively low-dose antihistamines and is almost symptoms free. Minor rash is occasionally noted with minimal impact on life quality.

Systematic review

Our search yielded 919 citations (Figure 1). Twenty-one previously published studies and the present case series fulfilled the inclusion criteria for a total of 22 studies (Table E1, available in this article's Online Repository at www.jaci-inpractice.org).^{12,15-34} Table II summarizes the main characteristics of the

included studies. A total of 48 patients were included. Two studies were prospective (grade A, 11 patients), 3 were retrospective (grade B, 6 patients), and 17 were either small case series or case reports (grade C, 31 patients). Sample sizes ranged from 1 to 10. All patients were older than 15 years (mean, 42 ± 19) except for the 2 children included in our case series. Of 32 cases reporting gender, 21 (66%) were female and 11 (34%) were male. The baseline IgE levels varied significantly, ranging from 13 to 2874 IU/mL. Before omalizumab initiation, all patients failed to control disease with antihistamines, followed by phototherapy (23%), leukotriene receptor antagonist (17%), systemic steroids (6%), azathioprine (2%), mycophenolate mofetil (2%), intravenous immunoglobulins (2%), chloroquine (2%), and plasmapheresis (2%). One study defined clinical response as a 10-fold decrease in MUD, Dermatology Life Quality Index score <6, or 50% improvement from baseline in SU on a visual analog scale.¹²

Treatment with omalizumab

Patients received omalizumab at monthly doses ranging from 150 to 750 mg over a follow-up period of 4 to 200 weeks. Thirty-eight patients (79%) experienced clinical improvement. Of 33 cases providing adequate data, 17 (52%) had a 10-fold decrease from baseline in MUD and were free of symptoms. Ten patients (21%) who failed to improve received monthly omalizumab doses ranging from 150 to 300 mg for 4 to 16 weeks. Four patients (11%) had gastrointestinal intolerance, periorbital edema, local reaction, and short-term asthenia. None had a severe adverse effect.

DISCUSSION

The current study summarizes the up-to-date evidence on the efficacy and safety of omalizumab in the treatment of patients with SU. Omalizumab was found to be effective in achieving clinical improvement in approximately 80% of patients of whom approximately half remained free of symptoms.

Our case series included 5 patients with severe SU refractory to antihistamines and leukotriene receptor antagonist. Of note, the European guidelines for the treatment of CSU advocate the up dosing of up to 4-fold of the same antihistamine in severe cases.³⁵ However, 4-fold dosing of a single antihistamine is not possible due to lack of medical insurance coverage in our country. Therefore, we routinely administer a combination of different types of antihistamines allowing a high therapeutic dose of antihistamines without exceeding the maximal recommended dose for each antihistamine.⁷ All omalizumab-treated patients experienced clinical improvement: 4 remained symptom free and 1 showed mild improvement. Four of 5 patients could return to normal outdoor activity. Their improvement was objectively verified by negative photoprovocations. It is noteworthy that our series included 2 children (6 and 10 years old) who experienced a sustained response over a long-term period (more than 17 months), supporting omalizumab's efficacy in this setting.

The presented systematic review of 22 studies, including our present series, covered a total of 48 patients with SU.^{12,15-34} In accordance with the EAACI/LEN/EDF/WAO urticaria guidelines, all patients failed to achieve disease control with H₁-antihistamines before omalizumab initiation.³⁶ In all, 79% of patients experienced partial or complete clinical response. In contrast, in a relative large series of 11 patients with antihistamine refractory SU, cyclosporine was shown to provide only

