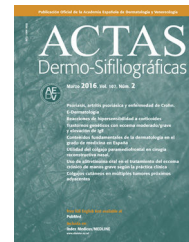




ACTAS Derma-Sifiliográficas

Full English text available at
www.actasdermo.org



PRACTICAL DERMATOLOGY

Omalizumab in the Treatment of Chronic Inducible Urticaria[☆]



P. Chicharro,* P. Rodríguez, D. de Argila

Servicio de Dermatología, Hospital Universitario de La Princesa, Madrid, Spain

Received 31 March 2016; accepted 26 July 2016
Available online 22 April 2017

KEYWORDS

Chronic inducible urticaria;
Omalizumab;
Cold urticaria;
Solar urticaria;
Delayed pressure urticaria;
Cholinergic urticaria;
Heat urticaria

PALABRAS CLAVE

Urticaria crónica inducible;
Omalizumab;
Urticaria por frío;
Urticaria solar;
Urticaria por presión retardada;
Urticaria colinérgica;
Urticaria por calor

Abstract Omalizumab is a recombinant humanized monoclonal antibody that inhibits immunoglobulin E. It has been approved for the treatment of severe asthma and chronic spontaneous urticaria refractory to other treatments. Its use in the management of chronic inducible urticaria (a type triggered by certain stimuli) is still considered off-label, although this use has been discussed in some consensus papers. This review brings together case reports and case series describing the use of omalizumab to treat chronic inducible urticaria. We analyze the most important aspects of the cases and the outcomes reported. The results seem to position omalizumab as a potentially effective, safe treatment alternative in some cases of chronic inducible urticaria.

© 2016 Elsevier España, S.L.U. and AEDV. All rights reserved.

Omalizumab en el tratamiento de la urticaria crónica inducible

Resumen Omalizumab es un anticuerpo monoclonal recombinante humanizado anti-IgE actualmente aprobado para el tratamiento del asma grave y de la urticaria crónica espontánea refractarios a otros tratamientos. Su empleo en el manejo de las urticarias crónicas inducibles (aquellas que se desencadenan ante determinados estímulos), si bien está contemplado en algunas guías de consenso, sigue siendo un uso «fuera de indicación». El objetivo de esta revisión es reunir los casos y series de casos publicados de este tipo de urticarias tratadas con omalizumab, analizando las características más relevantes y los resultados terapéuticos. Los resultados parecen posicionar a omalizumab como una potencial alternativa eficaz y segura en el tratamiento de algunos casos de urticaria crónica inducible.

© 2016 Elsevier España, S.L.U. y AEDV. Todos los derechos reservados.

[☆] Please cite this article as: Chicharro P, Rodríguez P, de Argila D. Omalizumab en el tratamiento de la urticaria crónica inducible. Actas Dermosifiliogr. 2017;108:423–431.

* Corresponding author.

E-mail address: somniem@gmail.com (P. Chicharro).

Introduction

Omalizumab is a recombinant humanized anti-immunoglobulin (Ig) E monoclonal antibody. By binding to IgE at the site that interacts with the receptors on target cells, this drug reduces the levels of free IgE in plasma, resulting in a reduction of the number of high-affinity IgE receptors on basophils and mast cells.^{1,2}

Initially approved for treating moderate to severe asthma, omalizumab was approved by the US Food and Drug Administration and the European Medicines Agency for the treatment of chronic spontaneous urticaria (CSU) in 2014. The current consensus-based guidelines of the European Academy of Allergology and Clinical Immunology, the Global Allergy and Asthma European Network, the European Dermatology Forum, and the World Allergy Organization classify omalizumab as a third-line treatment for chronic urticaria refractory to high-dose antihistamine therapy.³

Omalizumab has proven highly effective in treating CSU, and its safety profile is good. The most severe adverse effect, an anaphylactic reaction, has been reported only rarely in postapproval vigilance systems established to reduce risk.^{1,4}

Omalizumab for the treatment of inducible chronic urticaria (InCU), which develops in response to certain stimuli, usually physical ones, continues to be an off-label use, but case reports referring to this alternative therapy are increasing in number. The various types of InCU are listed in Table 1.

Table 1 Types of Inducible Chronic Urticaria.

From Physical Inducers	From Nonphysical Inducers
Chronic cold urticaria	Cholinergic urticaria
Solar urticaria	Aquagenic urticaria
Delayed-pressure urticaria	Contact urticaria
Dermographia (urticaria factitia)	
Heat chronic urticaria	
Vibratory angioedema	

We reviewed the published cases of omalizumab-treated InCU, analyzing clinical characteristics and outcomes. Each InCU subtype was analyzed separately. Case reports were found in MEDLINE through PubMed, using the ClinicalKey search engine. We also searched for clinical trials in ClinicalTrials.gov.

Chronic Cold Urticaria

Chronic cold urticaria appears after the skin is exposed to low temperatures and can also appear in response to eating cold food.⁵ This form accounts for about 3% of CSU cases.⁶

Table 2 lists 9 cases of cold urticaria treated with omalizumab. In addition, the case series by Metz et al.¹³ and Sussman et al.¹⁴ described 5 and 6 more cases, respectively, bringing the total to 20. Those series only provided us with data related to treatment characteristics and outcomes,

Table 2 Cases of Chronic Cold Urticaria Treated With Omalizumab.

