Off-Label Drug Uses

Zafirlukast: Chronic Urticaria

Joyce A. Generali, RPh, MS, FASHP (Editor),* and Dennis J. Cada, PharmD, FASHP, FASCP†

This *Hospital Pharmacy* feature is extracted from *Off-Label Drug Facts*, a publication available from Wolters Kluwer Health. *Off-Label Drug Facts* is a practitioner-oriented resource for information about specific drug uses that are unapproved by the US Food and Drug Administration. This new guide to the literature enables the health care professional or clinician to quickly identify published studies on off-label uses and determine if a specific use is rational in a patient care scenario. References direct the reader to the full literature for more comprehensive information before patient care decisions are made. Direct questions or comments regarding *Off-Label Drug Uses* to jgeneral@ku.edu.

RATIONALE

Chronic urticaria (CU), a relatively common condition that can significantly interfere with quality of life, typically manifests as a result of cutaneous mast cell release of histamine. Release can be induced specifically by immunoglobulin E and nonspecifically by various agents or compounds (eg, food, medications, infections, immune disorders). The goal of treatment is complete symptom relief, and the mainstay of treatment is nonsedating antihistamines. When treating urticaria, the approaches to consider are omission of eliciting drugs (if any), avoidance of physical and other stimuli in inducible urticaria, treatment of infectious agents, dietary modification, and symptomatic treatment. Although the goal in managing CU is the identification of a treatable cause, this may not be possible. Conventional treatment (eg, histamine H₁ antagonists) is not effective in all patients. As leukotrienes may be involved in the pathogenesis of urticaria, leukotriene receptor antagonists have been suggested as useful agents, either as monotherapy or add-on therapy in some patients with CU.^{1,2}

POPULATION

Adults with CU.

DOSING STUDIED

Oral: 20 mg twice daily.^{3,4}

DISCUSSION

Guidelines

American Academy of Allergy, Asthma & Immunology (AAAAI); American College of Allergy, Asthma & Immunology (ACAAI); and the Joint Council of Allergy, Asthma & Immunology (JCAAI)

Practice parameters created by the Joint Task Force on Practice Parameters for AAAAI, ACAAI, and JCAAI proposed a step-care approach for the management of CU. Step 1 includes the use of monotherapy with second-generation antihistamines and the avoidance of triggers as first-line therapy. Step 2 may include one or more of the following measures: higher doses of second-generation antihistamines used in step 1 with or without the addition of another second-generation antihistamine, a H₂-antagonist, a leukotriene receptor antagonist, or a first-generation antihistamine (at bedtime). Step 3 involves the dose advancement of potent antihistamines (eg, hydroxyzine or doxepin) as tolerated. Step 4 recommends the addition of alternative agents such as omalizumab, cyclosporine, other anti-inflammatory agents, immunosuppressants, or biologics. Although not included in the step-approach algorithm, the short-term use of corticosteroids (1 to 3 weeks) may be required for the management of exacerbations, although no controlled trials support this use.¹

*Editor-in-Chief, *Hospital Pharmacy*, and Clinical Professor, Emeritus, Department of Pharmacy Practice, University of Kansas, School of Pharmacy, Kansas City/Lawrence, Kansas, e-mail: jgeneral@ku.edu; †Founder and Contributing Editor, *The Formulary*, and Editor, *Off-Label Drug Facts*, e-mail: Dennis.Cada@wolterskluwer.com.

World Allergy Organization

World Allergy Organization guidelines for the diagnosis and treatment of urticaria and angioedema state that second-generation nonsedating H_1 -antihistamines represent the mainstay of treatment for urticaria (high-quality evidence; strong recommendation); in an algorithm for the treatment of CU, these agents are recommended as first-line therapy at labeled doses. If symptoms persist after 2 weeks, higher doses (up to 4 times the labeled dose) may be used (moderate-quality evidence; weak recommendation). If symptoms persist after 1 to 4 weeks of therapy, a leukotriene antagonist may be added (low-quality evidence; weak recommendation) or a change may be made to another nonsedating antihistamine. Short courses (3 to 7 days) of systemic oral corticosteroids at minimally effective doses may be useful for the management of exacerbations (low-quality evidence; weak recommendation). If symptoms continue to persist after 1 to 4 weeks, the algorithm states that the addition of one of several agents may be considered, including cyclosporine A (moderate-quality evidence; weak recommendation), H_2 -antihistamines (moderate-quality evidence; weak recommendation), dapsone (low-quality evidence; weak recommendation), and anti-IgE (low-quality evidence; weak recommendation).²

