

Long-term management of chronic spontaneous urticaria with omalizumab

M. Pinto Gouveia,¹ A. Gameiro,¹ A. Pinho¹ and M. Gonalo^{1,2}

¹Dermatology Department, Coimbra University Hospital Centre, Coimbra, Portugal; and ²Clinic of Dermatology, Faculty of Medicine, University of Coimbra, Coimbra, Portugal

doi:10.1111/ced.13173

Summary

Background. Clinical trials have shown the efficacy of omalizumab efficacy in refractory chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU), but real-life management strategies are lacking.

Aim. To assess the long-term efficacy and safety of omalizumab, and to identify predictive factors and optimum dosage regimens.

Methods. This was a prospective study of 13 patients (11 women, 2 men) with severe CSU [weekly urticaria activity score (UAS7) > 28] resistant to anti-H1 antihistamines. Patients were started on omalizumab 150 mg subcutaneously every 4 weeks. Dose and interval between administrations were adjusted according to clinical response (189 administrations; treatment duration range 2–38 months).

Results. Mean UAS7 was 36.3 ± 5.4 . Of the 13 patients, all had experienced angio-oedema, while in addition, 7 had delayed pressure urticaria (DPU) and 1 had solar urticaria (SU). After omalizumab treatment, 4 (30.8%) of the 13 patients had complete response (CR), and the remaining 8 (61.5%) had partial response. CR was achieved with a dose of 150 mg every 4 ($n = 2$ patients) or 5 ($n = 2$) weeks. One of these patients remained disease-free after stopping treatment. Partial responses were achieved with 150 mg every 4 weeks ($n = 4$) and with 300 mg ($n = 4$) at intervals of 5 weeks ($n = 1$), 4 weeks ($n = 2$) or 3 weeks ($n = 1$). Only one patient (7.7%) did not show significant improvement, despite a dose of 300 mg every 4 weeks. There were no significant differences in epidemiological, clinical and laboratory data between the different response groups. Only two adverse events were observed: one was mild headache and the other was severe angio-oedema and aggravation of urticaria within 6 h of omalizumab administration.

Conclusion. Omalizumab dose and interval between administrations could be individualized for long-term management of CSU.

Correspondence: Dr Miguel Pinto Gouveia, Dermatology Department, Coimbra University Hospital Centre, Av. Bissaya Barreto, Praceta Prof. Mota Pinto, 3000-045 Coimbra, Portugal
E-mail: miguelpgouveia@gmail.com

Conflict of interest: MG Margarida Gonalo participated in Portuguese and international meetings of the Novartis Advisory Board concerning omalizumab use in chronic spontaneous urticaria, and was a speaker at international meetings on urticaria sponsored by Novartis. The other authors declare that they have no conflicts of interest.

Accepted for publication 15 November 2016

Introduction

Chronic urticaria, defined by the presence of weals and angio-oedema for > 6 weeks, is a common disease with an estimated prevalence of 1%.¹ It can be either spontaneous (chronic spontaneous urticaria, CSU) or inducible (chronic inducible urticaria, CIndU), and both types can occur in the same patient.

The EAACI/GA²/LEN/EDF/WAO urticaria guidelines specify nonsedating antihistamines (H1 antihistamines) on a daily basis as the first-line treatment.² As second-

line therapy, up to four times the licensed antihistamine dose may be beneficial, but about 45% of patients still fail to respond.³ In such cases, ciclosporin, montelukast, or omalizumab are recommended as add-on therapies for third-line treatment, although only omalizumab is a licensed option.

Clinical trials (ASTERIA I,⁴ ASTERIA II⁵ and GLACIAL⁶) and many isolated clinical reports have demonstrated that omalizumab is a valid and safe treatment for recalcitrant CSU and many cases of CIndU.^{7–12} Consequently, omalizumab has been approved by the European Medical Agency (EMA) and the US Food and Drug Administration (FDA) for treatment of CSU at dosages of 300 mg (EMA) or 150–300 mg (FDA) every 4 weeks.

