Potential clinical and serological predictors of chronic spontaneous urticaria relapse in patients under omalizumab treatment

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Background: Omalizumab is not considered a disease-modifying drug and, accordingly, a large proportion of patients experience a relapse following withdrawal from treatment. **Patients & methods:** A total of 42 patients who underwent at least one cycle of treatment with omalizumab were enrolled. Two groups of relapsed and not-relapsed subjects were compared. Then, patients were divided into subgroups. **Results:** Female patients relapse more frequently than male subjects. Patients who relapsed complained a long duration of disease, while patients who did not relapse had short a history of disease. Very early responders are thought to have a high recurrence rate. Basal IgE levels were increased in early responders and cholesterol levels were high in very early responders, who relapse following withdrawal from omalizumab. High D-dimer levels were observed in late responders. **Conclusion:** The identification of clinical and serological predictors will play a pivotal role in the future management of patients treated with omalizumab.

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Keywords: angioedema • biomarkers • cholesterol • chronic spontaneous urticaria • D-dimer • histamine • IgE • mast cell • omalizumab • relapse

Chronic spontaneous urticaria (CSU) is a common skin disorder characterized by the spontaneous onset of wheals, with associated itch and/or angioedema, lasting for six or more weeks [1]. CSU is estimated to affect around 50 million people, with symptoms that heavily impact on quality of life [2,3]. To date, the pathophysiology of CSU is only partially understood. Histamine appears to be the central mediator of CSU: a massive release of this molecule from local basophils and mast cells occurs in the disease, reason why anti-H1 antagonists are highly effective in treating CSU [4–8]. At the same time, an increased production of cytokines of the TH2 subset, mast cell proteases, IL-8 as well as IFN- γ , TNF- α and IL-6 cytokines, is involved in the pathogenesis of CSU [9].

Basophils and mast cells are key players in the pathogenesis of CSU, although the mechanisms underlying their overactivation are still not fully understood. More than one mechanism of autoimmunity has been proposed for the pathogenesis of CSU, encompassing the spectrum of type II and type I autoimmune reactions.

According to the Type II autoallergy model, IgG auto-antibodies (IgGAABs) binding the α -subunit of the high-affinity IgE receptor Fc ϵ RI are detected in a subgroup of patients with CSU. IgGAABs are responsible for the direct basophil and mast cells activation and degranulation, which relies on complement acting as major amplifier of the histaminergic cascade [10–12]. Autoimmunity related to CSU is based on the presence of circulating histamine-releasing IgGAABs directed either against Fc ϵ RI α on mast cells, basophils or against IgE [13–16].

Type I-autoallergy was recently identified to be mediated by specific IgE-autoantibodies (IgEAABs) targeting autoallergens such as thyroperoxidase, double-stranded DNA and IL-24 [10,11,13]. Coagulation may be involved in up to 50% of patients with severe CSU, that show signs of activation of the coagulation/fibrinolysis system. Hyperexpression of tissue factor by activated eosinophils could act as initiator of the extrinsic pathway, which is primarily implied, while the intrinsic pathway has a secondary role [17–19]. This pathologic mechanism is thought to correlate with severity of CSU [20,21] and supported by experimental evidence that thrombin, the final enzyme of the coagulation cascade, increases vascular permeability and induces mast cell degranulation [22,23].

Omalizumab, a recombinant humanized monoclonal IgG antibody targeting free IgEs, is an effective and safe treatment for patients with CSU [1]. Omalizumab is registered by the US FDA and the EMA since 2014 for the treatment of patients aged 12 years and older [24,25]. The Italian Medical Agency (AIFA) restricts the prescription of omalizumab (300 mg/every 4 weeks) only to CSU patients with inadequate response to treatment with antihistamines. The mechanisms for the efficacy of omalizumab in the treatment of CSU are multiple and still have to be fully elucidated. Among the most accepted actions, omalizumab is able to induce a decrease of free IgE levels, together with the downregulation of FcεRI on basophils and mast cells, which take place at different times during omalizumab treatment [26–28]. Response to omalizumab may be observed at an early or late time point following administration of the drug, suggesting that different mechanisms affect the rate of response [29–31].

The aim of our monocentric observational study is to describe the clinical and serological features of relapsing patients with CSU. In relation to their different timing of response to omalizumab, patients are classified into three groups: very early responders (VER), early responders (ER) and late responders (LR) [30].

Patients & methods

We performed a monocentric observational study on subjects with CSU resistant to first- and second-line antihistamine therapy, eligible for treatment with omalizumab according to EAACI guidelines [1].