Author	Age and Comorbidity	Time Since Onset	Total IgE at Baseline	Dosage and Duration	Response
Boyce ⁷	12 y Atopic dermatitis; asthma; allergy to pollen, cats, mites	2 y	1078 IU/mL	375 mg/2 wk, > 5 mo	CR, including negative challenge tests but with recurrence on suspension
Metz et al. ⁸	19 y None	4 y	64 IU/mL	150 mg/mo, > 6 mo	CR, including negative challenge tests
Brodská et al. ⁹	53 y HBV infection	4 mo	207 IU/mL	300 mg/mo, 4 mo	CR, maintained, including negative challenge tests
Brodská et al. ⁹	30 y None	1 y	20.8 IU/mL	300 mg/mo, 8 mo	No response, treatment suspended
Le Moing et al. ¹⁰	66 y None described	6 y	89 IU/mL	300 mg/2 wk, 2 mo	CR maintained
Le Moing et al. ¹⁰	42 y Atopic dermatitis, asthma	3 y	493 IU/mL	300 mg/2 wk, 2 mo	CR, 2 recurrences controlled by retreatment with 300 mg
Le Moing et al. ¹⁰	21 y Atopic dermatitis, asthma	8 y	1772 IU/mL	300 mg/2 wk, 2 mo	CR, 1 recurrence controlled by retreatment with 300 mg
Alba Marín et al. ¹¹	2 y None	6 mo	14.9 IU/mL	75 mg/mo, > 9 mo	CR, including negative challenge tests
Zimmer et al. ¹²	71 y Solar urticaria	11 y	740 IU/mL	300 mg/mo, > 6 mo	PR, positive challenge tests; after treatment suspension, recurrence obliged continuing treatment

Abbreviations: CR, complete response; HBV, hepatitis B virus; Ig, immunoglobulin; PR, partial response.

Table 3 Solar Urticaria Treated With Omalizumab.

Author	Age and Comorbidity	Time Since Onset	Total IgE at Baseline	Dosage and Duration	Response
Güzelbey et al. ¹⁷	52 y None reported	1 y	22 IU/mL	150 mg/mo, > 1 mo	CR, including negative challenge tests
Waibel et al. ¹⁸	16 y None	6 mo	851 IU/mL	400 mg/2 wk, 3 mo	PR, with improvement in challenge tests
Metz et al. ⁸	29 y None	25 y	322 IU/mL	300 mg/mo, Unknown	CR, including negative challenge tests
Metz et al. ⁸	55 y None	15 y	22 IU/mL	150 mg/2 wk, unknown	CR, including negative challenge tests
Duchini et al. ¹⁹	24 y None reported	3 y	77 IU/mL	150 mg/mo, 4 mo	No clinical or challenge-test response; treatment suspended
Zimmer et al. ¹²	71 y Cold urticaria	11 y	740 IU/mL	300 mg/mo, > 6 mo	PR, positive challenge test and recurrence after treatment suspension; treatment was then continued
Pérez-Plaza et al. ²⁰	50 y None reported	25 y	1382 IU/mL	150 mg/2 wk, 1.5 mo	No clinical or challenge-test response; treatment suspended
Baliu-Piqué and Aguilera-Peiró ²¹	43 y None reported	6 y	1500 IU/mL	300 mg/mo, 8 mo	CR
Baliu-Piqué and Aguilera-Peiró ²¹	58 y None reported	15 y	2874 IU/mL	450 mg/mo, > 3 mo	CR
Baliu-Piqué and Aguilera-Peiró ²¹	49 y None reported	3 y	980 IU/mL	300 mg/mo, 6 mo	CR
Arasi et al. ²²	16 y Atopic dermatitis	1.5 y	228 IU/mL	300 mg/mo, 8 mo	CR maintained
Levi et al. ²³	6 y Dermatitis	1.5 y	2004 IU/mL	300 mg/mo, 12 mo	CR, including negative challenge tests
De Dios-Velázquez et al. ²⁴	41 y Atopic dermatitis, asthma, allergy to mites and shellfish	3 y	186 IU/mL	300 mg/mo, 8 mo	CR, including negative challenge tests
Müller et al. ²⁵	64 y None reported	28 y	12 IU/mL	150 mg/mo, 3 mo	No clinical or challenge-test response; treatment suspended

Abbreviations: CR, complete response; Ig, immunoglobulin; PR, partial response.

although more information was available for some cases that had been previously reported individually.

The most frequent comorbidities recorded, asthma and atopy (Table 2), showed no apparent associated variations in response to treatment. Similarly, pretreatment IgE levels were variable and lacked a clear correlation with response. Omalizumab doses ranged from 75 mg/mo in 1 pediatric patient to 375 mg/2 wk. Seven out of 9 patients (78%) showed complete response and resolution of symptoms. Recurrence after treatment stopped was approached in 2 ways: by administering occasional additional doses or by reinstating the previous therapeutic regimen. Symptoms resolved with both approaches. In a case reported by Zimmer et al.¹² the patient had 2 types of InCU: cold urticaria and solar urticaria. Only partial control of both types was achieved in this patient, although treatment led to significant improvement in quality of life.

