

Letters

Omalizumab for chronic urticaria in children younger than 12 years



Chronic urticaria (CU), defined by recurrent wheals, angioedema, or both lasting more than 6 weeks, is subclassified into chronic spontaneous urticaria (CSU) and inducible urticaria (IU).¹ CU is disabling and impairs work and school performance.¹ Current treatment guidelines recommend a stepwise approach starting with escalating doses of nonsedating antihistamines.¹ Omalizumab (anti-IgE monoclonal antibody) is approved as an add-on therapy for patients (≥ 12 years old) with antihistamine-resistant CSU; however, omalizumab is not approved for CSU in children younger than 12 years.² CU in children is not uncommon,¹ and up to one-third of patients are antihistamine resistant.³ For these challenging pediatric patients, therapeutic options are limited, and systemic immunosuppressants with significant adverse effects, such as oral corticosteroids or cyclosporine, are often used.^{1,4} In this brief report, we compile the experience of using omalizumab for treating CU in children younger than 12 years through a systematic literature review and a report of our single-practice experience.

We searched the PubMed and Embase databases in December 2018 using the following terms: *child*, *children*, OR *pediatric* AND *urticaria* AND *omalizumab*. No time restriction was applied. Articles were filtered to exclude duplicates and to include English-language human studies. Original prospective, retrospective, and case studies using omalizumab in children younger than 12 years with CSU or IU were included in our review. Studies were assessed using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) system, and clinical variables of interest were extracted. Our primary outcome was response to omalizumab defined as complete (if author indicated complete resolution), partial (subjective or objective improvement), or no response (omalizumab failure). Secondary outcomes included adverse events and predictors of response to omalizumab.

The database search identified 157 articles, and of these, 10 studies (14 patients) fulfilled the inclusion criteria (Table 1). eFigure 1 shows a diagram summarizing the systematic review process according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.⁵ We included 2 male patients younger than 12 years with CSU from our own clinical practice successfully treated with omalizumab for a total of 16 patients. eTable 1 summarizes the clinical characteristics of these patients. The median age at time of omalizumab treatment was 9.5 years (range, 2–11 years). CSU was the most common type (81% of patients), followed by solar (13%) and cold-induced urticaria (6%).

The median weekly urticarial activity score (UAS-7) was 28 (range, 5–42; $n = 6$). All patients had persistent symptoms despite various combinations of high-dose histamine₁ blockers (93%), histamine₂ blockers (44%), and leukotriene receptor antagonists (67%). Five patients (31%) had received cyclosporine, and 9 (56%) had received oral corticosteroids before starting omalizumab therapy. The monthly omalizumab dose ranged from 75 to 600 mg. Overall, lower monthly doses were required to achieve a clinical response in patients younger than 6 years compared with older children (150 vs 300 mg, $P = .02$, Mann-Whitney U test). A 150- to 300-mg monthly dose of omalizumab resulted in a complete response in 81% and a partial response in 19% of patients with CSU. One patient with a partial response underwent up-dosing to 300 mg bimonthly and subsequently attained a complete response. The median time to response was 4 weeks (range, 0.14–32.0 weeks). Two patients with solar urticaria had a complete response to omalizumab (dose range, 150–600 mg per month). One patient with cold-induced urticaria had a partial response with a 75-mg monthly dose. Response pattern was not affected by patient sex, concomitant angioedema, atopy, or elevated IgE levels (above the upper limit of normal) ($P > .90$ for all these variables, Fisher exact test). The median omalizumab therapy duration was 7.5 months (range, 5–36 months), with no major adverse events reported in any of the patients.

In adolescents and adults with CSU, a clinically meaningful response to omalizumab often occurs within 2 weeks of starting therapy and the response is dose dependent.⁶ Our study suggests that in children younger than 12 years, a clinical response may be attained with a monthly dose of 150 to 300 mg within 4 weeks of starting treatment, and lower doses may be sufficient to achieve a clinical response in children younger than 6 years. The small number of patients included in our review limited our ability to assess a dose-response relationship. However, 1 patient with a partial response to 300 mg monthly achieved a complete remission with up-dosing to 300 mg bimonthly. Our findings also support a recent review that found that omalizumab can be effective for treating not only CSU but also IU.⁷

A recent study⁸ concluded that patient sex, concomitant angioedema, and atopic comorbidities were not predictive of clinical response to omalizumab, and our findings support this assertion. Low baseline IgE levels (<15.2 IU/L) have been recently linked to a lack of response to omalizumab⁹; however, most patients included in our analysis (approximately 60%) had elevated IgE levels, and only 1 patient had an IgE level less than 15.2 IU/L, which limited our ability to study this relationship.

