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Original Article

Treatment and retreatment with omalizumab in chronic spontaneous urticaria: Real life experience with twenty-five patients

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ANA, anti-nuclear antibody;

CMS, concomitant medication score;

CRP, C-reactive protein; CSU, chronic

spontaneous urticaria; ESR, erythrocyte

sedimentation rate; Tg, thyroglobulin;

TPO, thyroid peroxidase; UAS, urticaria

activity score

ABSTRACT

Background: Previous data have shown the high efficacy of omalizumab in chronic spontaneous urticaria (CSU). However, factors that may be effective on the response to therapy, relapse rates after drug discontinuation, and efficacy of retreatment remain unclear. This study aimed to determine the efficacy of omalizumab in CSU refractory to conventional therapy, to identify possible factors affecting treatment response and relapse, and also to evaluate the efficacy of retreatment on relapsed disease.

Methods: The data of CSU patients treated with 300 mg/month omalizumab for at least 3 months were retrospectively analyzed. In order to evaluate the efficacy of treatment and retreatment, baseline and follow-up concomitant medication score (CMS) and urticaria activity score (UAS) were calculated. Possible factors affecting treatment response and relapse were identified.

Results: Twenty-five patients were included. The median duration of omalizumab therapy was 6 (6–12) months. Of the patients with baseline UAS 6 (5.5–6) and CMS 13 (10–15), 8 (32%) had complete response (UAS = 0) and 2 (8%) were non-responders after 3 months of therapy. None of the complete responders were positive for IgG-anti-TPO. After discontinuation of omalizumab therapy, 11 (61%) patients experienced relapse and 10 of them received retreatment with omalizumab. Half of the patients had complete response, and half had partial response (UAS = 1–4) after retreatment. No treatment related adverse events were documented.

Conclusions: Omalizumab has high efficacy in both the treatment and retreatment of CSU; however, relapse rates after discontinuation are high. Autoimmune markers may be helpful in predicting treatment response and relapse.

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Introduction

Chronic spontaneous urticaria (formerly called chronic idiopathic urticaria) (CSU) is a disease characterized by recurrent itching, wheals and/or angioedema that lasts for more than 6 weeks in the absence of a precipitating external factor. Since the disease may sometimes last for years,¹ it negatively affects the patients' quality of life and may cause socioeconomical problems. Non-sedating H1-antihistamines are the drug of choice for the first-line treatment and up to a four-fold dose increase is recommended if there is no improvement.² However, high dose antihistamines are ineffective in approximately half of the patients,³ and in these cases leukotriene receptor antagonists, cyclosporine A, H2-

antihistamines or systemic glucocorticoid combinations are also used in addition to H1-antihistamines.^{2,4} Recently, studies on the high efficacy of omalizumab in patients that are refractory to conventional therapy have been reported. Use of omalizumab in CSU patients was approved both in the USA and the EU in 2014 and it became the first drug approved for use in patients refractory to H1-antihistamines.^{5,6}

Omalizumab (Xolair[®], Novartis, Switzerland) is a monoclonal humanized IgG antibody that attaches to unbound IgE and prevents its attachment with the high or low-affinity receptors (FcεRI and FcεRII) on mast cells, basophils, eosinophils and lymphocytes. Thus it causes a decrease in free IgE levels and a down-regulation of receptors on cell membranes.⁷ Its mechanism of action in CSU is not fully understood. As a modification of allergic response is not aimed at it is in asthma, a fixed dose of the therapy is recommended. Even though the doses may differ among centers, the evidence-based highest efficient dose is 300 mg/4 weeks.^{8,9}

Most previous studies including real life data are based on drug efficacy. Knowledge on the optimal duration of treatment and

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management after therapy discontinuation are not clear. Data on the possible effective factors on treatment response, relapse rates and retreatment efficacy are very limited. Thus in this study we aimed to establish efficacy of omalizumab in CSU refractory to conventional therapy, to identify factors that may be effective on therapeutic response and relapse, and to evaluate the efficacy of retreatment in relapsed cases.

Methods

This single-centered retrospective study evaluated the data of patients diagnosed with CSU that were treated with omalizumab from 2013 to 2016. The center is located within the university hospital and it is the only reference allergy-clinical immunology clinic in the city and the surrounding region.