Metz et al.¹³ analyzed a series of 6 cases that included one of the patients included in the Table 8; they found that response to omalizumab was complete in 3 patients (50%).

Two of them had been treated at a dosage of 150 mg/mo, and 1 patient required 150 mg/wk to achieve the same effect. Responses were complete in the series of 6 patients described by Sussman et al.¹⁴ at dosages of 150 mg/mo (4 patients) and 300 mg/mo (2 patients).

Omalizumab treatment led to complete response in 15 out of the 20 cases (75%) in total.

No important adverse effects were reported. The patient described by Brodská and Schimd-Grendelmeier⁹ experienced fatigue and drowsiness. As that patient did not respond, treatment was suspended.

Solar Urticaria

Solar urticaria is a rare condition in which wheals appear after exposure to sunlight, visible light, or UV light. Epidemiological data are unavailable because of the low prevalence of this InCU.^{15,16} Information for the 14 individual reports of patients treated with omalizumab is summarized in Table 3.

Table 4 Delayed-Pressure Urticaria Treated With Omalizumab.

Author	Age and Comorbidity	Time Since Onset	Total IgE at Baseline	Dosage and Duration	Response
Bindslev-Jensen and Skov ²⁹	39 y None described	10 y	32 IU/mL	150 mg/2 wk, > 3 mo	CR
Magerl et al. ³⁰	37 y CSU	4.7 y	90 IU/mL	150 mg/mo, unknown	PR
Ivyanskiy et al. ³¹	46 y None	3 y	98 IU/mL	150 mg/2 wk, 12 mo	PR
Rodríguez-Rodríguez et al. ³²	45 y Not described	11 y	600 IU/mL	300 mg/mo, 16 mo	CR, including negative challenge tests; recurrence after treatment suspension; treatment then continued
Müller et al. ³³	61 y None described	1 y	179 IU/mL	300 mg/mo, 12 mo	CR, but recurrence after treatment suspension; treatment then continued
Kasperska-Zajac et al. ³⁴	34 y CSU and angioedema	3 y	740 IU/mL	150 mg/6 wk, 8 mo	CR, but recurrence after treatment suspension; treatment then continued
Kasperska-Zajac et al. ³⁴	23 y CSU	1 y	43 IU/mL	150 mg/6 wk, 5 mo	CR, but recurrence after treatment suspension; treatment then continued
Kasperska-Zajac et al. ³⁴	59 y CSU and angioedema	20 y	Not reported	300 mg/mo, 2 mo	PR and suspension
Geller ³⁵	33 y CSU and angioedema	3 y	488 IU/mL	300 mg/mo, 10 mo	CR

Abbreviations: CR, complete response; CSU, chronic spontaneous urticaria; Ig, immunoglobulin; PR, partial response

Two additional patients were included in the series analyzed by Metz et al.,¹³ but treatment data and response were reported for only one of them.

The most common comorbidity described in the table, as in cases of other types of InCU, was atopy; comorbidity did not appear to be associated with response variations. In contrast, although baseline IgE findings varied, a certain tendency favoring greater response in patients with elevated levels seems to be present: 63% of patients with elevated IgE concentrations (5 out of 8 patients) experienced complete response (Table 3). Dosages ranged from 150 to 800 mg/mo. Overall, 9 out of 14 patients (64%) experienced complete response and resolution of symptoms. Eight patients continued treatment. Metz et al.⁸ reported that symptoms returned on suspension of treatment in 1 patient, but full control of symptoms was again achieved on restarting therapy. Two of the 14 patients (14%) achieved partial response and 3 (21%) showed no response. As mentioned above, the patient described by Zimmer et al.¹² was unusual for having 2 types of InCU: both cold and solar urticaria. Partial control of both types was achieved.

One of the 2 additional patients in another series by Metz et al.¹³ had a complete response and the other had a partial response.

Ten out of 16 patients (62.5%) experienced complete response to omalizumab. No important adverse effects were reported. It is also important to note that treatment was safe in 2 young patients (6 and 16 years of age) at a dosage of 300 mg/mo. Both had complete responses. A partial

response was reported for a third pediatric patient (16 years of age).

Aubin et al.²⁶ recently published a phase II study in which 10 patients with solar urticaria were treated at a dosage of 300 mg/mo for 2 months (3 doses in all). These patients were evaluated through exposure to both artificial light and sunlight (UV-A, UV-B, and the full solar spectrum). The outcome measure was the percentage of patients whose solar urticaria lesions remained under control at week 12 when exposed to UV radiation 10-fold higher than the minimum urticarial dose at baseline. Approximately 40% experienced initial improvement, but efficacy as measured by the main outcome was not statistically significant. However, limitations affecting the study were the lack of a placebo group and the small number of patients enrolled.