In patients older than 12 years, omalizumab treatment for CSU has not been associated with major adverse events.⁶

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Table 1

Summary of Articles Reporting Omalizumab Use for Chronic Urticaria in Children Younger Than 12 Years

Study	Study type	QOE ^a	Age, y	Sex	Diagnosis	Angioedema	Total IgE, IU/L	UAS-7	Reported treatments attempted	Omalizumab		Response	Duration, mo	Adverse events
										Dose, mg	Interval, wk			
Levi et al, 2014	Case report	Very low	6	M	Solar urticaria	Yes	2004	-	High-dose H ₁ -blocker, LTRA	75	2	None	36	None
Netchiporouk et al, 2015	Case series	Very Low	4	F	CIU	Yes	919	21	High-dose H ₁ -blocker	150	2	Partial	6	None
			5	F	CIU	Yes	65	42	High-dose H ₁ -blocker, LTRA, CS ^b	300	2	Complete		
			10	F	CIU	No	41	21	High-dose H ₁ -blocker, CS ^b	150	4	Complete		
Asero et al, ⁷ 2014	Case report	Very Low	11	M	CIU	Yes	NL	5	H ₁ -blocker, LTRA, CS, CsA	300	4	Partial	6	None
Viswanathan et al, ⁸ 2013	Retros-pective	Low	8	M	CIU	NR	270	NR	CsA	300	2	Complete	6	None
Sussman et al, 2014	Pros-pective		9	M	CIU	NR	NR	NR	High-dose H ₁ -blocker, H ₂ -blocker, LTRA, CS, CsA	300	4	Complete	11	None
			11	F	CIU	NR	NR	NR	High-dose H ₁ -blocker, H ₂ -blocker, LTRA	150	4	Complete	NR	None
			10	M	CIU	NR	NR	NR	High-dose H ₁ -blocker	300	4	Complete	NR	None
Uysal et al, 2014	Case report	Very Low	10	M	CIU	NR	94.5	NR	LTRA, CS	150	2	Complete	9	None
Leonardi et al, 2018	Case report	Very Low	7	F	CIU	No	200	37	High-dose H ₁ -blocker, CS	300	4	Complete	9	None
Alba et al, 2015	Case report	Very Low	2	F	Cold induced	No	14.9	NR	High-dose H ₁ -blocker, LTRA	75	4	Complete	9	None
Ossorio-García et al, 2016	Case report	Very Low	8	F	CIU	NR	3281	38	High-dose H ₁ -blocker, LTRA, CsA	300	2	Complete	6	None
Snast et al, 2018	Case series	Very Low	10	F	Solar urticaria	No	243	NR	High-dose H ₁ -blocker, LTRA	150	4	Complete	17	None
Present study	Case series	Very Low	11	M	CIU	Yes	NR	NR	High-dose H ₁ -blocker, H ₂ -blocker, LTRA,	300	4	Complete	11	None
			10.6	M	CIU	No	1147	NR	High-dose H ₁ -blocker, H ₂ -blocker, LTRA, CsA	300	4	Complete	5	None

Abbreviations: CIU, chronic idiopathic urticaria; CS, corticosteroid; CsA, cyclosporine A; H₁, histamine 1; H₂, histamine 2; LTRA, leukotriene receptor antagonist; NR, not reported; QOE, quality of evidence; UAS-7, weekly urticaria activity score.

^aBased on the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system.

^bOn an intermittent basis.

Furthermore, omalizumab has been safely used in children 6 to 11 years of age with severe asthma.¹⁰ In our review, no adverse events related to omalizumab were reported, suggesting that omalizumab can be a safe therapeutic option for patients with CU in this age group.

Our systematic review has a number of limitations. First, the number of patients included in our analysis was small, likely because omalizumab is not approved by the US Food and Drug Administration for CU treatment in children younger than 12 years. Second, the studies included in our review were case reports or small case series, which translates into weak evidence. Third, given the heterogeneity of reports, we relied on descriptive outcomes rather than validated efficacy end points, such as changes in UAS-7. Nonetheless, our study provides preliminary data that support the use of omalizumab for treating CU in children younger than 12 years and highlights the need for randomized controlled trials to better investigate the safety and efficacy of omalizumab in this age group.