Nevertheless, there remain many questions concerning the use of omalizumab, and the literature lacks long-term management strategies. The objectives of our study were to assess the long-term efficacy and safety of omalizumab, and to identify predictive factors and optimum dosage regimens.

Methods

The study was approved by the Commission of Pharmacy and Therapeutics of our hospital and by INFARMED (the authority for medication and health products of the Portuguese national health system), and all patients provided informed consent.

This was a prospective observational study of patients with resistant CSU attending the Urticaria Clinic at our Department of Dermatology (University Hospital of Coimbra, Portugal) who were started on omalizumab. Selected patients were aged > 18 years, with severe CSU [defined as weekly urticaria activity score (UAS7) > 28] unresponsive to second-generation H1-antihistamines at up to four times the licensed dose. CSU diagnosis was based on patient history and clinical observation, and for CIndU, on provocation tests as well.

We analysed patients' demographic data, clinical features of urticaria, laboratory parameters and previous therapies. Skin biopsies and extended laboratory analysis, including C-reactive protein (CRP), total IgE, antinuclear antibodies (ANA) and anticytoplasmic antibodies, and thyroid auto-immunity and function. Occasionally, autologous serum skin test (ASST) was performed to identify predictive factors for response.

Initial omalizumab dosage was 150 mg subcutaneously 4 weeks. In case of no or incomplete response, the dosage was increased to 300 mg every 4 (or if necessary every 3) weeks in cases of relapse

just prior to the next scheduled injection. In patients who achieved complete and sustained response, the dose was tapered or the interval between administrations was extended until the optimum dosage schedule was obtained.

Efficacy was assessed using weekly urticaria activity score (UAS7), and outcomes were classified as complete (UAS7 = 0), partial (UAS7 = 0–28), or no response (UAS7 > 28). In CIndU, efficacy was assessed by subjective clinical response.

Results

Patients

Demographics and baseline clinical and laboratory characteristics are summarized in Table 1. The study enrolled 13 patients (11 women, 2 men; mean age 49.3 ± 16.2 years, range 21–78) with severe CSU. Mean UAS7 was 36.3 ± 5.4 years (range 28–42), average disease duration was 9.4 ± 10.1 years (range 1–36), and average disease onset was 39.8 ± 18.6 years (range 13–68).

Symptoms and previous treatments

All patients had experienced angio-oedema; 7 patients also had concurrent DPU, and 1 had SU. All had previously received > 2 treatments (mean 3.3 ± 0.9 ; range 2–5) other than anti-H1, including mainly short courses of corticosteroids ($n = 13$), ciclosporin ($n = 12$) and montelukast ($n = 8$), but either had been unresponsive or had been forced to discontinue treatment due to adverse events (AEs).

Omalizumab treatment

Overall, there were 189 administrations of omalizumab (mean 14.6 ± 9.5 treatments/patient: range 2–29) during the treatment periods (range 2–38 months). The dosage regimens and treatment responses are summarized in Table 2. We observed positive responses for both CSU and CIndU in 12 (92.3%) patients, of whom 4 (30.8%) showed complete response (CR) and 8 (61.5%) showed partial response (PR). One patient (7.7%) failed to show improvement, and treatment was discontinued after four administrations.

Outcome

In the four patients showing CR, two achieved CR at a dosage of 150 mg every 4 weeks, whereas the other

Table 1 Demographics and baseline characteristics.