A total of 42 ($n = 42$) adult patients who had completed at least one course of treatment with omalizumab for CSU were enrolled in this study. Subjects were selected among 153 patients, 43 males and 110 females, aged above 18 years, who consulted our dermatology department with a diagnosis of CSU (from 1 September 2016 to 31 October 2019).

A total of 116 of them (33 males and 83 females) are currently under treatment follow-up for CSU. The disease was diagnosed following the current criteria of the EAACI guidelines, requiring a history of spontaneous urticaria for 6 weeks or longer, with relative treatment. A total of 54 ($n = 54$) of our patients (15 males and 39 females) resulted unresponsive to first- and second-line therapy with second-generation ant-H1 antihistamines and were candidate to omalizumab treatment. Patients were thoroughly informed on the risks and benefits of the proposed treatment, as well as on the alternative treatment options, and each of them signed the informed consent before the initiation of treatment. According to national AIFA recommendations, patients are treated with omalizumab 300 mg every 4 weeks for a first 6-month course of therapy. Patients who experience disease relapse, identified according to EAACI guidelines by a UAS7 score above 16, are candidates for additional treatment cycles. Concomitant medications were adjusted on a case-by-case basis according to clinical response at monthly follow-up visits. The severity of disease at baseline and the response to therapy were assessed using weekly urticaria activity score (UAS7). According to the response to omalizumab, patients were grouped in VER ($n = 10$), ER ($n = 13$), LR ($n = 12$), partial responders (PR, $n = 3$), and nonresponders (NR, $n = 4$) (Table 1).

VER were defined patients who experienced an immediate improvement of urticaria ($\text{UAS} < 2$) within 24 h after the first administration of omalizumab; ER those who experienced improvement to $\text{UAS7} < 2$ within 1 week from the first administration; LR those in whom improvement occurred after 12 weeks from the beginning of treatment; PR those who had a decrease in UAS7 score but $\text{UAS7} > 6$; NR those whose UAS7 remained above 16 and mostly unchanged after completion of the first treatment cycle. Each patient was reassessed 8 weeks after completion of treatment. Patients were then followed up for 1 year for the relapse of symptoms ($\text{UAS7} > 16$).

The main purpose of our study was to identify possible clinical and serological markers of relapse after omalizumab that could be useful in the future therapeutic management and follow-up of CSU.

Patients' clinical data (sex, age at diagnosis, disease duration, history of atopy, autoimmune diseases, angioedema and/or chronic inducible urticaria), laboratory parameters (antinuclear antibodies, basal total serum IgE, antithyroid antibodies, D-dimer, fibrinogen, cholesterol, basophil activation test) and previous therapies were analyzed in order to identify clinical and serological parameters that may be predictive of disease relapse and of the timing of response to therapy with omalizumab.

Laboratory tests were performed at baseline and the following thresholds were used for each parameter: serum IgE > 100 kilo unit (KU)/l, D-dimer > 0.90 $\mu\text{g/ml}$, serum cholesterol > 200 mg/dl, fibrinogen > 450 mg/dl, basophil activation test > 15 , antinuclear antibodies $> 1:160$, antithyroid peroxidase antibodies > 16 UI/ml and antithyroglobulin antibodies > 100 UI/ml.

Table 1. Descriptive table of quantitative variables.

Variables	n (%)
First access for urticaria	153
– Male	43 (28.1)
– Female	110 (71.9)
CSU	116
– Male	33 (28.4)
– Female	83 (71.6)
Patients treated with omalizumab	54
<1 Course	12 (22.2)
≥1 Course	42 (77.8)
– Male	15 (27.8)
– Female	39 (72.2)
Response to treatment	42
– Very early responder (<24 h)	10 (23.8)
– Early responder (<1 week)	13 (30.9)
– Late responder (>12 weeks)	12 (28.6)
– Partial responder	3 (7.1)
– Nonresponder	2 (4.7)
– Adverse reaction	1 (2.4)
– Lost of efficacy	1 (2.4)

CSU: Chronic spontaneous urticarial; N: Number.

Table 2. Relapse and correlation with age and sex.

Quantitative variables	Total media (SD); median (min;max) n = 42	Relapse media (SD); median (min;max) n = 28	Not relapsed media (SD); median (min;max) n = 14	p-value
Age Mean; SD (min;max)	48.89;18.72 (19;83)	51.32;18.72 (19;83)	42.86;18.05 (20;78)	0.140 [†]
Gender				
Female N (%)	31 (73.8)	24 (77.4)	7 (22.6)	0.024[‡]
Male N (%)	11 (26.2)	4 (36.4)	7 (63.6)	

[†]p-value Mann–Whitney.[‡]p-value Fisher's exact test.