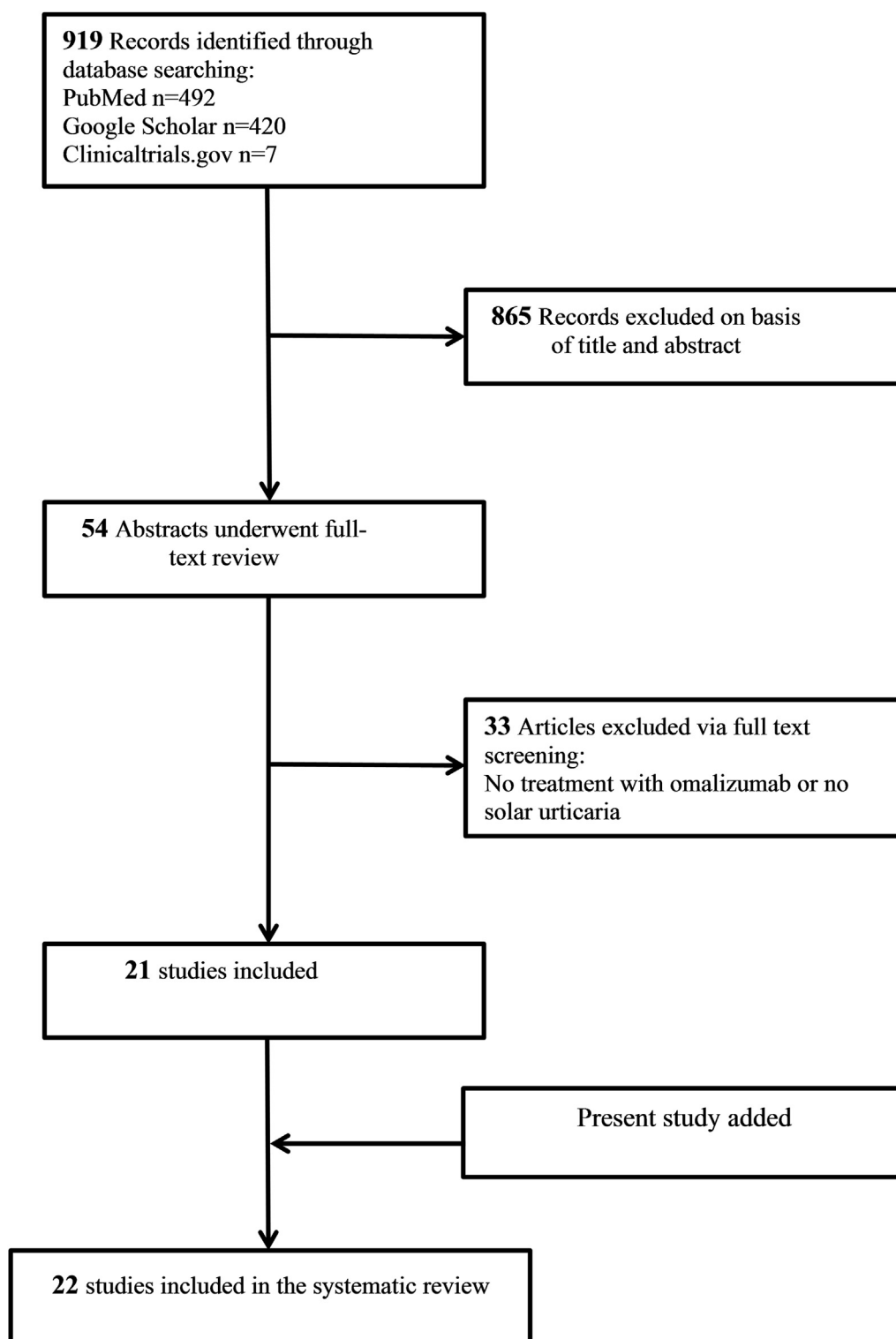


FIGURE 1. Systematic literature search according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

18% response rate.³⁷ In another study of 9 patients with severe, antihistamine refractory SU, a single course of intravenous immunoglobulins was clinically efficacious in 6 of 9 (67%) patients (2 of 9 [22%] patients also showed MUD10 response on

photoprovocation). However, response was maintained after 24 weeks in only 2 patients and after 48 weeks in only 1 patient.³⁸

We selected the MUD10 response as our secondary outcome due to its use in the only available phase II clinical trial by Aubin

TABLE II. Summary of information from studies included in the systematic review

No. of patients	48
Mean age (SD)	42 (17)
Female (%)	21 (66%*)
Median baseline IgE (IU/mL) (range)	294 (13-2874)
Atopic background	8 (27%)
Previous treatment	
Antihistamines (%)	48 (100%)
Antileukotriene (%)	8 (17%)
Phototherapy (%)	11 (23%)
Systemic steroids (%)	3 (6%)
Azathioprine	1 (2%)
Mycophenolate mofetil	1 (2%)
Intravenous immunoglobulins	1 (2%)
Chloroquine	1 (2%)
Plasmapheresis	1 (2%)
Omalizumab monthly dosage (mg)	150-750
≥300 dose	40 (87%*)
<300 dose	6 (13%*)
Duration of omalizumab treatment (wk)	4-200
Clinical response (%)	38 (79%)
Ten-fold decrease in MUD (%)	17 (52%*)
Clinical failure (%)	10 (21%)
Adverse effect (%)	4 (11%*)

MUD, Minimal urticaria dose; SD, standard deviation.

