

Successful treatment of chronic urticaria with leukotriene antagonists

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Chronic urticaria is often difficult to treat and may not be controlled by antihistamines alone. In this report I note 2 patients with severe chronic urticaria and aspirin sensitivity that were successfully treated with a leukotriene antagonist.

CASE REPORTS

Case 1

Aspirin sensitivity manifested by onset of severe acute urticaria and erythema developed in a 33-year-old man within 1 hour of ingesting aspirin. He had no evidence of sinusitis or nasal polyps. One year after becoming aspirin sensitive, chronic urticaria and angioedema developed that has lasted for the past 10 years. The urticaria was of sufficient severity to require 2 emergency department visits and epinephrine injections to reverse upper airway obstruction. Before his initial office visit, he had 6 weeks of daily

urticaria unresponsive to diphenhydramine 50 mg 4 times daily. Screening laboratory studies included a normal complete blood cell count, sedimentation rate, and chemistry panel. The urticaria persisted despite treatment with loratadine 10 mg 4 times daily and cetirizine 10 mg 4 times daily in addition to diphenhydramine. He next began taking zafirlukast 20 mg twice daily, and within 24 hours he felt significantly better but still had some hives. Weeks later he was switched from zafirlukast to zileuton 600 mg orally 4 times daily, and within 3 hours he noticed even more improvement. While taking zileuton, he felt significantly better and did not require antihistamines for several days.

After receiving informed consent, objective confirmation of his response to leukotriene antagonists was undertaken. After a washout period, he underwent 3 weeks of double-blind, double-dummy, placebo-controlled evaluation. He took 4 opaque capsules per day from a first container and 2 opaque capsules per day from a second container. He was randomly assigned to 3 treatment combinations at 1-week intervals composed of zileuton 600 mg 4 times daily plus placebo, zafirlukast 20 mg twice daily plus placebo, or placebo plus placebo. Rescue antihistamines were added as needed. At the end of the trial and before breaking the code, he ranked the effectiveness of the treatment combinations from best to worst on scale of 1 to 10. A score of 1 indicated very poor control requiring high-dose rescue antihistamines. A score of 10 meant excellent control of urticaria with no need for antihistamines. Factors used to judge effectiveness included need for rescue antihistamines in addition to intensity and extent of urticaria and pruritis. The patient ranked zileuton best, with a score of 9, followed by zafirlukast, with a score of 5. The week on double placebo was his worst, with a score of 1.

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Case 2

A 44-year-old man was recently evaluated with aspirin sensitivity, nasal polyps, sinusitis, steroid-dependent asthma, and severe chronic urticaria. Three years ago he experienced severe facial swelling, erythema, and acute wheezing 1 hour after taking aspirin. One year after becoming aspirin sensitive, asthma and chronic urticaria requiring daily oral corticosteroids to control developed in this patient. Within 24 hours of starting zileuton 600 mg 4 times daily his respiratory status improved, and the urticaria resolved. He has been hive-free for over a month while taking daily zileuton.

DISCUSSION

Leukotrienes are generated by a number of cells, including mast cells, basophils, neutrophils, and eosinophils, which are present in airways of asthmatic subjects but may also be present in the skin.¹ Zileuton and zafirlukast have demonstrated effectiveness in blocking some of the adverse effects of leukotrienes in asthmatic subjects; however, little is known regarding what effect, if any, leukotriene antagonists have in control of chronic urticaria. I was unable to find any published articles on the use of leukotriene antagonists in the treatment of urticaria other than 2 recent abstracts and a Letter to the Editor in the *Journal of Allergy and Clinical Immunology*. Norris and Sullivan² report studying 15 adult patients with severe urticaria requiring systemic corticosteroids to achieve acceptable control. The addition of zafirlukast 20 mg twice daily achieved control in 9 of 15 (60%). Four of the 6 refractory patients achieved control when treated with combined H₁ and H₂ antihistamines and cyclosporin. Chiu and Warren³ report their results using zafirlukast in a nonrandomized, open series of 15 subjects with urticaria. Eight of the 15 patients with urticaria improved, including 2 patients who were able to successfully discontinue oral steroids. Seven patients

with urticaria were not helped with zafirlukast. In addition, Spector and Tan⁴ report 2 patients with chronic urticaria whose symptoms were inadequately controlled while receiving multiple antihistamines. One patient's urticaria responded to zafirlukast, and the other was helped by zileuton.

In conclusion, a subset of patients with chronic urticaria experience improved control using leukotriene antagonists. In patients with chronic urticaria, the prevalence of sensitivity to aspirin and nonsteroidal antiinflammatory drugs is estimated to be between 21% and 30%.⁵ The pathogenesis of aspirin sensitivity most likely involves inhibition of cyclooxygenase by aspirin or nonsteroidal antiinflammatory drugs resulting in a change in the balance of arachidonic acid metabolites, with an increase in leukotriene LTB₄, LTC₄, LTD₄, and LTE₄. Because of this imbalance, patients with aspirin sensitivity and chronic urticaria may be more likely to respond to leukotriene antagonists than those lacking this sensitivity. Further research into the use of leukotriene antagonists in patients with chronic urticaria, particularly those with aspirin sensitivity, is warranted.

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