Patients who were treated with omalizumab without any break for at least 3 months were included. Omalizumab was administered 300 mg/4 weeks to every patient at the outpatient clinic under surveillance. Concomitant medications were adjusted at monthly controls according to the clinical response. The baseline and follow-up concomitant medication scores (CMS) of patients were calculated retrospectively. Symptom scores were obtained from patient charts.

The CMS of patients were calculated in a similar way to previous studies: antihistamines (regular dose, 2 points; 4 times the regular dose, 8 points), oral glucocorticoids (<11 mg, 5 points; 11–25 mg, 10 points; >25 mg, 15 points), cyclosporine 3.0 mg/kg (8 points), hydroxychloroquine (6 points) and montelukast (2 points).¹⁰ Therapeutic efficacy was evaluated by urticaria activity score (UAS). According to this, at their monthly follow-up, patients were asked to score their symptoms categorically as wheals (none: 0 points, <20 wheals: 1 point, 20–50 wheals: 2 points, >50 wheals: 3 points) and pruritus (none: 0 point, mild: 1 point, moderate: 2 points, severe: 3 points), making up 0–6 points in total.^{2,11}

According to the responses to omalizumab, patients were grouped as follows: complete responders (UAS = 0 and no increase in symptoms during follow-up), partial responders (UAS = 1–4), and non-responders (UAS ≥ 5 or gradually increasing UAS at follow-up). The patient characteristics of the complete and partial control groups were compared.

In all patients with complete or partial response, discontinuation of omalizumab was tried at a time after 6 months. Retreatment was initiated if the recurred disease couldn't be controlled with concomitant medications. The characteristics of patients who were symptomatic and asymptomatic after discontinuation of omalizumab were compared. At the time of the study, 4 patients had not completed their 6 month-therapy and 1 patient was resistant to all therapies. Therapy discontinuation was not tried in these 5 patients and they were excluded from that comparison. Study design is summarized in Figure 1. Data related to other possible triggers and comorbidities such as serum total IgE, phadiatop and sIgE for food mix, vitamin B12, thyroid autoantibodies, eosinophil counts, rheumatological markers, fecal *Helicobacter pylori* antigen, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), anti-endomysium and anti-gliadin autoantibodies were recorded retrospectively. Possible effects of these variables on clinical response were evaluated.

Statistical analysis

Data were analyzed using SPSS 17.0 (SPSS, Inc., Chicago, IL, USA). Parameters were expressed as median (25–75 interquartile range; IQR) unless stated otherwise. Chi-square, Mann–Whitney U and repeated measures ANOVA tests were used for comparing variables.

Table 1
Patient characteristics.

Variables (N = 25)	Median (IQR)
Age	39 (31.8–49)
Female gender; n (%)	18 (72)
Comorbidities; n (%)	
Hypothyroidism	5 (20)
Asthma	4 (16)
Diabetes mellitus	2 (8)
Rheumatologic disorders	1 (4)
CRP; mg/L	3.4 (3.3–11.2)
Eosinophil count; %	1.7 (0.9–2.8)
Eosinophil count; cells/mL	130 (79–195)
Total IgE; IU/mL	226 (56–340)
ESR; mm/h	10 (4–20)
ANA positivity; n (%)	6 (24)
Phadiatop positivity; n (%)	9 (36)
Food mix positivity; n (%)	1 (4)
IgG anti-TPO positivity; n (%)	7 (28)
IgG anti-Tg positivity; n (%)	3 (12)
Anti-endomysium positivity; n (n = 10)	0
AGA-IgG positivity; n (n = 10)	1
AGA-IgA positivity; n (n = 10)	1
Fecal <i>H. Pylori</i> antigen positivity; n (n = 21)	11

IQR, Interquartile range; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ANA, Anti-nuclear antibody; TPO, Thyroid peroxidase; Tg, Thyroglobulin; AGA, Anti-gliadin antibody.