*Of cases providing data.

et al,¹² which investigated omalizumab in 10 patients with SU, reporting a MUD10 in 20% of the patients at week 12. The discrepancy between the limited MUD10 responses in the trial by Aubin et al compared with the favorable clinical response of omalizumab in our series and in the systematic review may be attributable to several factors. First, the MUD10 response may be an overly stringent outcome to determine the success of SU treatments as approximately 80% patients in our systematic review achieved clinical improvement, yet only 50% achieved MUD10 response. Similarly, when considering patient-based outcomes (ie, SU severity score), Aubin et al reported that 50% of patients responded favorably to omalizumab. Secondly, in this trial, patients used a fixed monthly dose of 300 mg; however, some patients may require higher monthly dosages to achieve response. Thirdly, because of the study's small sample size, the 95% confidence interval of patients' proportion achieving MUD10 was wide ranging from 3% to 56%; thus larger studies are needed to pinpoint the MUD10 response rate of omalizumab.

Approximately 20% of patients failed to achieve any clinical response under a monthly dosage of 150 to 300 mg of omalizumab. A previous systematic review has shown that omalizumab's effect is dose dependent in CSU.³⁹ As 6 of 48 (13%) patients in our systematic review used monthly omalizumab doses above 300 mg to achieve clinical response, patients failing to show initial response with standard dosages (≤300 mg/month) may benefit from the incremental dosage increase. Likewise, 2 of 5 patients in our case series required more than a 300 mg monthly dose to achieve complete clinical response.

In the systematic review, about quarter of patients had atopic disorders, contrasting with 80% prevalence found in our case series. The small size of our series as well as underreporting of

childhood atopic disorder in previous reports may account for this discrepancy.

No patient experienced severe adverse effects during treatment with omalizumab, although 11% had mild adverse effects including gastrointestinal intolerance, periorbital edema, local reaction, and short-term asthenia. The majority of studies had short follow-up periods and was underpowered to capture uncommon and late side effects. However, previous systematic reviews of omalizumab in CSU have shown that omalizumab had similar adverse effect rates to placebo groups.³⁹ Likewise, in our case series, none of the patients experienced adverse effects.

Our study has a number of methodological limitations. First, because of the rarity of SU, a low number of studies were included comprised mainly of case reports and small case series. Second, as SU may have a fluctuating course and none of the studies had a comparator group, efficacy conclusions are somewhat limited; thus randomized controlled trials are required to draw more substantial conclusions concerning omalizumab efficacy for SU. Third, we were unable to conduct subgroup analyses based on omalizumab dose and disease severity because of the limited data and inconsistency across outcome measurements.

In conclusion, our study shows that in patients with antihistamine refractory SU treatment with omalizumab resulted in clinical improvement in 80% of patients and approximately 50% become symptom free. Patients who fail to improve on standard dose may benefit from higher monthly dosages.

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TABLE E1. Studies on treatment with omalizumab in patients with solar urticaria

Study	N	Level of evidence	Sex/age	Medical history	Previous treatments	Treatment duration and dosage	Baseline IgE level (IU/mL)	Baseline photoprovocation	Follow-up photoprovocation	Clinical response	Ten-fold baseline MUD decrease	Adverse events	Comment
Aubin et al 2016 ¹²	10	A	NA	NA	AH	300 mg once every 4 wk (3 administrations in total)	NA	4 J/cm ² (UVA)	5 J/cm ² (UVA)	5/10	2/10	None	Clinical response defined as 10-fold decrease in MUD, Dermatology Life Quality Index score < 6 or 50% improvement from baseline in solar urticaria on a visual analog scale
								3 J/cm ² (UVA)	7 J/cm ² (UVA)				
								0.3 J/cm ² (UVA); 0.01 J/cm ² (UVB)	0.5 J/cm ² (UVA); 0.01 J/cm ² (UVB)				
								2 J/cm ² (UVA)	2 J/cm ² (UVA)				
								0.072 J/cm ² (UVA); 0.014 J/cm ² (UVB)	0.14 J/cm ² (UVA); 0.417 J/cm ² (UVB)				
								0.5 J/cm ² (UVA)	0.5 J/cm ² (UVA)				
								4 J/cm ² (UVA)	>40 J/cm ² (UVA)				
								1 J/cm ² (UVA); 0.06 J/cm ² (UVB)	1 J/cm ² (UVA); 0.06 J/cm ² (UVB)				
								1 J/cm ² (UVA)	3 J/cm ² (UVA)				
								0.6 J/cm ² (UVA); 0.08 J/cm ² (UVB)	>6 J/cm ² (UVA); >0.24 J/cm ² (UVB)				
Pinto Gouveia et al 2017 ²⁰	1	A	F/53	HTN	AH, CS, CsA, AL, phototherapy	150 mg once every 4 wk (2 administrations in total)	40	NA	NA	1/1	NA	NA	Partial response
Rodríguez-Jiménez et al 2017 ²⁴	1	C	F/53	Allergic rhinitis	AH, phototherapy	300 mg once every 4 wk over 48 wk	502	30 min after VL (irradiance/power NA)	Negative	2/3	1/3	Mild local reaction (patient 3)	Complete response
	1	C	F/65	PLE	AH	300 mg once every 4 wk over 24 wk	17	30 min after fluorescent light (irradiance/power NA)	NA				Partial response
	1	C	F/50		AH	150 mg once every 2 wk over 6 wk	1382	<0.6 J/cm ² (UVA); 0.01 J/cm ² (UVB)	No change				No response
Combalia et al 2017 ²³	1	C	F/21		AH	300 mg once every 4 wk over 48 wk	294	7 J/cm ² (UVA) UVB NEG	Negative (UVA+UVB)	1/1	1/1	None	Complete response
Kowalick et al 2017 ²²	1	C	F/50		AH	300 mg once		0.1 J/cm ² (UVA); 5 J/cm ² (UVA ₁); <0.001 J/cm ² (UVB)	0.4 J/cm ² (UVA); 5 J/cm ² (UVA ₁); 0.02 J/cm ² (UVB)	1/1	0/1		Partial response