Delayed-Pressure Urticaria

The lesions of delayed-pressure urticaria typically appear 4 to 6 hours after pressure of varying degrees has been applied to the skin (e.g., as a result of sitting or wearing tight clothing). About 37% of these rare reactions may be associated with CSU, although the lesions may not be noticed because of the delay.^{27,28} The 9 published cases treated with omalizumab are summarized in Table 4. The series of Metz et al.¹³ included 8 additional cases, although only partial information was provided.

Table 5 Dermographia Treated With Omalizumab.

Author	Age and Comorbidity	Time Since Onset	Total IgE at Baseline	Dosage and Duration	Response
Krause et al. ³⁶	48 y None described	3 y	341 IU/mL	300 mg/2 wk, 3 mo	CR, including negative challenge tests; recurrence after suspension
Metz et al. ⁸	49 y None	4 y	245 IU/mL	300 mg/mo, > 6 mo	CR, including negative challenge tests
Metz et al. ⁸	46 y None	2 y	20 IU/mL	300 mg/mo, > 6 mo	PR only after dosage increase from 150 to 300 mg/mo

Abbreviations: CR, complete response; Ig, immunoglobulin; PR, partial response.

The most common comorbidity mentioned in the reports (Table 4) was CSU, present with or without angioedema. The CSU prevalence (55%, in 5 of the 9 patients) was higher than generally reported in the literature but unrelated to response to omalizumab. Baseline IgE levels were highly variable and were once again unrelated to response. Müller et al.³³ reported an interesting case of delayed bullous urticaria. The dosages used in these cases, which ranged from 150 mg/6 wk to 300 mg/mo, were lower than those prescribed for other types of InCU. Two thirds (6 out of 9 patients) showed complete response and resolution of symptoms. Nearly all of them reported full improvement within only 48 hours of the first injection. Kasperska-Zajac et al.³⁴ spaced the doses until their patient's symptoms reappeared, applying an optimization strategy made possible because omalizumab acts rapidly.

Seven of the 8 patients (88%) described by Metz et al.¹³ achieved complete response to therapy, although further details were not provided.

In 13 of the total of 17 published cases (76%) response was complete and in 4 (24%) it was partial. There were no therapeutic failures. Nor were there significant adverse effects.

Dermographia

Dermographia, also known as symptomatic dermatism or urticaria factitia, is a rare InCU in which pruritic wheals are induced by rubbing or scratching the skin.³⁶

Table 5 summarizes the characteristics of the 3 individual case reports in which omalizumab was used. Response

was complete in 2 of them (66%). The third had a partial response after the initial dosage was increased. Interestingly, this patient was the only one with a total IgE level that was not elevated at baseline.⁸ Omalizumab was prescribed at a dosage of 300 mg every 2 or 4 weeks. No adverse effects were reported.

Two patients were described by Metz et al.⁸ in their first report; their second series described a total of 5 cases of dermatism, 2 of which were the ones reported earlier. All 5 patients achieved complete response to treatment.

In summary, 7 out of 8 of the patients with dermatism (87.5%) had complete responses to omalizumab, 1 patient had a partial response, and there were no therapeutic failures.

Chronic Heat Urticaria

Chronic heat urticaria is a rare InCU that is difficult to manage. The reaction is triggered by a local effect of heat from a variety of sources: hot water, hot objects, sunlight (exposed and nonexposed areas), or artificial light.³⁷

Table 6 summarizes the 4 reported cases treated with omalizumab. Three of the 4 patients (75%) achieved complete response. The fourth did not improve except for a slight increase (2°C) in the temperature required for a positive challenge test result.⁸ In general these patients did not have concurrent diseases of note, with the exception of one who had hypogonadism, which the authors deemed to be of no clinical relevance.³⁸ Response seems to have been unrelated to baseline IgE levels. Dosages ranged from 300 mg/mo

Table 6 Chronic Heat Urticaria Treated With Omalizumab.

Author	Age and Comorbidity	Time Since Onset	Total IgE at Baseline	Dosage and Duration	Response
Bullerkotte et al. ³⁸	42 y Hypogonadism	3 y	429 IU/mL	450 mg/2 wk, > 19 mo	CR, including negative challenge tests
Metz et al. ⁸	63 y None	5 y	111 IU/mL	300 mg/2 wk, 3 mo	No response
Carballada et al. ³⁹	34 y None described	1 y	56.8 IU/mL	300 mg/mo, 6 mo	CR, but recurrence after suspension
Carballada et al. ³⁹	63 y None described	4 y	14.7 IU/mL	300 mg/mo, 6 mo	CR, including negative challenge tests; recurrence after treatment suspension, requiring continuance

Abbreviations: CR, complete response; Ig, immunoglobulin.

Table 7 Cholinergic Urticaria Treated With Omalizumab.