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Supplementary Data

Supplementary data related to this article can be found online at <https://doi.org/10.1016/j.anai.2019.05.003>.

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The first pathological specimen from a rare local reaction after subcutaneous allergen immunotherapy



Local cutaneous reactions typically described as injection site tenderness, pain, induration, and erythema are frequently experienced by patients undergoing subcutaneous immunotherapy (SCIT), occurring with a frequency of 0.7% to 7.3% of injections.^{1–3} We describe a curious and rare case of bullous vesicles forming in a delayed local reaction to SCIT. We also provide and discuss the pathological results of shave and punch biopsies obtained from this reaction to consider a possible mechanism of action.

A 57-year-old man with a history of allergic rhinitis and nasal polyposis presented approximately 24 hours after SCIT injection in his left arm because of the formation of blistering lesions of his skin at the injection site. The initial formation of these blisters occurred several hours after his subcutaneous injection. The patient denied any local pruritus, pain, burning, or systemic symptoms such as malaise, fever, headache, or vomiting. He had a history of a single World Health Organization grade 2 systemic reaction to immunotherapy approximately 5 months prior, and he had no history of prior abnormal local cutaneous reactions. His SCIT extract contained grasses, weeds, dog hair, and cat dander, and treatment was initiated approximately 7 months prior. His goal maintenance dosing was 0.5 mL of a 1:1 v/v concentration every 4 weeks, which he had reached 1 month before this reaction. Of note, on initiation of his maintenance dose, the frequency of injections was extended to every 4 weeks from his buildup dose frequency of once- to

twice-weekly injections. All extracts were administered in a single injection at each visit. Despite recommended avoidance, the patient owned 3 dogs at home, and this reaction occurred late in the local grass season and during the peak of the local weed season. Other medical therapies for his chronic rhinitis included daily cetirizine, montelukast, and intranasal fluticasone. He had no personal or family history of autoimmunity or bullous skin disease.

On physical examination, two erosions from ruptured bulla, each approximately 2 cm in diameter, as well as 2 tense bulla containing clear, serous fluid, each approximately 1 cm in diameter, were observed on the left posterior arm of the patient at the injection site. All were grouped into a close proximity, and they had surrounding erythema extending out approximately 1 cm from the lesions. Shave and punch biopsies were performed on the day of presentation. Pathology reported a nonspecific, subepidermal vesicular dermatitis containing neutrophils and abundant eosinophils with underlying superficial perivascular lymphohistiocytic inflammation with neutrophils and eosinophils (Fig 1). Direct immunofluorescence staining was performed using immunoglobulin (Ig) A, IgG, IgM, C3, and fibrinogen, which failed to reveal a known diagnostic pattern of antibody deposition, such as in bullous pemphigoid or other autoimmune blistering diseases. Fluid stains and cultures obtained from the vesicular fluid failed to identify bacterial or fungal organisms.

The patient's lesions were treated symptomatically with sterile wound dressings, which he changed at home as needed until his lesions healed. Of note, he was not prescribed antibiotics, steroids,