Patient	Sex	Age, years	Medical history	Type of urticaria	Histology	Age at disease onset, years	Disease duration, years	Angio-oedema	CRP, mg/dL	IgE, IU/mL	ANA	Auto-immunity	Previous treatments apart from anti-H1	Baseline UAS7
1	F	49	Atopy	CSU	Vasc; Eos	12	36	Yes	< 0.5	26	+	ASST +	Cort, AZA, CY, IVIg, MTX	42
2	F	45	–	CSU + DPU	–	41	4	Yes	3.6	112	+++	–	Cort, AZA, CY, MTX	28
3	M	56	Psoriasis	CSU + DPU	–	54	1.5	Yes	0.81	42	++	ASST –	Cort, CY, LCT	36
4	F	78	–	CSU	Vasc; Eos	61	17	Yes	0.37	57	+++	ASST +	Cort, CY, LCT, IVIg	37
5	F	31	–	CSU + DPU	–	21	10	Yes	< 0.5	29	+	anti-TPO+	Cort, AZA, CY	40
6	F	43	Thyroidectomy	CSU + DPU	Eos	30	13	Yes	0.8	140	++	–	Cort, CY	40
7	F	21	–	CSU	–	21	1	Yes	1.4	50	–	–	Cort, LCT	40
8	F	70	Parotid tumour	CSU	–	68	1.5	Yes	< 0.5	388	–	–	Cort, CY, LCT	42
9	F	38	–	CSU + DPU	–	36	1.8	Yes	2.64	449	–	–	Cort, CY	30
10	F	50	–	CSU + DPU	Eos	47	2.5	Yes	2.06	500	+	Anti-dsDNA+	Cort, H2, CY, LCT	30
11	M	69	DM	CSU	Vasc; Eos	66	3.2	Yes	< 0.5	31	–	–	Cort, CY, LCT	39
12	F	38	DM	CSU + DPU	Eos	20	18	Yes	1.5	669	+	Anti-GADII+	Cort, CY, LCT, Sulfa	40
13	F	53	HT	CSU + SU	–	40	13	Yes	< 0.5	40	+	–	Cort, CY, LCT, UVA/UVB	28
Total: 7		Mean ± SD	Atopy (n = 1); DM (n = 2); HT (n = 1); psoriasis (n = 1); thyroidectomy (n = 1)	CSU; (n = 13); DPU; (n = 7); SU; (n = 1)	Vasc: (n = 3); Eos: (n = 6)	Mean ± SD: 39.8 ± 18.6	Mean ± SD: 9.4 ± 10.1	Total: (n = 13)	Mild elevation (1.5 × and 4 × ULN); moderate elevation (> 4 × ULN); (n = 3)	Mean ± SD: 193.6 ± 224.6	Total: (n = 6)	ASST: (n = 2); anti-GPC: (n = 1); anti-TPO: (n = 1); anti-ds-DNA: (n = 1); anti-GADII: (n = 1)	Cort (n = 13); CY (n = 12); LCT (n = 8); AZA (n = 3); IVIg (n = 2); MTX (n = 2); anti-H2; Sulfa (n = 1); UVA/UVB (n = 1)	Mean ± SD: 36.3 ± 5.4

ANA, anti-nuclear and anti-cytoplasm antibodies; anti-GADII, anti-glutamic acid decarboxylase antibodies; anti-GPC, anti-gastric parietal cell antibodies; anti-TPO, anti-thyroid peroxidase antibodies; ASST, autologous serum skin test; AZA, azathioprine; Cort, corticosteroids; CSU, chronic spontaneous urticaria; CRP, C-reactive protein (normal value 0.5 mg/dL); DM, diabetes mellitus; DPU, delayed pressure urticaria; dsDNA, double-stranded DNA; Eos, presence of a significant number of eosinophils in the dermal infiltrate; H2, anti-H2; HT, hypertension; IgE, total serum IgE (normal value < 100 IU/mL); IVIg, intravenous immunoglobulin; LCT, leucotriene antagonists; MTX, methotrexate; SU, solar urticaria; Sulfa, sulfasalazine; ULN, upper limit of normal; Vasc, vascular aggression.

Table 2 Dosage regimens and treatment responses.

