Urticaria: A comprehensive review

Treatment of chronic urticaria, special populations, and disease outcomes

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Learning objectives
After completing this learning activity, participants should be able to develop an initial treatment plan for a patient with acute or chronic urticaria; identify second-, third-, and fourth-line treatment options when initial treatments are ineffective; discuss outcomes of the disease; and describe possible disease course with patients.

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Second-generation antihistamines are considered first-line agents in the treatment of chronic urticaria because of their safety and efficacy profile. Some patients require higher doses of H_1 antihistamines alone or in combination with other classes of medications, including H_2 antihistamines, leukotriene receptor antagonists, or first-generation H_1 antihistamines. One major therapeutic advance has been omalizumab, a humanized monoclonal anti—immunoglobulin E that was recently approved by the US Food and Drug Administration for the treatment of chronic urticaria that is unresponsive to H_1 antagonists. In addition, the second article in this continuing medical education series outlines several evidence-based alternative treatments for urticaria and the differences in recommendations between 2 major consensus groups (the European Academy of Allergy and Clinical Immunology/World Allergy Organization and the American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology Joint Task Force). (J Am Acad Dermatol 2018;79:617-33.)

Key words: acute; antihistamines; children; chronic; corticosteroids; elderly; leukotriene receptor antagonists; management; omalizumab; quality of life; urticaria.

H_1 ANTIHISTAMINES

Key points

- **Second-generation antihistamines are considered first-line agents because of their safety and efficacy profile**
- **For nonresponsive patients, higher than recommended doses of antihistamines are an acceptable option**
- **First-generation antihistamines have similar efficacy to second-generation antihistamines, but sedation makes them less favorable**

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Table I. Efficacy of histamine H_1 receptor antagonist randomized, double-blind, placebo-controlled studies

Study	N	Duration, weeks	Treatment	Comments
Breneman et al[9]	187	4	Cetirizine 10 mg vs astemizole* 10 mg vs placebo	Cetirizine was superior to astemizole in reducing the number of wheals Both agents were statistically superior to placebo at relieving CSU symptoms based on weekly patient rating
Nettis et al[10]	100	6	Levocetirizine 5 mg vs placebo	Complete symptom resolution in 53% of patients taking levocetirizine at the study endpoint compared with 0% in the placebo group
Finn et al[11] and Nelson et al[12]	489 and 418	4	Fexofenadine 20, 60, 120, and 240 mg† and placebo	Same study design for both trials Efficacy results were similar in the 60-, 120-, and 240-mg groups. All dosages were statistically superior to placebo and the 20-mg group in reducing mean pruritus score, mean number of wheals, and mean TSS when compared to baseline values
Kaplan et al[7]	255	4	Fexofenadine 180 mg vs placebo	Once-daily dosing of fexofenadine was superior to placebo for improvement in mean number of wheals, pruritus severity scores, and in TSS
Handa et al[13]	97	4	Cetirizine 10 mg vs fexofenadine 180 mg	Cetirizine showed superior overall efficacy, determined by subject rating on an analog scale Complete symptom resolution in 52% of patients taking cetirizine at the study endpoint compared with 4.4% in the fexofenadine group
Leynadier et al[14]	61	4	Mizolastine 10 mg vs loratadine 10 mg	Both agents had a similar reduction in urticarial episodes Mizolastine was associated with a greater reduction in the number of wheals compared to loratadine
Ortonne et al[3]	137	6	Desloratadine 5 mg vs placebo	Desloratadine was superior to placebo in improving pruritus scores

TSS, Total symptom score.
*Astemizole was removed from the market due to the rare but possible QTc prolongation and subsequent arrhythmia side effect.
†Twice daily dosing.

Second-generation antihistamines (sgAHs), such as loratadine, desloratadine, fexofenadine, cetirizine, levocetirizine, azelastine, and bilastine (not available in the United States) are considered first-line treatment for mild to moderate chronic urticaria (CU).[1,2] Several randomized controlled trials (RCTs) have demonstrated a high level of safety, efficacy, and tolerability.[3-7] Once daily dosing is recommended over an as-needed regimen to maximize clinical response and improve quality of life.[8] When comparing the efficacy of individual agents (Table I),[3,7,9-14] some studies[2,13,15-18] suggest the superiority of certain sgAHs over others, but data are limited.[19] More than 50% of patients with CU do not respond to sgAH doses that have been approved by the US Food and Drug Administration.[20] For these patients, higher than recommended doses are considered reasonable.[2,19,21] In fact, 2 to 4 times the "normal" doses are frequently needed with sgAHs. Anecdotal experience points to the fact that starting with the "normal" dose rarely is effective for patients with urticaria. Patients can be told to escalate the doses every few days if they have no side effects but do not respond to current dosages. Nonetheless, there are few clinical trials supporting this recommendation.[12,22-25] However, European and US guidelines recommend increasing sgAH doses 2- to 4-fold because of their tolerability, safety, and efficacy in many patients.[1] First-generation antihistamines (fgAHs) are clinically effective and act rapidly in adults.[26] However, they are associated with increased sedation, leading to impaired motor skills, because of their ability to cross the blood–brain barrier.[17,27,28] Nonetheless, studies have shown tolerance to performance impairment after 3 to 5 days of therapy.[26,29,30] These agents can cause excessive dryness and gastrointestinal side effects, such as constipation, because of their anticholinergic activity.[31] The original sgAHs, such as terfenadine and astemizole, caused Torsades de