Results

Patient characteristics are listed in Table 1. The majority of patients were female (72%), young and had few comorbidities. IgE levels prior to therapy were slightly high. Seven patients (28%) were positive for anti thyroid peroxidase (IgG-anti-TPO) and 3 (12%) were positive for anti thyroglobulin (anti-Tg) autoantibodies. Six patients (24%) had anti-nuclear antibody (ANA), one of them also had SS-A and SS-B positivity. Nine patients (36%) were positive for at least one of ANA, IgG-anti-TPO and IgG-anti-Tg antibodies. Fecal *H. pylori* antigen was positive in 11 patients.

Median time from appearance of urticaria symptoms to omalizumab therapy was 44 (15–72) months. Baseline median CMS was 13 (10–15) and UAS was 6 (5.5–6). At the third and sixth months CMS and UAS had decreased to 2 (0–6) and 1 (0–1), respectively (Table 2).

During the first three months, all patients had improved CMS and UAS. After three months, 2 patients experienced worsened symptoms and increased need for concomitant medication. They were accepted as non-responders and omalizumab therapy was discontinued after the 6th month and 10th month. One patient's prior systemic steroid and cyclosporine treatments were stopped until the 3rd month, but systemic steroid therapy was restarted due to symptomatic worsening. However, since the symptoms were still better than they were before omalizumab treatment, she was accepted as a partial-responder and continued omalizumab treatment. The data of these three patients are given in Table 3.

Fourteen (58%) patients had complete response at the end of their therapies. At the 3rd month, 8 patients (32%) had complete response. None of these complete-responders had IgG-anti-TPO autoantibody positivity when compared to partial-responders ($p = 0.058$). The time from first symptoms to omalizumab therapy was also markedly shorter in complete responders; however, the difference was not statistically significant [22 (7–51) months and 47 (18–80) months, respectively, $p = 0.12$]. Relapse ratios did not differ significantly between these two groups ($p = 0.63$) (Table 4). Fecal *H. pylori* antigen, phadiatop, ANA and IgG anti-Tg positivity, and CRP levels also did not differ between these groups. Non-responders were not included in statistical analyses since the number of patients was very low ($n = 2$).

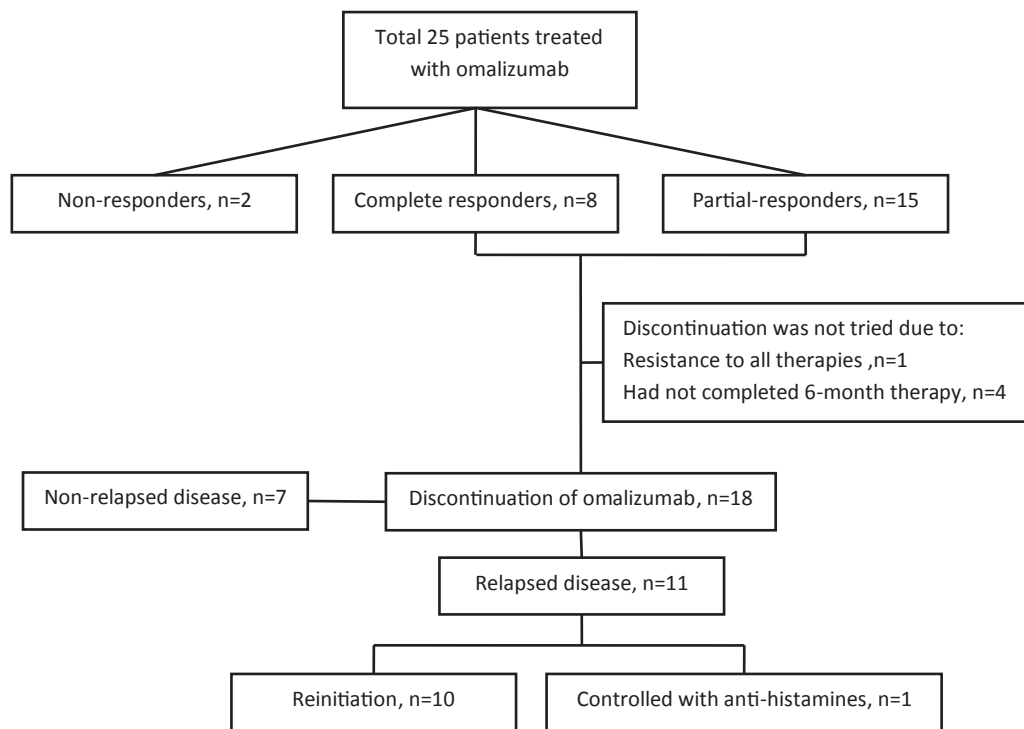


Fig. 1. Scheme of study design.