Patient	Treat-ments, <i>n</i>	Doses, mg	Interval, weeks	Optimum dosage	UAS7				Physical urticaria	Treatments to CR, <i>n</i>	Comments
					After first week	At 3 months	At 6 months	Final outcome			
1	4	150, 300	4	–	32	34	–	NR	–	–	4 months after stopping treatment, urticaria entered remission; maintained for follow-up of 30 months
2	29	150	4–6	150 mg every 5 weeks	0	0	0	CR	Remission	1	Response 48 h after first administration; sporadic lesions associated with flu-like syndrome
3	28	150	4–5	150 mg every 5 weeks	7	0	0	CR	Remission	1	Relapse after stopping at 12th administration; response regained with 150 mg every 5 weeks; rare sporadic and mild lesions
4	21	75, 150	4–6	150 mg every 4 weeks	8	0	0	CR	–	3	Relapse after stopping at 10th administration; response regained with 150 mg every 4 weeks
5	24	150, 300, 450	3–4	300 mg every 3 weeks	3	8	12	PR	Less intense	–	Irregular response (UAS7 = 0–28); occasional severe episodes with angio-oedema under treatment; rescue treatment with corticosteroids needed; response regained after one dose of 450 mg
6	25	150, 300	3–4	300 mg every 4 weeks	10	7	11	PR	Less intense	–	Tolerated 4-week interval (UAS7 = 0–12) but periodically severe lesions prior to next administration; occasional need for anti-H1.
7	9	150, 300	4	150 mg every 4 weeks	3	7	0	CR	–	6	Rescue medication initially needed; medication discontinued at ninth administration with disease remission
8	11	150, 300	3–4	300 mg every 4 weeks	42	9	14	PR	–	–	300 mg showed better response than 150 mg but still UAS7 = 4–10; 3-week interval was not better than 4 weeks; regular need for anti-H1.
9	12	150	4	150 mg every 4 weeks	6	6	8	PR	Remission	–	UAS7 = 0–10 between administrations

Table 2. continued

Patient	Treat-ments, <i>n</i>	Doses, mg	Interval, weeks	Optimum dosage	UAS7				Physical urticaria	Treatments to CR, <i>n</i>	Comments
					After first week	At 3 months	At 6 months	Final outcome			
10	9	150	4	150 mg every 4 weeks	10	4	3	PR	Less intense	–	UAS7 = 0–10 between administrations; lesions associated with psychological stress
11	8	150, 300	5	300 mg every 5 weeks	25	6	4	PR	–	–	300 mg greatly improved UAS7 = 0–6; shorter intervals not better than 5-week interval
12	7	150	4	150 mg every 4 weeks	19	0	4	PR	Remission	–	Several weeks without lesions, but occasionally moderate intensity urticaria (UAS7 = 0–12) with angio-oedema.
13	2	150	4	150 mg every 4 weeks	17	–	–	PR	Tolerates sunlight with no lesions	–	Great improvement in quality of life; after second administration, tolerates sun; UAS7 = 1–7.
Total: 189 Mean ± SD: 14.6 ± 9.5					CR: (<i>n</i> = 4) PR: (<i>n</i> = 8) NR: (<i>n</i> = 1)						
150 mg every 5 weeks (<i>n</i> = 2); 150 mg every 4 weeks: (<i>n</i> = 8); 300 mg every 5 weeks: (<i>n</i> = 1); 300 mg every 4 weeks: (<i>n</i> = 2); 300 mg every 3 weeks: (<i>n</i> = 1)											

CR, complete response (UAS7 = 0); PR, partial response (UAS7 = 0–28); NR, no response (UAS7 > 28); UAS7, weekly urticaria activity score.

two tolerated the interval being lengthened to 5 weeks, but not to 6 weeks. In one patient, dosage was reduced to 75 mg every 4 weeks, but recurrence of urticaria ensued.