Note: Statistical significant values are expressed in bold.

Min: Minimum; Max: Maximus; N: Number; SD: Standard deviation.

Statistical analysis

The frequency of relapse was measured considering, age, sex, clinical and laboratory investigations and response to treatment. Specifically, response to treatment was assessed using UAS7 as one of the following three: VER, ER, and LR. PR and NR were not taken into account for the assessments. Relapse index related to age and sex was assessed with p-value using Mann–Whitney and Fisher's exact test while relapse index related to the different response group was assessed with p-value using Fisher's exact test. Due to the limited number of patients, we did not perform a multiple regression. $p < 0.05$ was considered statistically significant.

Results

A total of 42 adult subjects, ten males and 32 females, who underwent at least one complete 6-month cycle of treatment were included. Patients were aged mean (min;max) = 48.89 (19;83) standard deviation (SD) = 18.72 years. A total of 28 ($n = 28$) out of 42 patients (66.6%) relapsed and 14 maintained remission after 1 year of follow-up (33.3%). Though mean age was higher in patients who relapsed (mean = 51.32; SD = 18.72) than in those who did not relapse (mean = 42.86; SD = 18.05), this difference was not statistically significant with Mann–Whitney test ($p = 0.140$). Female sex was associated to a significantly higher frequency of recurrence (77.4% in respect to male sex (36.4%) using Fisher's exact test ($p = 0.024$) (Table 2).

Table 3. Relapse and correlation with clinical and laboratory parameters.

Variables	Relapse n (%)	Not relapsed n (%)	Total n	p-value [†]
Total	28 (66.6)	14 (33.3)	42	
PRIST				
No	15 (53.6)	6 (46.2)	21	p = 0.457
Yes	13 (46.4)	7 (53.8)	20	
D-dimer				
No	18 (64.3)	7 (53.8)	25	p = 0.382
Yes	10 (35.7)	6 (46.2)	16	
Cholesterol				
No	13 (50)	7 (63.4)	20	p = 0.347
Yes	13 (50)	4 (36.4)	17	
FNG				
No	23 (82.1)	10 (76.9)	33	p = 0.449
Yes	5 (17.9)	3 (23.1)	8	
ANA				
No	23 (82.1)	11 (84.6)	34	p = 0.611
Yes	5 (17.9)	2 (15.4)	7	
ATPO				
No	23 (82.1)	9 (69.2)	32	p = 0.294
Yes	5 (17.9)	4 (30.8)	9	
ATGB				
No	24 (85.7)	12 (92.3)	36	p = 0.486
Yes	4 (14.3)	1 (7.7)	5	
BAT				
No	28 (100)	10 (76.9)	38	p = 0.027
Yes	0	3 (23.1)	3	
AE				
No	13 (46.4)	5 (35.7)	18	p = 0.373
Yes	15 (53.6)	9 (64.3)	24	
CINDU				
No	24 (85.7)	10 (71.4)	34	p = 0.240
Yes	4 (14.3)	4 (28.6)	8	

[†]p-value Fisher's exact test.

Some patients did not report the required laboratory data.

Note: Statistical significant values are expressed in bold.

AE: Angiooedema; ANA: Antinuclear antibodies; ATPO: Antithyroid peroxidase antibodies; ATGB: Antithyroglobulin antibodies; BAT: Basophil activation test; CINDU: Chronic inducible urticarial; FNG: Fibrinogen; PRIST: Total IgE.

Table 4. Response to omalizumab and correlation with age and sex.

Quantitative variables	Total media (SD); median (min;max) n = 42	Very early media (SD); median (min;max) n = 10	Early responder media (SD); median (min;max) n = 13	Late responder media (SD); median (min;max) n = 12
Age				
Mean; SD (min;max)	47; 18.72 (19;83)	57; 19.35 (21;80)	44; 18.83 (19;78)	49.5; 19.39 (23;83)
Age per gender mean (SD)				
Female	52.13 (18.04)	60.5 (14.87)	45 (20.67)	52 (18.80)
Male	40.47 (15.99)	25.5 (6.36)	42.5 (13.96)	34 (24.02)

Min: Minimum; Max: Maximum; n: Number; SD: Standard deviation.

The analysis of laboratory and clinical parameters showed an association with relapse only of basophil activation test, that was more frequently positive in patients who did not relapse compared with the relapse group, were no positive results were assessed (Fisher's exact test; p = 0.027). Other variables showed no statistically significant differences between the two groups of relapse and no relapse (Table 3).