Table 2
Therapy management and overall responses to omalizumab treatment.

Variables	Median (IQR)				
Initial therapy period; months	6 (6–12)				
Discontinuation of omalizumab; n (%)	20 (80)				
Relapse after omalizumab discontinuation; n (%), n = 18 [†]	11 (61)				
Retreatment with omalizumab; n (%), n = 18 [†]	10 (56)				
	Baseline n = 25	3rd month n = 25	6th month n = 21	9th month n = 10	p
CMS	13 (10–15)	2 (0–6)	2 (0–6)	3 (0–7.3)	<0.001
UAS	6 (5.5–6)	1 (0–2)	1 (0–2)	1 (0–1.3)	<0.001

IQR, Interquartile range; CMS, Concomitant medication score; UAS, Urticaria activity score.

[†] Non-responders are not included.

Eleven patients experienced relapse and omalizumab was restarted in 10 of them since other medications were not effective enough. After the reinitiation of omalizumab, 5 of these patients had complete response and 5 had partial response (therapy duration changing between 1 and 5 months). Seven patients achieved remission after discontinuation. Time from the last omalizumab dose was a minimum of 8 weeks and a maximum of 18 months for these patients. When relapsed and non-relapsed patients were compared, ANA was negative in all non-relapsed patients but 4 of 11 patients with relapse had positive ANA titers ($p = 0.12$) (Table 5). Distribution of genders, CRP levels, and fecal *H. pylori* antigen and phadiatop positivity were found similar between relapsed and non-relapsed patients. Omalizumab was well-tolerated in all patients and no drug induced adverse effects were recorded.

Discussion

This study shows the high efficacy and tolerability of omalizumab therapy in CSU patients refractory to combinations of high dose non-sedating H1-antihistamines combined with montelukast,

systemic steroids or cyclosporine. Fifty-eight percent of patients had complete response at the end of their therapies. After therapy was discontinued at the 6th month, 11 patients (61%) experienced relapse and 10 of them (91%) received retreatment with omalizumab since they had become refractory to other medications. After reinitiation, half of these patients had complete and half had partial response in 1–5 months.

The mechanism of action of omalizumab in CSU remains unclear. Even though a rapid clinical response from the very first day of administration has been shown, relapses after discontinuation suggest that the drug acts through a different mechanism than modifying the underlying disease.¹² One of the possible mechanisms is the presence of autoimmunity in these patients. An IgG against FcεRI or IgE, IgE against TPO or IgE against an unidentified autoantigen are considered to be effective in the pathogenesis.¹³ Nevertheless, at present no autoantibody alone can explain the whole pathogenesis. Even though the mechanism of action is not clear, the clinical efficacy of the drug in CSU has been shown in several placebo-controlled studies and studies presenting real life data.^{9,10,14–17} Similarly, in our study, 32% of patients had complete and 60% had partial-response at the 3rd month. Only 2 patients were non-responders to omalizumab. A total of 513 flacons of the drug were administered and no drug-related systemic adverse effect was reported. Two previous studies on the therapeutic responses of CSU patients reported complete response rates at the end of treatment as 35.7% (5/14 patients) and 61.5% (8/13 patients).^{14,16} In a study of 68 CSU patients, Sussman *et al.* found that the complete response rate at any time during treatment was 69%. In the same study, treatment was discontinued in 5 patients since they became refractory to therapy.¹⁰ Our data show the high efficacy of 300 mg/month omalizumab in CSU. Since its mechanism of action in CSU is not fully understood, which group of patients would most likely have a better response cannot be predicted. When evaluating factors on treatment response, Altrichter *et al.* found that patients with IgE-anti-TPO autoantibodies responded

Table 3
Concomitant medications and treatment responses of non-responders (Number 1 and 3), and a partial responder patient who had high resistance to all therapies (Number 2).