Author	Age and Comorbidity	Time Since Onset	Total IgE at Baseline	Dosage and Duration	Response
Metz et al. ⁴²	25 y Seasonal rhinitis	5 y	Not specified	300 mg/2 wk, > 6 mo	CR, including negative challenge tests
Otto and Calabria ⁴¹	25 y Seasonal rhinitis	8 y	103 IU/mL	300 mg/mo, > 5 mo	CR, including negative challenge tests
Sabroe ⁴³	27 y Allergy to cat hair	9 y	1523 IU/mL	300 mg/2 wk, 4 mo	No response, treatment suspended
Bantz et al. ⁴⁴	14 y None described	> 6 mo	54 IU/mL	150 mg/2 wk, > 2 mo	CR
Kutlu et al. ⁴⁵	49 y None described	3 y	980 IU/mL	300 mg/mo, 6 mo	CR

Abbreviations: CR, complete response.

Table 8 Response to Omalizumab in Different Varieties of Inducible Chronic Urticaria.

Type of Urticaria	Complete Response	Partial Response	No Response
Chronic cold urticaria ^a	15/20 (75%)	1/20 (5%)	4/20 (20%)
Solar urticaria ^a	10/16 (62.5%)	3/16 (18.75%)	3/16 (18.75%)
Delayed-pressure urticaria ^a	13/17 (76%)	4/17 (24%)	0/17 (0%)
Dermographia ^a	7/8 (87.5%)	1/8 (12.5%)	0/8 (0%)
Chronic heat urticaria	3/4 (75%)	0/4 (0%)	1/4 (25%)
Vibratory angioedema	0/1 (0%)	0/1 (0%)	1/1 (100%)
Cholinergic urticaria ^a	8/12 (67%)	1/12 (8%)	3/12 (25%)
Aquagenic urticaria	1/1 (100%)	0/1 (0%)	0/1 (0%)

^a Cases of certain varieties were reported in case series. The denominators include the number of patients described in both individual case reports and case series.

to 450 mg/2 wk. Once again, no important adverse effects were observed.

Vibratory Angioedema

Vibratory angioedema is one of the least common InCUs. It consists of wheals or angioedema induced by vibrations. Typical triggers are running, motorcycle riding, and using tools such as drills. Playing musical instruments has even been implicated. Only a single case of vibratory angioedema in the literature describes treatment with omalizumab. The patient was a 36-year-old woman whose symptoms had been present for 20 years. She had no concurrent diseases, and her baseline IgE level was 13 IU/mL. She showed no clinical improvement after 3 months of treatment with omalizumab (300 mg/mo). She did, however, experience a partial response after starting treatment with ketotifen. Improvement was evident in both clinical symptoms and a challenge test (forearm held over a mixer running at increasing speeds). No adverse effects were reported.⁴⁰

Cholinergic Urticaria

Cholinergic urticaria is a nonphysical InCU caused by a rise in body temperature. The trigger might be physical exercise, exposure to high ambient temperatures, or emotional stress. Approximately 5% of chronic urticarias are cholinergic.⁴¹

Five individual case reports (Table 7) have described omalizumab-treated patients with this form of urticaria. As in other InCUs, the main comorbidity was allergy (seasonal rhinitis or cat allergy) and baseline IgE levels varied considerably. Neither variable appeared to influence the results of treatment. Four of the 5 patients (80%) responded to omalizumab (1 complete response). Treatment failure was reported in 1 case. Dosages were 300 mg every 2 or 4 weeks.

In the series published by Metz et al.,¹³ there were 7 additional cases of cholinergic urticaria treated with omalizumab. Four of the patients achieved complete response, 1 responded partially, and 2 experienced no improvement.

In summary, in 8 of the 12 cases (67%) response to omalizumab was complete and there were no adverse effects.

Aquagenic Urticaria

Aquagenic urticaria is a rare nonphysical InCU. Symptoms appear after exposure to water of any temperature. Water intake does not usually cause symptoms. We were able to find only a single description of an omalizumab-treated patient with this type,⁴⁶ probably because of the low prevalence of this diagnosis. The patient was a 34-year-old woman with no concurrent diseases who had been experiencing symptoms for 2 years. After 2 months on omalizumab (300 mg/4 wk) she experienced complete resolution. Neither circulating IgE levels or adverse effects were reported.⁴⁶

Discussion

The indications for omalizumab have broadened in recent years, and this anti-IgE monoclonal antibody was recently approved for treating CSU. Various authors have argued in favor of its therapeutic potential based on the hypothesized role of IgE in the pathogenesis of CSUs or on the effect of IgE on cellular immunity.^{1,8}

At this time, descriptions of omalizumab treatment characteristics and outcomes are only available from case reports and small case series, a situation that presents serious limitations given the possibility of selection bias.

Another basic limitation is the lack of objective outcome criteria that would facilitate consistent analysis of therapeutic effects. In fact, until a short time ago we lacked clinical assessment tools useful for follow-up in InCU. Nothing comparable to scales for CSU in general (the Urticaria Activity Score or the Weekly Urticaria Activity Score) was on hand. After Weller et al.⁴⁷ described the Urticaria Control Test in a 2014 publication, it underwent cross-cultural adaptation to Castilian Spanish.⁴⁸ This tool establishes thresholds useful for following patients and monitoring disease control.^{49,50} However, as such systems were not used when most of the articles we reviewed were written, our analysis of clinical response is necessarily limited.

