supported by timely therapeutic intervention. Hematopoietic stem cell transplantation reverses most of the GATA2-deficient clinical phenotypes with good long-term outcomes.

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Antihistamine updosing reduces disease activity in patients with difficult-to-treat cholinergic urticaria

To the Editor:

Cholinergic urticaria (CholU) is a frequent skin disorder characterized by itchy wheals induced by physical exercise and passive warming. Although CholU affects up to 20% of young adults,[1] its etiopathogenesis is still not fully understood.[2] Second-generation antihistamines (sgAHs) are the first-line therapy in patients with CholU, but many patients do not respond to standard sgAH doses.[3,4] In these patients the European Academy of Allergy and Clinical Immunology/GA^{2}LEN/EDF/World Allergy Organization urticaria guidelines recommend sgAH updosing,[5] for which there is very little evidence.[6,7] One of the reasons for this is that CholU used to be difficult to study because of the lack of validated outcome measures. To address this gap, we developed a CholU severity index (CholUSI)[8] and a CholU activity score (CholUAS7; see the Methods section in this article's Online Repository at www.jacionline.org). Very recently, we also developed and published a standardized specific pulse-controlled ergometry (PCE) protocol for the diagnosis of CholU, as well as to objectively evaluate disease activity.[8]

Here we assessed the efficacy of sgAH updosing in patients with CholU refractory to standard treatment by using the CholUSI, CholUAS7, and PCE, as well as a skin health–related quality-of-life instrument, the Dermatology Life Quality Index (DLQI).

Patients with CholU who had been treated with at least 1 sgAH at the licensed dose without achieving sufficient symptom control were enrolled (for study design, see Fig E1 in this article's Online Repository at www.jacionline.org). Their severity of disease was assessed at baseline by using the CholUSI and physician global assessment (PGA). Patients documented their symptoms for 7 days without taking antihistamines, completed the DLQI, and performed the PCE provocation test (30-minute bicycle challenge with a controlled increase of 3 pulse beats/min).[8] Patients were subsequently treated with an sgAH at 4-fold the licensed dose for 7 to 28 days (mean treatment duration ± SD, 9.8 ± 4.9 days) and reassessed by using the PCE and DLQI at the end of the treatment phase. Throughout the study, patients documented their CholU signs and symptoms, as well as exposure to eliciting triggers, in a daily diary. The 7-day CholUAS7 score was calculated with these data and chosen to determine best changes in disease activity in response to treatment. For a detailed description of the study, applied methods and score descriptions, see the Methods section and Tables E1-E3 in this article's Online Repository. In total, 32 patients with CholU were screened for this study, and 28 of them (20 female patients; mean age, 34.0 years; mean duration of disease, 7.6 years; mean duration of wheal episodes, 1.5 hours) were included. Detailed clinical characteristics of the patients are listed in Table E4 in this article's Online Repository at www.jacionline.org.

Analyzing the diary-recorded disease activity, sgAH treatment at 4-fold the standard dose overall significantly ($P = .01$) reduced the CholUAS7 disease activity score by −41% (CholUAS7 components: Wheal7, −38% [$P = .01$]; Pruritus7, −41% [$P = .002$]; and Elicitor7, −3.5% [$P =$ not significant]; Table I) compared with baseline.

UAS score–based PCE provocation test results at 4-fold standard dose sgAH treatment also improved, although not significantly (UASprovo, −13% [$P = .08$]; Table I). Interestingly, PCE threshold levels (ie, time to wheal onset, time to sweating onset, and change in core body temperature before wheal onset were not reduced by high-dose sgAH treatment; Table I).

Health-related quality of life, as determined by using the DLQI, showed an improvement of 21% during high-dose sgAH treatment compared with baseline values ($P = .09$, Table I).

In the detailed responder analysis only 11 (39%) of 28 patients treated with high-dose sgAHs reported an improvement in the CholUAS7 disease activity score of 50% or greater (CholWheal7, 43% of patients; CholPruritus7, 46% of patients; Fig 1, *A*). Complete response, as defined by CholUAS7 improvement of greater than 90%, was achieved in only 1 patient (Fig 1, *A*). In the PCE responder analysis only 2 (7%) of 28 patients showed an

TABLE I. High-dose antihistamine treatment reduces disease activity in patients with CholU refractory to standard doses (n = 28)