	Baseline	3	6	9	10	12	15	
1	UAS 6 CMS 13 CM AH 4 × 1, DKT 4 mg	5 9 AH 2 × 1, DKT 4 mg	3 11 AH 2 × 1, ML, DKT 4 mg	NA NA NA	5 15 AH 4 × 1, ML, DKT 4 mg			Early clinical response was lost after 9th month. Omalizumab was discontinued and cyclosporine was prescribed.
2	UAS 6 CMS 18 CM AH 4 × 1, ML, CYC	2 4 AH 1 × 1, ML	3 8 AH 4 × 1	2 11 AH 3 × 1, MPRD 8 mg	2 11 AH 3 × 1, MPRD 8 mg	2 13 AH 3 × 1, ML, MPRD 8 mg	2 11 AH 2 × 1, ML, MPRD 4 mg	Omalizumab was continued because of previous non responsiveness to high dose systemic steroid and cyclosporine therapies.
3	UAS 4 CMS 8 CM AH 4 × 1	3 6 AH 3 × 1	5 8 AH 4 × 1					Steroid and cyclosporine were not prescribed previously due to patient's age (60), DM and HT history. Initially partial responder to omalizumab, then became non-responder and therapy discontinued with joint decision.

UAS, Urticaria activity score; CMS, Concomitant medication score; CM, Concomitant medications (AH, antihistamines; ML, montelukast; MPRD, methyl prednisolone; DKT, deflazacort; CYC, cyclosporine); HT, Hypertension; DM, Diabetes mellitus.

Table 4
Comparison of patients with different responses after 3 months of omalizumab therapy.

Variables	Partial-responders n = 15	Complete-responders n = 8	p
Female gender; n (%)	11 (73)	5 (63)	0.59
Age	38 (30–48)	40.5 (34–54)	0.52
Eosinophil count; cells/mL	130 (100–190)	79 (60–185)	0.29
Total IgE; IU/mL	134.5 (38–275)	245 (91–393)	0.36
IgG anti-TPO positivity; n (%)	6 (40)	0	0.058
Time from diagnosis to omalizumab therapy; months	47 (18–80)	22 (7–51)	0.12
Duration of initial therapy; months	8 (6–12)	6 (3.8–8.3)	0.2
Baseline CMS	13 (10–15)	13 (10.3–13)	0.45
3rd month CMS	4 (2–6)	0	<0.001
Baseline UAS	6	6 (5.3–6)	0.75
3rd month UAS	2 (1–2.3)	0	<0.001
Increased/stable symptoms after discontinuation of therapy (n = 18)	8/4	3/3	0.63

TPO, Thyroid peroxidase; CMS, Concomitant medication score; UAS, Urticaria activity score.

better to omalizumab and these patients also had markedly high levels of IgG-anti-TPO antibodies.¹⁸ This study also showed IgE-anti-TPO positivity in 54% of CSU patients. Thirty-six percent of our patients were also positive for at least one type of IgG type autoantibody. Interestingly, none of the complete responders had IgG-anti-TPO positivity. Our results do not corroborate those of Altricher *et al.*; however, since our sample size was too small to prove this hypothesis, future studies are needed to assess whether this subset of patients has better response to omalizumab.

The optimum duration of therapy and management of recurrent symptoms after discontinuation of omalizumab are still on debate. Previous studies reported a significant increase in symptoms after therapy.^{9,14,19} In a study in which patients were followed up after omalizumab discontinuation, symptom scores increased up to 40 weeks but they never reached the baseline values.¹⁹ In another study which evaluated omalizumab retreatment efficacy, which only included omalizumab reinitiated patients, Metz *et al.* demonstrated early relapse (2–8 weeks) in 23 and late relapse (4–7 months) in 2 of 25 CSU patients whose treatment was discontinued due to complete response.²⁰ All of these patients had a rapid and complete response from the very first dose after reinitiation. In a

Table 5
Comparison of relapsed and non-relapsed patients after omalizumab discontinuation.