This review, like the case series of Metz et al.,¹³ found that the patients who seem to benefit the most from treatment with omalizumab are those with dermographia or delayed-pressure urticaria. The complete response rates for these types were 87.5% and 76%, respectively, and there were no reports of treatment failure. The least favorable outcomes were in cases of solar urticaria, where the complete response rate was 62.5%. Response to omalizumab according to different types of InCU are summarized in Table 8.

It also appears that baseline IgE levels reported in the publications we reviewed were unrelated to response to omalizumab, in contrast with the pattern seen in asthma. In fact, there were cases of complete response in patients with both normal levels and elevated IgE levels. This observation, emphasized by Metz et al.¹³ earlier, is consistent with what we have seen in our review. Only in solar urticaria does there seem to be a tendency toward greater efficacy in patients with elevated IgE levels.

The dosages were highly variable in all subtypes of InCU. Regimens sometimes followed recommendations established for asthma (calculated according to IgE level and weight). Sometimes a dosage was prescribed empirically, however, or was based on recommendations for CSU. Francés et al.¹ suggested that the optimal dosage probably falls somewhere between 150 and 300 mg every 2 to 4 weeks.

At present it is impossible to recommend a treatment duration because of the great variation in the literature and external constraints, given that the reported applications were all off-label. However, based on our review and another retrospective analysis of reported cases of CSU,⁵¹ the reintroduction of omalizumab to maintain efficacy in patients who initially responded seems to be safe.

We must emphasize the absence of important adverse effects in any of the published cases. We found only a single case of a patient with cold urticaria who reported fatigue and drowsiness.⁹

Much more information about the effect of omalizumab on InCU will probably become available in the near future given that several clinical trials are in course. The CUN-OMAL-UCOL,⁵² CUTEX,⁵³ and UFO⁵⁴ trials are studying omalizumab for the treatment of cholinergic urticaria, cold urticaria, and dermographia, respectively. In fact, a phase II trial in patients with solar urticaria was recently published,²⁶ as mentioned in the introduction. The publication of such trials may allow us to establish more specific recommendations on indications, dosages, and durations of treatment.

For the moment, omalizumab is positioned as an effective, safe alternative treatment for InCU just as it is for CSU.

Ethical Disclosures

Protection of Human and Animal Subjects. The authors declare that no experiments were performed on humans or animals for this investigation.

Confidentiality of Data. The authors declare that no private patient data are disclosed in this article.

Right to Privacy and Informed Consent. The authors declare that no private patient data are disclosed in this article.

Conflicts of Interest

Drs Chicharro and Rodríguez declare that they have no conflicts of interest. Dr de Argila has served as a clinical advisor for Novartis and has participated in trials sponsored by that laboratory.

References

1. Francés L, Leiva-Salinas M, Silvestre JF. Omalizumab en el tratamiento de la urticaria crónica. *Actas Dermosifiliogr.* 2014;105:45–52.
2. Saavedra M, Sur S. Down regulation of the high-affinity IgE receptor associated with successful treatment of chronic idiopathic urticaria with omalizumab. *Clin Mol Allergy.* 2011;9:2.
3. Zuberbier T, Aberer W, Asero R, Bindslev-Jensen C, Brzoza Z, Canonica GW, et al. The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria: The 2013 revision and update. *Allergy.* 2014;69:868–87.
4. Cox L, Lieberman P, Wallace D, Simons FE, Finegold I, Platts-Mills T, et al., American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology. American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology Joint Task Force Report on omalizumab-associated anaphylaxis. *J Allergy Clin Immunol.* 2007;120:1373–7.
5. Koeppl MC, Bertrand S, Abitan R, Signoret R. Urticaria caused by cold: 104 cases. *Ann Dermatol Venereol.* 1996;123:627–32.
6. Buss YL, Sticherling M. Cold urticaria; disease course and outcome-An investigation of 85 patients before and after therapy. *Br J Dermatol.* 2005;153:440–1.
7. Boyce JA. Successful treatment of cold-induced urticaria/anaphylaxis with anti-IgE. *J Allergy Clin Immunol.* 2006;117:1415–8.

