

as ineffective (1). Therefore, in our opinion, a treatment with anti-IgE antibody (omalizumab) could contribute to a new therapeutic scenario for SU and throw light on the potential pharmacological mechanism of omalizumab in this disease. In fact, it is conceivable that omalizumab, depleting IgE, down-regulates mast cell activities and reduces mast cell-dependent inflammatory mechanisms (8).

Further studies are needed to identify patients with SU who could be treated earlier and successfully with omalizumab. In addition, randomized controlled trials are awaited to identify

both effective treatment schedule(s) and doses for eligible patient suffering from solar urticaria unresponsive to conventional treatment.

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Management of pediatric chronic spontaneous and physical urticaria patients with omalizumab: case series

To the Editor,

Chronic urticaria (CU) is defined by itchy hives and/or angioedema that reoccur for at least 6 weeks and affects 0.1 to 0.3% of children (1). When no specific eliciting trigger is identified, this condition is classified as chronic spontaneous urticaria (CSU). It is believed that up to 50% of cases are associated with pathogenic autoantibodies, which can be detected *in vivo* by autologous serum skin test or *in vitro* by basophil activation test (BAT) reflected by increased CD63 expression or histamine release. The first-line treatment for CSU is second-generation antihistamines and if not effective, the dosage can be increased up to four times (2). Unfortunately, 25 to 50% of patients do not respond to this treatment regimen and require other treatment modalities including antileukotrienes, cyclosporine, and more recently omalizumab (3).

Omalizumab is a recombinant humanized monoclonal anti-IgE antibody that was recently approved by the US Food and Drug Administration and the European Medicines Agency for antihistamine refractory patients with CSU who are at least 12 years of age (4, 5). It binds free serum IgE, prevents its attachment to the cognate high-affinity receptor on mast cells (FcεRI), and decreases receptor expression (5).

The Urticaria Activity Score (UAS) is a validated tool used in both clinical practice and trials for the assessment and monitoring of disease activity in patients with CSU. It measures key urticarial symptoms (wheals and pruritus) on a daily basis. The UAS7 is the weekly sum score with a range between 0 (no wheals, no itch) and 42 (maximum disease activity) per week (2).

In this study, we describe four pediatric cases presenting with severe CSU with or without delayed pressure urticaria with complete remission after treatment with subcutaneous omalizumab injections and propose the use of CD63⁺ as a potential cellular marker that could guide treatment (Table 1, in the Online Repository). All patients and/or their parents have signed an informed consent, and the study was approved by the Ethic Review Committee of McGill University Health Centre.

Case 1

A 4-year-old girl presented with CSU (wheals and angioedema, UAS7 of 21) for the last 2 years. She reported to our emergency department and allergy clinic every 2 weeks due to persistent hives and pruritus despite regular treatment with twice the daily recommended dose of second-generation

antihistamines. She was treated in the emergency department with systemic corticosteroids and epinephrine. Her investigations were within normal limits including a complete blood count, C reactive protein, and tryptase levels. In addition, due to an episode of syncope associated with her hives, she had a computer tomography scan of the head and an electroencephalogram (EEG) which did not reveal any pathology. Bone marrow biopsy did not show any evidence of mastocytosis. She achieved complete remission within 1 week of the first dose of omalizumab (150-mg subcutaneous injection) and was able to discontinue all antihistamines. Pre-treatment and post-treatment BAT results (based on CD63 expression) were comparable and within the previously reported normal range (6).

Case 2

A 16-year-old boy presented with CSU and delayed pressure urticaria resistant to four times the daily dose of antihistamines and antileukotrienes for 8 years (UAS7 of 28) (Fig. 1). He frequently missed school and avoided all sporting activities because of his symptoms. BAT results were similar and within normal range pre- and post-treatment. He achieved complete remission and stopped all antihistamines within 1 week of omalizumab (300 mg) treatment and resumed all physical activities.

Case 3

A 5-year-old girl with CSU (wheals and angioedema) was followed in our clinic for 3 years (UAS7 of 42), unresponsive to double dose of antihistamines and additional use of ketotifen and antileukotrienes. She was treated twice with oral corticosteroids leading to short-lasting remissions. She achieved complete remission within 5 days following the first dose of omalizumab (150 mg), and antihistamines were tapered. Pre- and post-treatment BAT was within previously described normal range (6).