(continued)

TABLE E1. (Continued)

Study	N	Level of evidence	Sex/age	Medical history	Previous treatments	Treatment duration and dosage	Baseline IgE level (IU/mL)	Baseline photoprovocation	Follow-up photoprovocation	Clinical response	Ten-fold baseline MUD decrease	Adverse events	Comment
Arasi et al 2017 ³⁰	1	C	F/16	Allergic rhinitis	AH, CS, AL	Between 150 mg once every 4 weeks to 375 mg once every 2 wk over 36 wk	228	Negative for UVA; >0.0012 J/cm ² (UVB)	Negative for UVA/UVB	1/1	1/1	NA	Complete response
Baliu-Piqué and Aguilera Peiró 2016 ²⁹	1	C	F/58		AH, AZA, phototherapy	Between 150 to 450 mg once every 4 wk over ~20 wk	2874	Negative for UVA/BB-UVB	Negative for UVA/BB-UVB	3/3	Unclear	NA	Complete response
	1	C	F/43		AH, phototherapy	Between 150 to 300 mg once every 4 wk over 32 wk	1500	Negative for UVA/UVB	Negative for UVA/UVB				
	1	C	F/49		AH	Between 150 to 300 mg once every 4 wk over 24 wk	980	Negative for UVA/BB-UVB	Negative for UVA/BB-UVB				
Brüning et al 2016 ²⁸	1	C	M/51		AH, CsA, AL, chloroquine	Between 300 to 450 mg once every 4 wk over 64 wk	NA	2.2 J/cm ² (UVA); 0.002 J/cm ² (UVB)	>35.8 J/cm ² (UVA); minimal response with UVB	1/1	1/1	None	Almost complete response
de Dios-Velázquez et al 2016 ¹⁸	1	C	M/41	Asthma, food allergy, oral allergy syndrome	AH	300 mg once every 4 wk over 32 wk	186	1 J/cm ² (UVA); negative for UVB	Negative for UVA/UVB	1/1	1/1	Short-term asthenia	Complete response
Duchini et al 2011 ¹⁹	1	C	M/24		AH	150 mg once every 4 wk (4 administrations in total)	77	6.3 J/cm ² (UVA); VL after 10 min irradiation with slide projector (irradiance/power NA)	No change	0/1	0/1	NA	No response
Ghazanfar et al 2016 ¹⁷	1	B	NA	NA	NA	NA	NA	NA	NA	0/1	NA	NA	No response
Güzelbey et al 2008 ²⁷	1	C	F/52		AH, rash phototherapy	150 mg once every 4 wk (duration NA)	22	1.4 J/cm ² (UVA)	Negative for UVA	1/1	1/1	NA	Complete response
Metz et al 2011 ¹⁶	1	C	M/29	NA	AH	300 mg once every 4 wk over several months	322	2.4 J/cm ² (UVA)	Negative for UVA	2/2	2/2	None	Complete response
	1	C	F/55	NA	AH	150 mg once every 4 wk over several months	22	1.1 J/cm ² (UVA)	Negative for UVA				
Metz et al 2014 ²⁵	1	B	NA	NA	AH			NA		1/1	NA	None	Complete response
Metz et al 2014 ³³	4	B	NA	NA	AH	Between 150 to 300 mg once every 4 wk over several months	NA		NA	4/4	NA	None	3 patients had complete response and 1 had partial response
Moncourier et al 2016 ³²	1	C	F/49		AH, phototherapy, IVIG	300 mg every 2 wk over 12 wk	NA	3 J/cm ² (UVA); VL 2 min (irradiance/power NA)	>20 J/cm ² (UVA); VL 5 min	4/4	Unclear	One patient had periorbital edema	All patients experienced marked improvement in quality of life
	1	C	M/49	Allergic rhinitis	AH, CsA	300 mg every 4 wk over 12 wk	NA	5.65 J/cm ² (UVA); VL 5 min; UVB >30 s	>20 J/cm ² (UVA)				
	1	C	F/16		AH	150 mg every 2 wk over 12 wk	NA	VL 15 min (irradiance/power NA)	VL >25 min				
	1	C	M/69		AH	300 mg once every 4 wk over 12 wk	NA	VL 5 min (irradiance/power NA)	Negative VL at 20 min				
Müller et al 2016 ³⁴	1	C	F/64		AH, phototherapy, MMF plasmapheresis	150 mg once every 4 wk (3 administrations in total)	13	10 J/cm ² (UVA ₁)	Worsening (NA)	0/1	0/1	NA	No response