Variables	Non-relapsed n = 7	Relapsed n = 11	p
Age	39 (33–43)	38 (31–47)	0.82
Eosinophil count; cells/mL	170 (120–190)	160 (68–233)	0.68
Total IgE; IU/mL	101 (37–308)	229 (54–371)	0.62
IgG anti-TPO positivity; n (%)	2 (29)	4 (36)	1
ANA positivity; n (%)	0	4 (36)	0.12
Time from diagnosis to omalizumab therapy; months	43 (12–53)	68 (17–88)	0.26
Duration of initial therapy; months	6 (6–9)	8.5 (6–14)	0.32
Baseline CMS	11 (10–13)	13 (10–13)	0.43
3rd month CMS	2 (0–4)	3 (0.5–5.5)	0.64
Baseline UAS	6 (5–6)	6	0.62
3rd month UAS	1 (0–2)	2 (0–3)	0.33

TPO, Thyroid peroxidase; ANA, Anti-nuclear antibody; CMS, Concomitant medication score; UAS, Urticaria activity score.

series of 51 CSU patients by the same researchers, after omalizumab therapy was discontinued, 12% of patients achieved complete remission in the 4–16 months follow-up period.²¹ In our study, after omalizumab discontinuation, 11 patients (61%) reported worsened symptoms and 10 of them had to be retreated with omalizumab since they were refractory to high dose H1-antihistamines and steroids. There are two possible explanations for the difference between our and Metz *et al.*'s relapse ratios. First of all, our study included an isolated patient group with CSU, whereas the previous study included both CSU and inducible urticaria patients. Secondly, in our study, at least 8 weeks had passed from the last dose of omalizumab in symptom-free patients; even so, any symptom that may develop during the long-term follow-up of these patients may change the results. Thus we may suggest that in this group of patients, the early symptom-free period may be misleading and long-term follow-up is needed.

Since omalizumab acts through IgE, better response rates can be expected in patients with higher baseline total IgE levels. Kessel *et al.* showed a significant association between increased total IgE levels and disease severity.²² Also, free IgE decrease was shown to be correlated with symptomatic reduction under omalizumab therapy.¹³ In our study, total IgE levels of complete responders and relapsed patients were almost two-fold higher than partial responders and non-relapsed patients, respectively, but, this

difference was not statistically significant. We ascribed this to our study's small sample.

Interestingly, some partial-responders had complete response after reinitiation, while some complete-responders had partial response later. Based on these data, despite our small sample size, we may argue that reinitiation of omalizumab may be a safe option with variable efficacy.

Finally, all non-relapsed patients were negative for ANA, but not for IgG-anti-TPO. This finding was not statistically significant when compared with relapsed patients; however, it may have clinical importance. In a large population study which compares ANA(+) and ANA(−) CSU patients, ANA(+) patients were found to be more refractory to antihistamine therapy and needed four-fold standard licensed dose more.²³ Also, after 2 months of standard licensed dose antihistamines, complete freedom from symptoms was reported to be higher in ANA(−) patients (61.7% vs 49.5%; $p = 0.035$). Similarly, Viswanathan *et al.* showed that the percentage of patients who were refractory to antihistamines was higher in ANA(+) CSU patients.²⁴ Though speculative, ANA positivity may be a possible marker for omalizumab resistance and relapses after discontinuation.

In conclusion, omalizumab seems to be an effective option for patients with refractory CSU. It is highly efficient in relapsed patients who previously responded well. Autoimmune markers may be helpful in predicting treatment responses and relapse and identifying the pathophysiology and possible subtypes of the disease may guide therapeutic decisions.

Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

MT, SNB and IY designed the study. MT and SNB collected data. MT and IY drafted the manuscript. MT performed the statistical analysis. MT, SNB and IY contributed to interpretation of the results. IY made the critical review. All authors read and approved the final manuscript.