8. Metz M, Altrichter S, Ardelean E, Kessler B, Krause K, Magerl M, et al. Anti-immunoglobulin E treatment of patients with recalcitrant physical urticaria. *Int Arch Allergy Immunol*. 2011;154:177–80.
9. Brodská P, Schimid-Grendelmeier P. Treatment of severe cold contact urticaria with omalizumab: Case reports. *Case Rep Dermatol*. 2012;4:275–80.
10. Le Moing A, Bécourt C, Pape E, Dejobert Y, Delaporte E, Staumont-Sallé D. Effective treatment of idiopathic cold urticaria with omalizumab: Report of 3 cases. *J Am Acad Dermatol*. 2013;69:e99–101.
11. Alba Marín JC, Martorell Aragones A, Satorre Viejo P, Gastaldo Simeon E. Treatment of severe cold-induced urticaria in a child with omalizumab. *J Investig Allergol Clin Immunol*. 2015;25:303–4.
12. Zimmer S, Peveling-Oberhag A, Weber A, Gilfert TT, Rady-Pizarro U, Staubach P. Unique coexistence of cold and solar urticaria and its efficient treatment. *Br J Dermatol*. 2015;174:1150–2.
13. Metz M, Ohanyan T, Church MK, Maurer M. Omalizumab is an effective and rapidly acting therapy in difficult-to-treat chronic urticaria: A retrospective clinical analysis. *J Dermatol Sci*. 2014;73:57–62.
14. Sussman G, Hébert J, Barron C, Bian J, Caron-Guay RM, Laflamme S, et al. Real-life experiences with omalizumab for the treatment of chronic urticaria. *Ann Allergy Asthma Immunol*. 2014;112:170–4.
15. Eguino P, Lasa O, Gardeazábal J, Díaz-Pérez JL. Urticaria solar. Estudio de 20 casos. *Actas Dermosifiliogr*. 2005;96:25–9.
16. Botto NC, Warshaw EM. Solar urticaria. *J Am Acad Dermatol*. 2008;59:909–20.
17. Güzelbey O, Ardelean E, Magerl M, Zuberbier T, Maurer M, Metz M. Successful treatment of solar urticaria with anti-immunoglobulin E therapy. *Allergy*. 2008;63:1563–5.
18. Waibel KH, Reese DA, Hamilton RG, Devillez R. Partial improvement of solar urticaria after omalizumab. *J Allergy Clin Immunol*. 2010;125:490–1.
19. Duchini G, Bäumler W, Bircher AJ, Scherer K. Failure of omalizumab (Xolair) in the treatment of a case of solar urticaria caused by ultraviolet A and visible light. *Photodermatol Photoimmunol Photomed*. 2011;27:336–7.
20. Pérez-Plaza A, Concha-Garzón MJ, Solano-López G, de Argila D. Failure of omalizumab in ultraviolet-induced severe solar urticaria. *Immunology*. 2014;33:147–8.
21. Baliu-Piqué C, Aguilera Peiró P. Three cases of solar urticaria successfully treated with omalizumab. *J Eur Acad Dermatol Venereol*. 2016;30:704–6.
22. Arasi S, Crisafulli G, Caminiti L, Guarneri F, Aversa T, Porcaro F, et al. Treatment with omalizumab in a 16-year-old Caucasian girl with refractory solar urticaria. *Pediatr Allergy Immunol*. 2015;26:583–5.
23. Levi A, Tal Y, Dranitzki Z, Shalit M, Claes DE. Successful omalizumab treatment of severe solar urticaria in a 6-year-old child. *Pediatr Allergy Immunol*. 2015;26:588–90.
24. De Dios-Velázquez A, González-de Arriba M, Beteta-Gorriti V, Macías E, Campanón-Toro V, Dávila I. Effectiveness of omalizumab in severe solar urticaria. *Ann Allergy Asthma Immunol*. 2016;116:256–64.
25. Müller S, Schempp CM, Jakob T. Failure of omalizumab in the treatment of solar urticaria. *J Eur Acad Dermatol Venereol*. 2016;30:524–5.
26. Aubin F, Avenel-Audran M, Jeanmougin M, Adamski H, Peyron JL, Marguery MC, et al. Omalizumab in patients with severe and refractory solar urticaria: A phase II multicentric study. *J Am Acad Dermatol*. 2016;74:574–5.
27. Kaplan AP. Urticaria and angioedema. In: Adkinson NF Jr, Brochner BS, Busse WW, editors. *Middleton's allergy: Principles and practice*. 7th ed. Philadelphia: Elsevier, Inc.; 2009. p. 1071–2.
28. Barlow RJ, Warburton F, Watson K, Black AK, Greaves MW. Diagnosis and incidence of delayed pressure urticaria in patients with chronic urticaria. *J Am Acad Dermatol*. 1993;29:954–8.
29. Bindslev-Jensen C, Skov PS. Efficacy of omalizumab in delayed pressure urticaria: A case report. *Allergy*. 2010;65:138–9.
30. Magerl M, Staubach P, Altrichter S, Ardelean E, Krause K, Metz M, et al. Effective treatment of therapy-resistant chronic spontaneous urticaria with omalizumab. *J Allergy Clin Immunol*. 2010;126:665–6.
31. Ivianskiy I, Sand C, Thomsen F. Omalizumab for chronic urticaria: A case series and overview of the literature. *Case Rep Dermatol*. 2012;4:19–26.
32. Rodríguez-Rodríguez M, Antolin-Amerigo D, Barbarroja-Escudero J, Sánchez-González MJ, Alvarez-Mon M. Successful treatment of severe delayed pressure angio-edema with omalizumab. *Allergol Immunopathol (Madr)*. 2014;42:78–80.
33. Müller S, Rafei-Shamsabadi D, Technau-Hafsi K, Renzel S, Jakob T. Bullous delayed pressure urticaria responding to omalizumab. *Acta Derm Venereol*. 2016;96:416–7.
34. Kasperska-Zajac A, Jarzab J, Żerdzińska A, Bąk K, Grzanka A. Effective treatment of different phenotypes of chronic urticaria with omalizumab: Case reports and review of literature. *Int J Immunopathol Pharmacol*. 2016;29:320–8.
35. Geller M. Successful treatment of occupational delayed pressure urticaria and angioedema with omalizumab. *Ann Allergy Asthma Immunol*. 2016;116:81–2.
36. Krause K, Ardelean E, Kessler B, Magerl M, Metz M, Siebenhaar F, et al. Antihistamine-resistant urticaria factitia successfully treated with anti-immunoglobulin E therapy. *Allergy*. 2010;65:1494–5.
37. Abajian M, Schoepke N, Altrichter S, Zuberbier T, Maurer M. Physical urticarias and cholinergic urticaria. *Immunol Allergy Clin North Am*. 2014;34:73–88.
38. Bullerkotte U, Wiczorek D, Kapp A, Wedi B. Effective treatment of refractory severe heat urticaria with omalizumab. *Allergy*. 2010;65:931–2.
39. Carballada F, Nuñez R, Martín-Lázaro J, Juárez Y, Castiñeira I, Fernández L, et al. Omalizumab treatment in 2 cases of refractory heat urticaria. *J Investig Allergol Clin Immunol*. 2013;23:519–21.
40. Pressler A, Grosber M, Halle M, Ring J, Brockow K. Failure of omalizumab and successful control with ketotifen in a patient with vibratory angio-oedema. *Clin Exp Dermatol*. 2013;38:151–3.
41. Otto HF, Calabria CW. A case of severe refractory chronic urticaria: A novel method for evaluation and treatment. *Allergy Asthma Proc*. 2009;30:333–7.
42. Metz M, Bergmann P, Zuberbier T, Maurer M. Successful treatment of cholinergic urticaria with anti-immunoglobulin E therapy. *Allergy*. 2008;63:247–9.
43. Sabroe RA. Failure of omalizumab in cholinergic urticaria. *Clin Exp Dermatol*. 2010;122:148–56.
44. Bantz SK, Calderon JG, Dreyfus DH. Successful treatment of refractory cholinergic urticaria with omalizumab in a pediatric patient. *J Allergy Clin Immunol*. 2013;131:AB28.
45. Kutlu A, Tanoglu A, Ozturk S. Healing effects of omalizumab in a patient with cholinergic urticaria associated severe dyspeptic complaints. *Chin Med J (Engl)*. 2015;128:1559–60.
46. Rorie A, Gierer S. A case of aquagenic urticaria successfully treated with omalizumab. *J Allergy Clin Immunol Pract*. 2016;4:547–8.
47. Weller K, Groffik A, Church MK, Hawro T, Krause K, Metz M, et al. Development and validation of the Urticaria Control Test: A patient-reported outcome instrument for assessing urticaria control. *J Allergy Clin Immunol*. 2014;133:1365–72.