Seven patients were classified as PR or NR and excluded from further assessment. The remaining 35 patients were assigned into three subgroups according to treatment response: VER (n = 10), ER (n = 13) and LR (n = 12). Previous analyses were repeated for each subgroup (Table 4). A total 24 of 35 patients (68.6%) relapsed and nine of ten VER patients (90%) relapsed suggesting a higher frequency of recurrence compared with ER and LR groups. As far as laboratory data are concerned, values according to different types of responders are shown in Table 5.

Table 5. Response to omalizumab and correlation with clinical and laboratory parameters.

Variables	Very early responders n (%)	Early responders n (%)	Late responders n (%)	Total n (%)
Gender				
Female	8 (29.6)	9 (33.3)	9 (37)	27 (77.1)
Male	2 (25)	4 (50)	3 (25)	8 (22.9)
Relapse				
No	1 (9.1)	6 (54.5)	4 (36.4)	11 (31.4)
Yes	9 (37.5)	7 (29.2)	8 (33.3)	24 (68.6)
Course				
<2	1 (2.9)	8 (22.9)	4 (11.4)	13 (37.1)
≥2	9 (25.7)	5 (14.3)	8 (22.9)	22 (62.9)
Total	10 (28.6)	13 (37.1)	12 (34.3)	35 (100)
PRIST				
No	4 (25)	5 (31.3)	7 (43.8)	16 (47)
Yes	5 (27.8)	8 (44.4)	5 (27.8)	18 (54)
D-DIMER				
No	6 (28.6)	9 (42.9)	6 (28.6)	21 (61.8)
Yes	3 (23.1)	4 (30.8)	6 (46.2)	13 (38.2)
Cholesterol				
No	2 (11.1)	8 (44.4)	8 (44.4)	18 (54.5)
Yes	7 (46.7)	4 (26.7)	4 (26.7)	15 (45.5)
FNG				
No	6 (21.4)	10 (35.7)	12 (42.9)	28 (82.4)
Yes	3 (50)	3 (50)	0	6 (17.6)
ANA				
No	9 (32.1)	10 (35.7)	9 (32.1)	28 (82.4)
Yes	0	3 (50)	3 (50)	6 (17.6)
ATPO				
No	8 (29.6)	10 (37)	9 (33.3)	27 (79.4)
Yes	1 (14.3)	3 (42.9)	3 (42.9)	7 (20.6)
ATGB				
No	8 (25.8)	12 (38.7)	11 (35.5)	31 (91.2)
Yes	1 (33.3)	1 (33.3)	1 (33.3)	3 (8.8)
BAT				
No	9 (26.5)	12 (35.3)	10 (29.4)	31 (91.2)
Yes	0	1 (2.9)	2 (5.9)	3 (8.8)
AE				
No	4 (23.5)	6 (35.3)	7 (41.2)	17 (48.6)
Yes	6 (33.3)	7 (38.9)	5 (27.8)	18 (51.4)
CINDU				
No	8 (27.6)	10 (34.5)	11 (37.9)	29 (82.9)
Yes	2 (33.3)	3 (50)	1 (16.7)	6 (17.1)

Partial responder (n = 3) and nonresponder patients (n = 4) are not considered in this table; in VER group we have considered only nine patient's data because one has never reported the results. However, these data do not currently have statistical significance given the small number of patients.

AE: Angioedema; ANA: Antinuclear antibodies; ATPO: Antithyroid peroxidase antibodies; ATGB: Antithyroglobulin antibodies; BAT: Basophil activation test; CINDU: Chronic inducible urticarial; FNG: Fibrinogen; PRIST: Total IgE; VER: Very early responders.

Mean duration of disease before initiating omalizumab was 88 months (min;max = 2;480) in patients who relapsed. All patients who did not relapse had a duration of disease ranging between 2 and 18 months.

Discussion

The pathogenesis of CSU takes into account a complexity of disease mechanisms, many of which are yet to be understood. Autoimmunity likely plays a role both in the pathogenesis of disease and in the response to omalizumab. The clinical observation of early response following first administration of omalizumab suggests the involvement of still unknown immunological mechanisms in the pathogenesis of CSU and in the response to therapy [32].

Omalizumab is not considered a disease-modifying drug and, accordingly, a large proportion of patients experiences a relapse following withdrawal of treatment [33–35]. In our study, 66.6% of patients relapsed after a successful cycle of therapy and needed further cycles of omalizumab.

Patients that do not relapse may have reached a spontaneous remission of the disease. We hypothesize that the relapse population subgroup is mainly represented by patients with a long-standing history of CSU.

Our results show that frequency of relapse is higher in females than in males. A tendency to relapse was also observed in relation to age, although the association was not statistically significant. From the evidence gathered, we could infer that sex and age are relevant parameters in preclinical patient evaluation. Concurrent angioedema or chronic inducible urticaria occurred indifferently in relapsing and nonrelapsing subjects.