References

1. Toubi E, Kessel A, Avshovich N, Bamberger E, Sabo E, Nusem D, et al. Clinical and laboratory parameters in predicting chronic urticaria duration: a prospective study of 139 patients. *Allergy* 2004;**59**:869–73.
2. 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.
3. Kaplan AP. Treatment of chronic spontaneous urticaria. *Allergy Asthma Immunol Res* 2012;**4**:326–31.
4. Kulthanan K, Tuchinda P, Chularojanamontri L, Chanyachailert P, Korkij W, Chunharas A, et al. Clinical practice guideline for diagnosis and management of urticaria. *Asian Pac J Allergy Immunol* 2016;**34**:190–200.
5. Bernstein JA, Lang DM, Khan DA, Craig T, Dreyfus D, Hsieh F, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. *J Allergy Clin Immunol* 2014;**133**:1270–7.
6. Goldenberg MM. Pharmaceutical approval update. *P T* 2014;**39**:415–23.
7. Chang TW, Chen C, Lin CJ, Metz M, Church MK, Maurer M. The potential pharmacologic mechanisms of omalizumab in patients with chronic spontaneous urticaria. *J Allergy Clin Immunol* 2015;**135**:337–42.
8. Saini SS, Bindslev-Jensen C, Maurer M, Grob JJ, Bülbül Baskan E, Bradley MS, 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.
9. Maurer M, Rosén K, Hsieh HJ, Saini S, Grattan C, Giménez-Arnau A, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med* 2013;**368**:924–35.
10. 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.
11. Miñyek A, Zalewska-Janowska A, Martus P, Staubach P, Zuberbier T, Maurer M. How to assess disease activity in patients with chronic urticaria? *Allergy* 2008;**63**:777–80.
12. Kolkhir P, Church MK, Weller K, Metz M, Schmetzer O, Maurer M. Autoimmune chronic spontaneous urticaria: what we know and what we do not know. *J Allergy Clin Immunol* 2016. <http://dx.doi.org/10.1016/j.jaci.2016.08.050>.
13. Kaplan AP, Giménez-Arnau AM, Saini SS. Mechanisms of action that contribute to efficacy of omalizumab in chronic spontaneous urticaria. *Allergy* 2017;**72**:519–33.
14. Bongiorno MR, Crimi N, Corrao S, Allotta A, Arena A, Brusca I, et al. Omalizumab for the treatment of chronic spontaneous urticaria in clinical practice. *Ann Allergy Asthma Immunol* 2016;**117**:703–7.
15. Büyükoztürk S, Gelincik A, Demirtürk M, Kocaturk E, Çolakoğlu B, Dal M. Omalizumab markedly improves urticaria activity scores and quality of life scores in chronic spontaneous urticaria patients: a real life survey. *J Dermatol* 2012;**39**:439–42.
16. Kulthanan K, Tuchinda P, Chularojanamontri L, Likitwattananurak C, Ungakornpairote C. Omalizumab therapy for treatment of recalcitrant chronic spontaneous urticaria in an Asian population. *J Dermatol Treat* 2017;**28**:160–5.
17. Silva PM, Costa AC, Mendes A, Barbosa MP. Long-term efficacy of omalizumab in seven patients with treatment-resistant chronic spontaneous urticaria. *Allergol Immunopathol* 2015;**43**:168–73.
18. Altrichter S, Peter HJ, Pisarevskaja D, Metz M, Martus P, Maurer M. IgE mediated autoallergy against thyroid peroxidase – a novel pathomechanism of chronic spontaneous urticaria? *PLoS One* 2011;**6**:e14794.
19. Kaplan A, Ledford D, Ashby M, Canvin J, Zazzali JL, Conner E, et al. Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination. *J Allergy Clin Immunol* 2013;**132**:101–9.
20. 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.
21. 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.
22. Kessel A, Helou W, Bamberger E, Sabo E, Nusem D, Panassof J, et al. Elevated serum total IgE – a potential marker for severe chronic urticaria. *Int Arch Allergy Immunol* 2010;**153**:288–93.
23. Magen E, Waitman DA, Dickstein Y, Davidovich V, Kahan NR. Clinical-laboratory characteristics of ANA-positive chronic idiopathic urticaria. *Allergy Asthma Proc* 2015;**36**:138–44.
24. Viswanathan RK, Biagtan MJ, Mathur SK. The role of autoimmune testing in chronic idiopathic urticaria. *Ann Allergy Asthma Immunol* 2012;**108**:337–41.