Of the four patients who had CR, two needed only one administration (with CR occurring within 48 h in one case), while the remaining two had CR after three and six administrations, respectively. After the first administration, UAS7 decreased to a mean value of 29.3 ± 6.1 (range 22.5–37) for these four patients, and medication was discontinued in three patients when CR was sustained, after 9, 10 and 12 administrations, respectively. Subsequently, only one patient remained disease-free, as relapse ensued in the other two, but similar CR recurred in these two patients upon re-introduction of the previous dosage. Overall, the urticaria was under control in three patients following 21, 28 and 29 administrations, respectively, even though all three chose to discontinue all their other CSU medication.

Among the patients with PR ($n = 8$), four responded to 150 mg every 4 weeks, whereas the other four required 300 mg at intervals of 5 weeks ($n = 1$), 4 weeks ($n = 2$) or 3 weeks ($n = 1$). In this group of patients, UAS7 decreased to this mean value of 19.6 ± 11.5 (range 0–37) after the first administration. In one patient, the condition was well controlled (UAS7=0–6) after eight administrations at 300 mg every 5 weeks. Five patients with spontaneous urticaria had mild symptoms (UAS7 <16, with occasional need for anti-H1) and five patients with physical urticaria (four delayed pressure and one SU) improved on dosages of 300 mg every 4 weeks ($n = 1$) and 150 mg every 4 weeks ($n = 4$). In two patients, the disease was partially controlled with 300 mg every 3 or 4 weeks, but both experienced short periods of unexplained aggravation for 1 or 2 months (UAS7 > 20), followed by PR thereafter, and both required rescue medication with very short courses of oral, corticosteroids and anti-H1. In one of these patients a single dose increase of omalizumab to 450 mg was effective in re-establishing control of CSU.

One patient showed no response to omalizumab after four administrations, even at 300 mg (UAS7 > 28 during treatment); however, 4 months after stopping the drug, her urticaria (which had been constant for 36 years) resolved, and she remained completely clear during a follow-up of 30 months.

Epidemiological data

There were no significant differences in sex or age between patients with differing outcomes. The patient

with longest disease duration (36 years) was the non-responder to omalizumab, but other patients with long-established disease responded positively (including CR) and there was no significant difference in disease duration between patients with PR and those with CR (4.9 ± 14.4 years and 5.0 ± 23.7 , respectively).

All patients had severe disease at baseline, with no significant differences in UAS7 (UAS7: 42 ± 0 in no response; 36.1 ± 5.7 in PR; 35.3 ± 5.1 in CR). No significant differences were found in baseline CRP or IgE between the different response groups.

Serological evidence of autoimmunity

In the CR group, all four patients were positive for ANAs and additionally, one had anti-thyroid peroxidase antibodies (anti-TPO) and one had a positive ASST result, while in the PR group, three had ANAs, one had anti-double-stranded DNA antibodies and one had anti-glutamic acid decarboxylase II antibodies. The patient who showed no response was positive for ASST, antigastric parietal cell antibodies and anti-TPO. Eosinophils in infiltrate were predominantly found in the PR group ($n = 4$), but also in the CR group ($n = 1$) and in the nonresponse patient. Histological findings showed minor vascular aggression in the non-response patient, but also in one patient with PR and one with CR.

Adverse events

We observed only two AEs possibly associated with omalizumab. The patient with no response reported a mild headache after the second administration of omalizumab 300 mg. In addition, one of the PR group reported aggravation of urticaria with malaise and fever approximately 6–12 h after receiving omalizumab 300 mg, but symptoms cleared in 24–48 h and did not recur after the following administration, which was performed on an inpatient basis.

Discussion

This was an observational study, limited by the small sample size and variable number of treatments, but with treatment periods of > 3 years, which is longer than most previous reports. We observed long-lasting improvement in CSU at rates similar to clinical trials lasting a few months^{4–6} and to other retrospective studies.^{8,11} We also observed symptomatic relief in delayed pressure urticaria and SU in patients who presented these types of CIndU associated with their CSU.