According to our results, 23.8% of patients showed treatment response within 24 h (VER) and 30.9% within 1 week (ER) after the first administration of omalizumab. Interestingly, VERs seem to be also the ones to experience high rates of recurrence after withdrawal from treatment, requiring therefore additional cycles of omalizumab. We also focused our attention on the clinical severity of CSU, inferring that patients with high skin disease burden, measured as number of urticarial lesions and disease persistence, are the ones to show a prompt response after the first injection of omalizumab; these patients however also show a constant relapse rate within the first 2 months from the end of the treatment cycle.

In accordance with our findings, Ertas *et al.* showed that high total serum IgE levels seem to be linked to a faster relapse after discontinuation of omalizumab therapy in patients with CSU [36]. The same study also shows that timing of response to omalizumab therapy is associated with the rate of recurrence.

Our results showed high basal IgE levels (above 100 KU/l) in ER patients. These patients were also the ones who showed frequent occurrence of relapse following the end of the cycle.

Interestingly, high cholesterol levels – over 200 mg/dl – were recorded in VERs; as already pointed out, these patients were early relapsing patients after treatment dismission.

In addition to baseline IgE levels, also D-dimer levels are reported to be higher in responders to omalizumab compared with nonresponders [37]. In our sample, D-dimer levels were elevated above 0.90 µg/ml in LRs.

A study from Asero *et al.* demonstrated that elevated D-dimer levels are associated with disease severity [20], however, at present time there are no clear data on the correlation between baseline D-dimer levels and the response rate to omalizumab therapy [38–40]. Also, the relationship between basophil activation test and the response to omalizumab is unclear. A recent study investigated the possible association between the therapeutic success of omalizumab and a negative basophil activation test [40]. Another study reported positive results of basophil activation test and autologous serum skin test in association to late response to omalizumab [41].

Our results showed basophil activation test negativity in the majority of patients, and in all patients who relapsed, but this finding may be attributed to the limited accuracy and standardization of the techniques.

Conclusion

Current literature on CSU proposed several clinical and laboratory parameters as potential biomarkers of disease activity and response to therapy, while little has been reported on the predictors of relapse [42].

In the era of precision medicine, researchers and clinicians must join efforts to identify all clinical and laboratory markers that may aid in patient management. Predicting not only the response to treatment but also the risk of relapse is necessary to predict the duration of disease and to guide choice of the best drug on a single patient basis. Achieving a tailored therapy approach to the treatment of CSU is expected to significantly improve the quality of life in our patients.

Author contributions

L Dies enrolled patients, contributed in the conception of the manuscript, read and approved all draft manuscripts during its preparation. A Sernicola contributed to the writing – review and editing. C Chello participated in the selection and registration of patients, completed and analyzed the basic documentation during the study and also read and approved all draft manuscripts during its preparation. N Gagliostro participated in the selection and registration of patients, completed and analyzed the basic documentation during the study and also read and approved all draft manuscripts during its preparation. G Paolino contributed to the conceptualization of the study, improved the article, read and approved all draft manuscripts during its preparation. T Grieco enrolled patients, contributed in the conception of the manuscript, read and approved all draft manuscripts during its preparation.

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Ethical conduct of research

The authors state that they have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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Summary points

- Chronic spontaneous urticaria is a common skin disorder characterized by the spontaneous onset of wheals associated with pruritus and/or angioedema and lasting for 6 or more weeks.
- Omalizumab, a recombinant humanized monoclonal IgG antibody targeting free IgE, is a safe, effective and well-tolerated treatment for patients with chronic spontaneous urticaria.
- The aim of our observational study was to describe the clinical and serological markers of relapse in chronic spontaneous urticaria, which occurs in the majority of patients after discontinuation of omalizumab.
- Patients who relapsed after one cycle of omalizumab are mostly female and may be older than not-relapsed patients.
- Patients who relapsed complained a long duration of disease before initiating omalizumab, while patients who did not relapse had a short history of disease.
- Very early responders achieve remission within 24 h of omalizumab injection but are thought to have a high recurrence rate.
- Basal IgE level are increased to >100 KU/l in early responders, who showed response within 1 week after the first administration of omalizumab and relapse following the end of the cycle.
- High cholesterol levels >200 mg/dl are reported in very early responders, who respond after 24 h from the first administration of omalizumab and usually relapse following withdrawal from treatment.
- High D-dimer levels >0.90 µg/ml, which is associated to disease severity in the literature, were observed in late responders; however, the possible relation to relapse is unclear.

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