	Baseline, mean ± SD (median; [range])	End of high-dose sgAH treatment, mean ± SD (median; range)	Improvement (%)	*P* value
Diary-documented disease activity and quality of life impairment				
Disease activity				
CholUAS7*	43.6 ± 28.5 (37.0; 9 to 114)	25.9 ± 15.4 (24.0; 0 to 68)	40.6	**.01**
Wheal7	8.4 ± 5.8 (9.0; 0 to 21)	5.2 ± 5.7 (4.0; 0 to 21)	38.1	**.01**
Pruritus7	10.2 ± 5.1 (9.0; 2 to 21)	6.0 ± 4.6 (5.5; 0 to 20)	41.2	**.002**
Intensity of elicitors				
Elicitor7†	20.1 ± 4.8 (21.0; 7 to 28)	20.8 ± 4.3 (21.0; 7 to 28)	−3.5	.44
Quality of life				
DLQI score‡	9.7 ± 6.3 (8.5; 1 to 26)	7.6 ± 7.2 (5.5; 0 to 27)	21.6	.09
PCE provocation test results				
PCE-induced CholU activity				
UASprovo score	4.7 ± 1.1 (5.0; 2 to 6)	4.1 ± 1.2 (4.0; 2 to 6)	12.8	.08
Whealprovo score	2.8 ± 0.5 (3.0; 1 to 3)	2.7 ± 0.6 (3.0; 1 to 3)	3.6	.22
Pruritusprovo score	1.9 ± 0.9 (2.0; 1 to 3)	1.5 ± 1.0 (1.0; 0 to 3)	21.1	.15
PCE-induced wheal onset				
Time to wheal onset (min)	11.3 ± 10.0 (12.5; 0 to 28)	12.2 ± 10.4 (13.0; 0 to 29)	7.4	.78
Increase in HR (beats/min) at wheal onset	33.3 ± 32.7 (26.5; −16 to 109)	35.1 ± 31.6 (38.5; 0 to 99)	5.1	.53
Increase in BCT at wheal onset (°C)	0.4 ± 0.7 (0.1; −0.3 to 2.7)	0.6 ± 1.0 (0.2; −0.5 to 3.3)	33.3	.48
PCE-induced onset of sweating				
Time to onset of sweating (min)	14.9 ± 6.2 (15.5; 0 to 26)	13.3 ± 7.0 (13.5; 0 to 28)	−12.0	.63
Increase in HR at onset of sweating (beats/min)	41.9 ± 28.5 (44.0; −1 to 99)	32.9 ± 30.4 (37.5; 0 to 91)	−27.4	.28
Increase in BCT at onset of sweating (°C)	0.4 ± 0.5 (0.3; −0.2 to 1.7)	0.6 ± 0.8 (0.3; −0.5 to 3.4)	33.3	.64

Values in boldface indicate statistical significance.

BCT, Body core temperature; *HR*, heart rate.

*CholUAS7 = 7-day sum of ([Whealday + Itchday] × Intensity of Elicitorday); range = 0 to 168.

†Elicitor7 = 7-day sum of intensity of Elicitorday [no exposure to elicitors = 4, exposure to mild elicitor = 3, exposure to moderate elicitor = 2, and exposure to strong elicitor = 1 point]; range = 0 to 28.

‡DLQI; range = 0 to 30 (no impairment = 0-1 points; mild impairment = 2-5 points; moderate impairment = 6-10 points; very large impairment = 11-20 points; and extremely large impairment = 21-30 point).

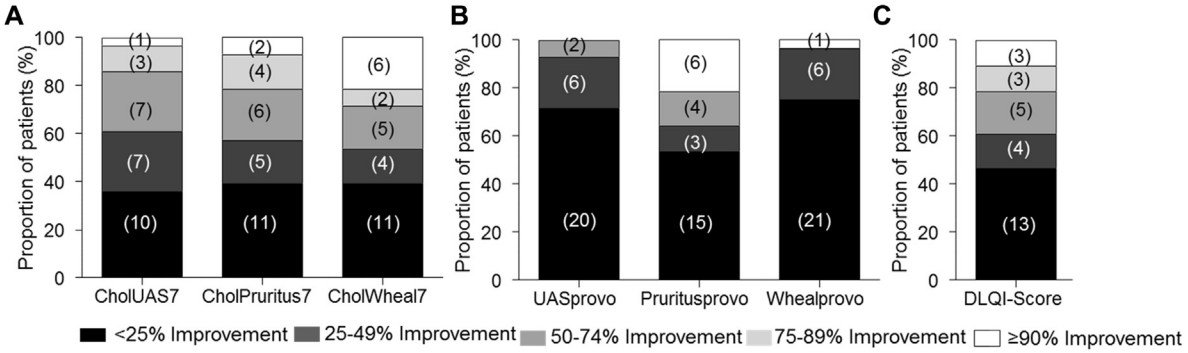

FIG 1. Less than half of all patients with CholU treated with high-dose antihistamines experience complete protection. Five categories of improvement are depicted, and proportions of patients in each category are shown. Absolute numbers of patients are shown in parentheses. **A,** Thirty-nine percent, 43%, and 46% of patients with CholU had 50% or greater improvement with high-dose antihistamines in the CholUAS7 score, the composite pruritus score 7 (CholPruritus7), and the composite wheal score 7 (CholWheal7), respectively. **B,** Only 7% of patients with CholU had 50% or greater improvement in the UASprovo score. Improvement was primarily seen in itch severity (36%) but not in wheal intensity (4%). **C,** Thirty-nine percent of the patients with CholU reported a DLQI score reduction of 50% or greater. *CholUAS7* = 7-day sum of ([Whealday + Itchday] × Intensity of Elicitorday); range = 0 to 168. *CholPruritus7* = 7-day sum of (Pruritusday × Intensity of Elicitorday); range = 0 to 84. *CholWheal7* = 7-day sum of (Whealday × Intensity of Elicitorday); range = 0 to 84. *UASprovo* = Whealprovo + Itchprovo; range = 0 to 6. *Pruritusprovo*: range = 0 to 3. *Whealprovo*: range = 0 to 3. *DLQI*: range = 0-30 (no impairment = 0-1 points; mild impairment = 2-5 points; moderate impairment = 6-10 points; very large impairment = 11-20 points; and extremely large impairment = 21-30 points).

improvement in their UASprovo scores of 50% or greater (Whealprovo, 4%; Itchprovo, 36%; Fig 1, *B*). With PCE, none of the patients had a greater than 90% reduction in UASprovo score.

In the responder analysis less than half of all patients had a substantial improvement in the DLQI score during high-dose sgAH treatment (Fig 1, *C*). Patients whose CholUAS7