In agreement with our results, DPU and symptomatic dermographism have been reported to be particularly sensitive to omalizumab,⁷ and the drug may also be a potentially interesting treatment for SU.¹²

With the limited number of patients in our study, we did not find any clinical or laboratory factors predicting response to omalizumab treatment. Improvement in disease control seemed to be independent of age, sex, previous therapies, disease severity (baseline UAS7), CRP, pretreatment IgE level, histopathological findings and serological evidence of autoimmunity.

According to previous studies, some patients treated with omalizumab experience rapid onset of symptom control, as soon as 24–48 h after start of treatment (rapid responders),^{7,9,13} which cannot be explained by a reduction in density of IgE receptors, but could be via removal of soluble IgE and auto-allergen sequestration.¹⁴ Furthermore, in our study, we found that initial response did not correlate with long-term response, as there was no significant difference in immediate improvement (i.e. decrease in UAS7 scores) between CR and PR.

This long-term experience suggests that, despite providing effective symptom control or relief, omalizumab does not alter the natural course of the disease, which is characterized by spontaneous remission and exacerbation. Patients who discontinued treatment developed UAS7 scores similar to their baseline, which accords with the findings of previous studies.^{5,13} Only one patient had disease remission after sustained CR, but it is not certain this was due to omalizumab rather than to spontaneous resolution. Similarly, we observed that symptoms worsened at suboptimal dosages for each patient, but response was restored when the previous dosage was reinstated. These findings support those of other studies,^{8,10} confirming both on-demand and regular treatment as viable management options.

In this study, we found that omalizumab was capable of controlling symptoms for long periods; however, patients cases displayed marked fluctuations in response despite being maintained on the same dose, and such an unexplained fluctuation has not been described in previous reports. This response profile seems not to be due to loss of drug efficacy, as the patients responded to further administrations, but rather to natural exacerbations of the disease, which may occasionally require higher doses.

Omalizumab also has a good safety profile, with the majority of AEs being mild or moderate.^{4,6} The symptoms following omalizumab administration, reported by one patient with angio-oedema and urticaria aggravation, have been described and eventually misattributed

to anaphylaxis.¹⁵ Nevertheless, contrary to anaphylaxis, the symptoms in the present study were slow to develop and did not repeat on subsequent exposure, therefore were attributed mainly to aggravation of the disease just prior to the next dose of omalizumab taking effect.

Currently, there is no detailed information on optimum dosages of omalizumab for urticaria. We had success with the following treatment schedules: 150 mg every 5 weeks; 150 mg every 4 weeks; 300 mg every 5 weeks; 300 mg every 4 weeks; and 300 mg every 3 weeks.

Although clinical trials point to 300 mg every 4 weeks,⁵ and some recent studies even advocate 300 mg every 2 weeks,¹⁶ we consider it reasonable to start with 150 mg every 4 weeks and to increase the dose if patients do not respond, as reported in another real-life study.¹⁷ In practice, some patients may even benefit from dosages greater than 300 mg every 3 weeks,^{11,18} as observed in one of our patients. Dose intervals can also be adjusted, making them more frequent if urticaria activity increases just prior to the next administration, or extending the interval to achieve the minimum effective dosage in cases where CR is achieved. Although not usually reported, throughout treatment, the dosage may eventually require adjustment due to disease worsening. Treatment should then be maintained until symptoms are controlled, after which discontinuations should be attempted since spontaneous remissions may occur.

In our experience, omalizumab might provide an effective option for long-term management of severe CSU and some CIndU. Our results also suggest that dose and administration interval should be individualized in order to improve each patient's response. However, further studies are required to investigate the need for individualization and the best way to make these adjustments.

What's already known about this topic?

- Omalizumab is a valid and safe treatment for recalcitrant chronic spontaneous urticaria and many cases of chronic inducible urticaria.