Terrani et al 2016 ²⁶	1	C	M/53	Chronic spontaneous urticaria	AH	150-300 mg once every 4-8 wk over 64 wk	NA	VL (MUD NA); negative for UVA/UVB	Negative	1/1	1/1	NA	Complete response
Sivaramakrishnan et al 2015 ¹⁵	1	C	M/41		AH, phototherapy, systemic immuno-suppression (type NA)	150 mg once every 4-8 wk over ~200 wk	137	Positive (MUD NA)	Negative	2/2	2/2	None	Complete response
	1		F/44	Gastroparesis	AH, phototherapy, systemic immuno-suppression (type NA)	300 mg once every month over 16 wk	797	Positive (MUD NA)				Gastrointestinal intolerance	
	1		F/34		AH, phototherapy, systemic immuno-suppression (type NA)	150-300 mg once every 4 wk over 20 wk	179	Positive (MUD NA)	No change	0/1	0/1	NA	No response
Zimmer et al 2016 ³¹	1	C	F/71	HTN, hyperlipidemia	AH, phototherapy	300 mg once every 4 wk over 16-24 wk	740	3.6 J/cm ² (UVA)	6.3 J/cm ² (UVA)	1/1	0/1	None	Partial response
Waibel et al 2010 ²¹	1	C	M/16		AH	400 mg once every 2 wk over 12 wk	851	5 J/cm ² (UVA); 0.02 J/cm ² (UVB)	5 J/cm ² (UVA); 0.04 J/cm ² (UVB)	1/1	0/1	NA	Partial response
Present study	1	C	F/29	AD, asthma, sinusitis	AH, AL, CS	300 mg once every 4 wk over 24 wk	NA	10 J/cm ² (UVA); 30 J/cm ² (VL)	Negative (VL)	1/1	1/1	None	Complete response
	1	C	F/10	Asthma, food allergy	AH, AL	150 mg once every 4 wk over 68 wk	243	50 J/cm ² (VL)	Negative (VL)	1/1	1/1	None	Complete response
	1	C	M/40	Allergic rhinitis, sinusitis	AH, AL	300 mg once every 4 wk over 28 wk	NA	50 J/cm ² (VL)	Negative, only asymptomatic erythema (VL)	1/1	1/1	None	Complete response
	1	C	F/30		AH, AL	300-450 mg once every 3-4 wk over 16 wk	684	2 J/cm ² (UVA); 1 J/cm ² (VL)	NA	1/1	NA	None	Partial response
	1	C	M/6	AD, allergic rhinitis, ADHD	AH, AL	300 mg once every 2-4 wk over 144 wk	2004	30 J/cm ² (VL)	Negative (VL)	1/1	1/1	None	Almost complete response

AD, Atopic dermatitis; ADHD, attention deficit hyperactivity disorder; AH, antihistamines; AL, leukotriene antagonist; AZA, azathioprine; CS, corticosteroids; CsA, cyclosporine; HTN, hypertension; IVIG, intravenous immunoglobulin; MMF, mycophenolate mofetil; MUD, minimal urticaria dose; NA, not available; PLE, polymorphic light eruption; UVA, ultraviolet A; UVB, ultraviolet B; VL, visible light.

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