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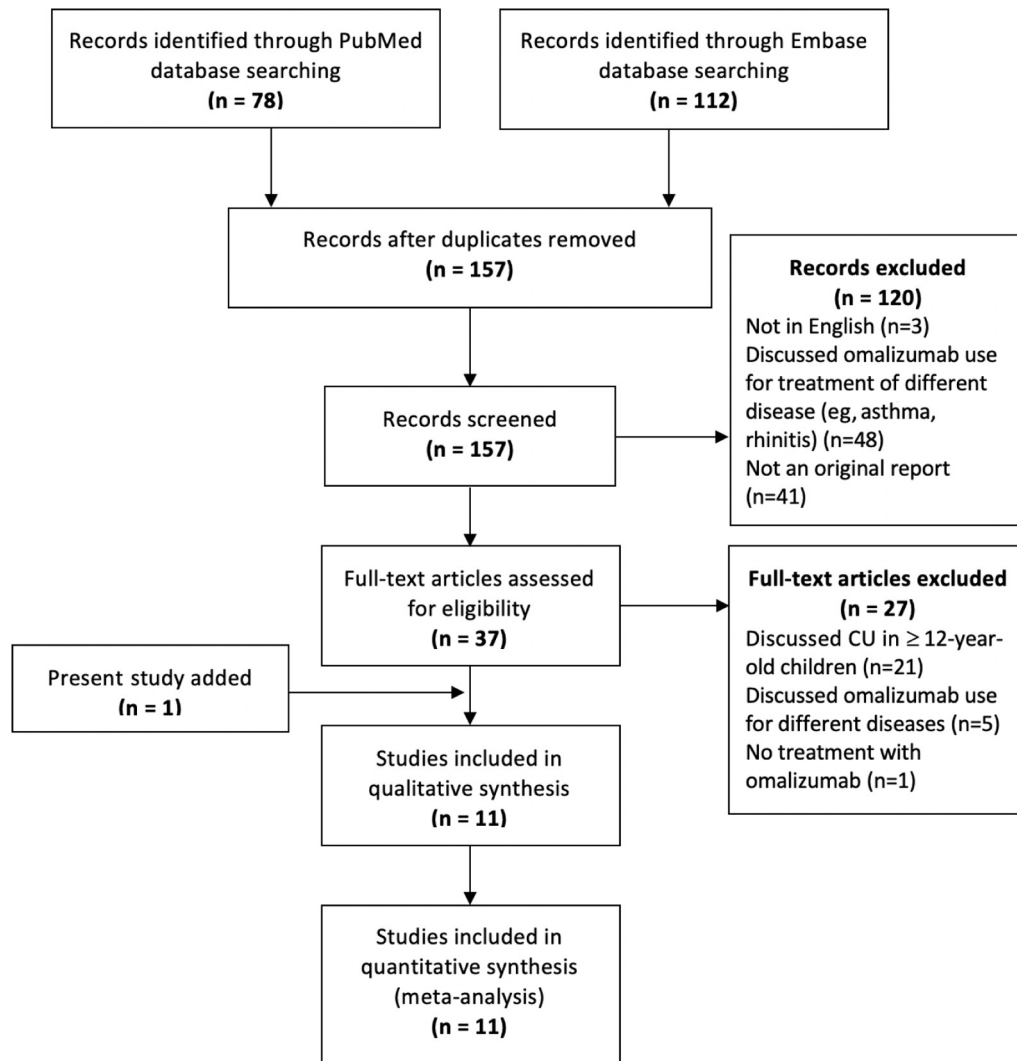


Figure 1. Systematic literature search as recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. CU indicates chronic urticaria.

eTable 1
Summary of Patient Characteristics and Omalizumab Therapy

Variable	Finding ^a
Age, median (range), y	9.5 (2–11)
Sex	
Male	9/16 (56)
Female	7/16 (44)
CU type	
Spontaneous	13/16 (81)
Inducible	3/16 (19)
Concomitant angioedema	5/12 (42)
Duration of disease, median (range), y	1.17 (0.2–3)
Pr-treatment UAS-7	28 (5–42)
Atopic comorbidities	6/9 (67)
Allergic rhinitis	4/9 (44)
Asthma	3/9 (33)
Atopic dermatitis	3/9 (33)
Food allergy	2/9 (22)
IgE level	
Normal	5/12 (42)
Elevated	7/12 (58)
Prior medications	
H ₁ -blockers	15/15 (100)
High-dose H ₁ -blockers	14/15 (93)
H ₂ -blockers	4/9 (44)
LTRA	10/15 (67)
Cyclosporine	5/16 (31)
Oral corticosteroids	9/16 (56)
Omalizumab therapy	
Monthly dose, median (range), mg	300 (75–600)
75 mg monthly	1/16 (6)
150 mg monthly	6/16 (37)
300 mg monthly	8/16 (50)
600 mg monthly	3/16 (19)
Duration of therapy, median (range), mo	7.5 (5–36)
Response	
Complete	13/16 (81)
Partial	3/16 (19)
None	0/16 (0)
Adverse events reported	0/16 (0)

Abbreviations: CU, chronic urticaria; H₁, histamine 1; H₂, histamine 2; LTRA, leukotriene receptor antagonist; UAS-7, weekly urticaria activity score.

^aData are presented as number (percentage) of patients unless otherwise indicated.

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