Case 4

A 10-year-old girl was diagnosed with antihistamine-resistant CSU of 3 years duration (UAS7 of 21). She required short courses of systemic corticosteroids twice a year due to urticaria exacerbations. Pre-treatment BAT revealed high percentage of CD63⁺ basophils (62.16%, Fig. 2) which decreased to 40.45% 1 month following omalizumab administration. She achieved only partial improvement (UAS7 of 10) after the second dose (300 mg). Furthermore, she experienced an exacerbation (UAS7 of 42) after her 4th dose. At that time, her CD63 positivity, as measured using BAT, was 82.75%. Hence, after 4 months of therapy, we elected to change her management and administer subcutaneously omalizumab 300 mg every 2 weeks rather than monthly. Within a few days, her hives ceased to occur and CD63⁺ levels went down to 69.86% after 2 weeks of this new regimen. CD63⁺ levels further decreased to 27.7% 1 month later and the patient successfully discontinued antihistamines at that time.

None of these patients experienced any adverse effects and all of them remain currently on treatment (treatment duration 3–11 months). The cases described suggest an important role for omalizumab in the management of severe CSU/delayed pressure urticaria. Further, we report, for the first time, a potential role for the use of BAT in predicting the clinical efficacy of omalizumab management in CSU.

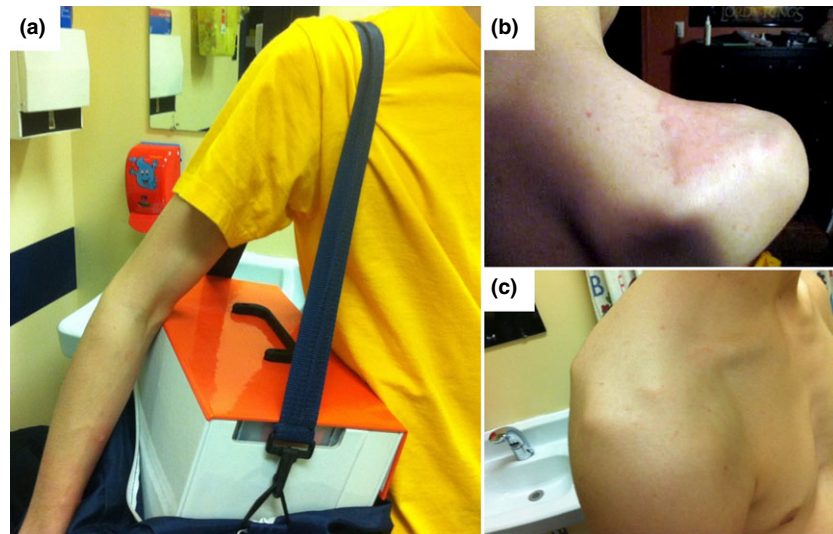
Cross-linking of the high-affinity IgE receptor (FcεRI) which is expressed on all basophils and mast cells leads to cellular activation and degranulation of preformed granules containing vasoactive mediators such as histamine (7). Up to 50% of patients with CSU are reported to have an autoimmune etiology due to the presence of mast cell-activating antibodies (IgG type) against the IgE receptor or IgE itself (8). IgE type autoantibodies against autoantigens such as thyroperoxidase or DNA have also been reported to be frequent in patients with CSU (9). CD63 molecule is expressed on activated basophils, correlates with cell degranulation, can be

Table 1 Patients' demographics, pertinent laboratory finding, and response to treatment

No.	Age (years)	Sex	CSU duration (years)	Weekly UAS at baseline	Type of urticaria	Total IgE (μ/ml)	CD63 expression (%) at baseline	Dose and interval of omalizumab administration	Time to complete response (weeks)
1	4	F	2	21	CSU (wheals and angioedema)	919	0.86	150 mg monthly	1
2	16	M	8	28	CSU (wheals) and Delayed pressure urticaria	4080	0.48	300 mg monthly	1
3	5	F	3	42	CSU (wheals and angioedema)	65	1.90	150 mg monthly	<1
4	10	F	1	21	CSU (wheals)	41	62.16	300 mg monthly for 4 months followed by 300 mg every second week	20

CSU, chronic spontaneous urticaria; UAS, urticaria activity score.

Figure 1 Delayed pressure urticaria before and after omalizumab therapy. (a) Confirmatory provocation test using a 7 kg weight suspended over the shoulder for 15 min. (b) Positive test prior to the omalizumab treatment defined by the appearance of hives/skin swelling at the site of weight application 4 h later. (c) Negative provocation test after 1 week of treatment with omalizumab.



measured by flow cytometry, and is suggested to correlate with the presence of autoantibodies activating mast cells and basophils (7). CD63 measurements were performed in all patients before initiating the treatment with omalizumab and within 2 weeks after administration of the SC injections and at the time of clinical improvement using a previously described protocol (10). Cutoff for positive BAT was defined as 2.2%, representing the mean CD63 expression in healthy controls plus two standard deviations as previously published (6).