What does this study add?

- Individualized omalizumab dose and interval might be beneficial for long-term management of CSU.

• Throughout treatment, the dose and interval may eventually require adjustment due to disease worsening.

References

- 1 Powell RJ, Du Toit GL, Siddique N *et al.* BSACI guidelines for the management of chronic urticaria and angio-oedema. *Clin Exp Allergy* 2007; **37**: 631–50.
- 2 Zuberbier T, Aberer W, Asero R *et al.* The EAACI/GA(2) LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy* 2014; **69**: 868–87.
- 3 Staevska M, Popov TA, Kralimarkova T *et al.* The effectiveness of levocetirizine and desloratadine in up to 4 times conventional doses in difficult-to-treat urticaria. *J Allergy Clin Immunol* 2010; **125**: 676–82.
- 4 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**: 67–75.
- 5 Maurer M, Rosen K, Hsieh HJ *et al.* Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med* 2013; **368**: 924–35.
- 6 Kaplan A, Ledford D, Ashby M *et al.* Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. *J Allergy Clin Immunol* 2013; **132**: 101–9.
- 7 Metz M, Ohanian T, Church MK *et al.* 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.
- 8 Sussman G, Hebert J, Barron C *et al.* Real-life experiences with omalizumab for the treatment of chronic urticaria. *Ann Allergy Asthma Immunol* 2014; **112**: 170–4.
- 9 Le Moing A, Becourt C, Pape E *et al.* Effective treatment of idiopathic chronic cold urticaria with omalizumab: report of 3 cases. *J Am Acad Dermatol* 2013; **69**: e99–101.
- 10 Uysal P, Eller E, Mortz CG *et al.* An algorithm for treating chronic urticaria with omalizumab: dose interval should be individualized. *J Allergy Clin Immunol* 2014; **133**: 914–15.e2.
- 11 Labrador-Horrillo M, Valero A, Velasco M *et al.* Efficacy of omalizumab in chronic spontaneous urticaria refractory to conventional therapy: analysis of 110 patients in real-life practice. *Expert Opin Biol Ther* 2013; **13**: 1225–8.
- 12 Aubin F, Avenel-Audran M, Jeanmougin M *et al.* Omalizumab in patients with severe and refractory solar urticaria: A phase II multicentric study. *J Am Acad Dermatol* 2016; **74**: 574–5.
- 13 Silva PM, Costa AC, Mendes A *et al.* Long-term efficacy of omalizumab in seven patients with treatment-resistant chronic spontaneous urticaria. *Allergol Immunopathol (Madr)* 2015; **43**: 168–73.
- 14 Chang TW, Chen C, Lin CJ *et al.* The potential pharmacologic mechanisms of omalizumab in patients with chronic spontaneous urticaria. *J Allergy Clin Immunol* 2015; **135**: 337–42.
- 15 Savic S, Marsland A, McKay D *et al.* Retrospective case note review of chronic spontaneous urticaria outcomes and adverse effects in patients treated with omalizumab or ciclosporin in UK secondary care. *Allergy Asthma Clin Immunol* 2015; **11**: 21.
- 16 Clark JJ, Secrest AM, Hull CM *et al.* The effect of omalizumab dosing and frequency in chronic idiopathic urticaria: Retrospective chart review. *J Am Acad Dermatol* 2016; **74**: 1274–6.
- 17 Ensina LF, Valle SO, Juliani AP *et al.* Omalizumab in chronic spontaneous urticaria: a Brazilian real-life experience. *Int Arch Allergy Immunol* 2016; **169**: 121–4.
- 18 Gimenez-Arnau AM, Toubi E, Marsland AM *et al.* Clinical management of urticaria using omalizumab: the first licensed biological therapy available for chronic spontaneous urticaria. *J Eur Acad Dermatol Venereol* 2016; **30**(Suppl 5): 25–32.