48. García-Díez I, Curto-Barredo L, Weller K, Pujol RM, Maurer M, Giménez-Arnau AM. Adaptación transcultural del cuestionario Urticaria Control Test del alemán al castellano. *Actas Dermosifiliogr.* 2015;106:746–52.
49. Magerl M, Borzova E, Giménez-Arnau A, Grattan CE, Lawlor F, Mathelier-Fusade P, et al. The definition and diagnostic testing of physical and cholinergic urticarias-EAACI/GA2LEN/EDF/UNEV consensus panel recommendations. *Allergy.* 2009;64:1715–21.
50. Magerl M, Altrichter S, Borzova E, Giménez-Arnau A, Grattan CE, Lawlor F, et al. The definition, diagnostic testing and management of chronic inducible urticarias - Update and revision of the EAACI/GA(2) LEN/EDF/UNEV 2009 consensus panel recommendations. *Allergy.* 2016;71:780–802.
51. Metz M, Ohanyan T, Church MK, Maurer M. Retreatment with omalizumab results in rapid remission in chronic spontaneous and inducible urticaria. *JAMA Dermatol.* 2014;150:288–90.
52. Multicenter randomized, double-blind, placebo-controlled parallel clinical trial to assess efficacy and safety of omalizumab (Xolair[®]) in a new indication: Cholinergic urticaria. In: *ClinicalTrials.gov* (Internet). Bethesda (MD): National Library of Medicine (US); 2000 [cited 2016 Mar 12]. Available from: <http://clinicaltrials.gov/show/NCT02012387>
53. A two-center, double blind, placebo-controlled study in parallel design to assess the efficacy and safety of 150 and 300 mg omalizumab in subjects with antihistamine-resistant cold contact urticaria (CCU). In: *ClinicalTrials.gov* (Internet). Bethesda (MD): National Library of Medicine (US); 2000 [cited 2016 Mar 20]. Available from: <http://clinicaltrials.gov/show/NCT01580592>
54. Double-blind, placebo-controlled 12-week, parallel-group study with a 6 weeks follow up period to demonstrate efficacy and safety of subcutaneous omalizumab in patients with urticaria factitia refractory to standard treatment. In: *ClinicalTrials.gov* (Internet). Bethesda (MD): National Library of Medicine (US); 2000 [cited 2016 Mar 20]. Available from: <http://clinicaltrials.gov/show/NCT02169115>