Although all four patients achieved complete remission, the patient with high percentage of activated basophils required change of protocol involving more frequent injections to

achieve remission. Consistent with other reports in CSU and pollen allergy, decrease in the CD63 expression was noted after omalizumab (11–13), but we are the first to exemplify that cases that are more resistant to omalizumab treatment (Fig. 1) are associated with increased CD63 levels and that an increase in these levels might be associated with a delayed and less pronounced clinical response. Because omalizumab has been shown to reduce the level of free IgE by 96% within 3 days and decrease FcεRI expression on basophils by 73% after 7 days (12), we hypothesize that in CSU patients with very high load of circulating antibodies and/or FcεRI density reflected by high percentage of CD63 expression, omalizumab treatment may be

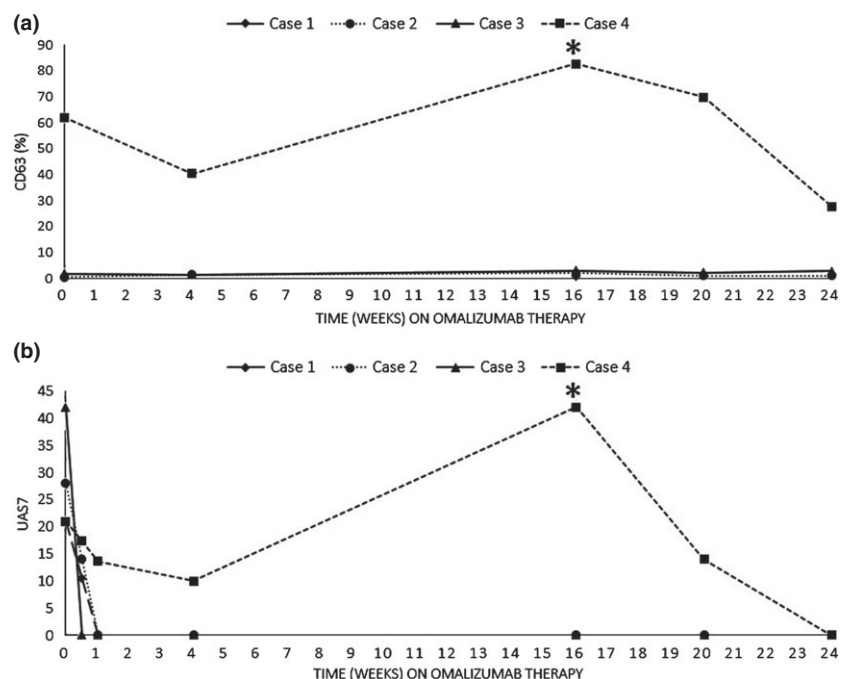


Figure 2 (a) Urticaria activity score (UAS7) in function of duration of omalizumab therapy. (b) Basophil activation changes reflected by the level of CD63 expression (%) were measured in four patients before and after the treatment with omalizumab. Elevated CD63 levels were detected in patient 4 prior to initiation of omalizumab and during disease flare (indicated by an asterisk (*)). Reduction of CD63 expression was observed following successful change in treatment protocol.

more challenging and require adjustment in the standard recommended protocol.

To our knowledge, this is the first report of successful and safe use of omalizumab in children <12 years of age for CSU and the first report of successful treatment of delayed pressure urticaria in children. Our small case series demonstrates that omalizumab is very effective in CSU patients with normal CD63 levels and that high CD63 expression level may indicate more persistent forms that may require more frequent injections or higher dosage. Larger studies are required to establish the role of CD63 expression as a potential marker for CSU management.

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Successful omalizumab treatment of severe solar urticaria in a 6-year-old child

To the Editor,

Solar urticaria (SU) is a rare photodermatosis classified as a form of inducible urticaria. Clinically, SU is characterized by sudden onset of transient erythema, whealing, and pruritus on sun-exposed areas, occurring during or minutes after sun exposure (1). It is considered Type I hypersensitivity reaction, and as such it might well be accompanied by other characteristic symptoms and signs, most commonly angioedema (2). The action spectrum (i.e. the light waves which trigger urticaria in an individual patient) for SU includes ultraviolet A (UVA), visible light (VL), and less frequently UVB. Patients may be sensitive to multiple action spectra, and the spectrum might change within a single individual during the course of illness (2).

Patients with action spectra in the UVB and UVA2 spectra often obtain sufficient light protection by broad-spectrum sunscreens (3). However, sensitization to action spectra in the longer wavelengths often requires complete avoidance from light exposure, which obviously bears a major impact on their quality of life. Therefore, in patients sensitive to UVA1 or VL, antihistamines are often prescribed with various degrees of success (4, 5). Leukotriene-receptor antagonists as monotherapy or in combination with antihistamines can also be beneficial (4, 5). Another accepted treatment modality is UV-hardening in which a patient is gradually exposed to increasing light doses (6) on increasing body surface area. It consists of multiple light exposures for consecutive several days. Other treatments less commonly used with variable efficacy include