Controlled Trials

In a double-blinded, placebo-controlled, crossover trial, 52 adult patients with refractory CU were randomized to receive zafirlukast 20 mg twice daily or placebo twice daily. Prior to study initiation, a washout period of at least 1 week occurred, during which all medications, except for acrivastine (up to 8 mg 3 times daily), were stopped. Acrivastine (not available in the United States) was also allowed during the study as a rescue antihistamine. Each 6-week treatment period was separated by a 1-day washout period. Efficacy parameters were scored and self-reported via a patient diary and included itching, disturbance of daily activity and sleep, intensity of erythema, and number, extent, and size of wheals. Overall, clinical benefit was scored by both patients and investigator. A total of 46 patients completed the study. There was no difference between the zafirlukast and placebo groups for patient or physician assessment of efficacy parameters or the mean number of acrivastine tablets used as rescue medication (1.23 vs 1.09 tablets daily, respectively). A total of 7 (15%) patients had complete resolution of symptoms, 4 during the placebo

period and 3 during the zafirlukast period. Marked improvement in symptoms occurred in 12 (26%) patients, 7 and 5 during the placebo and zafirlukast groups, respectively. Analysis of patient subgroups (eg, forms of CU) did not reveal any differences between the groups. The authors concluded that zafirlukast did not provide benefit over placebo at the dose studied.⁴

In a double-blind, placebo-controlled study, patients (older than 12 years) with refractory CU received cetirizine (10 mg daily) and placebo (twice daily) for a 1-week run-in period. Those with persistent hives ($n = 95$) were randomized to receive 3 weeks of treatment with cetirizine monotherapy (10 mg daily + placebo twice daily) or in combination with zafirlukast (20 mg twice daily). All patients were allowed the use of diphenhydramine (up to 50 mg 4 times daily) as a rescue medication. Upon initial evaluation, patients also underwent autologous serum skin testing (ASST) in the dorsal forearm using positive (histamine) and negative (saline) controls. During the 3-week treatment period, hives were evaluated by both physician and patient via a 10-cm visual analogue scale (VAS) measuring number and size of lesions and an 11-point treatment effectiveness score (TES) assessing efficacy of treatment. Follow-up visits for physician assessment were performed weekly during the comparative portion of the study. Three patients in the combination group and 6 in the monotherapy group did not complete the study. When all 3 weekly visits were considered, significant differences between the 2 groups were found only for physician and patient VAS scores. Twenty-two patients tested positive for ASST and were identified as having autoimmune CU. When ASST status was considered in patients receiving combination therapy, there was a significant improvement in mean physician TES scores ($P < .01$) and patient VAS scores ($P < .02$) for those who were ASST positive compared to ASST negative. ASST status did not impact results in the placebo group. Adverse events were not reported in this trial. Based on these results, the authors concluded that the addition of zafirlukast to the current treatment regimen may be of benefit in patients with autoimmune (ASST positive) CU refractory to histamine-1 monotherapy.³

RISK/BENEFIT CONSIDERATIONS

This is a limited safety profile. Refer to package labeling for complete prescribing information (eg, Warnings/Precautions, Adverse Reactions, Drug Interactions).

THERAPEUTIC CONSIDERATIONS

Data from controlled, double-blinded trials are conflicting regarding the use of zafirlukast as monotherapy or in combination with antihistamines for the management of CU refractory to antihistamine monotherapy.^{3,4} Zafirlukast in combination with antihistamines may be more effective in patients with autoimmune (positive ASST) CU.³

Based on clinical practice guidelines by AAAAI and ACAAI and the World Allergy Organization for the diagnosis and management of acute urticaria and CU, a leukotriene receptor antagonist may be added to antihistamine therapy in patients who do not respond to antihistamines.^{1,2}

REFERENCES

1. Bernstein JA, Lang DM, Khan DA, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. *J Allergy Clin Immunol*. 2014;133(5):1270-1277.
2. Sánchez-Borges M, Asero R, Ansotegui IJ, et al; WAO Scientific and Clinical Issues Council. Diagnosis and treatment of urticaria and angioedema: A worldwide perspective. *World Allergy Organ J*. 2012;5(11):125-147.
3. Bagenstose SE, Levin L, Bernstein JA. The addition of zafirlukast to cetirizine improves the treatment of chronic urticaria in patients with positive autologous serum skin test results. *J Allergy Clin Immunol*. 2004;113(1):134-140.
4. Reimers A, Pichler C, Helbling A, Pichler WJ, Yawalkar N. Zafirlukast has no beneficial effects in the treatment of chronic urticaria. *Clin Exp Allergy*. 2002;32(12):1763-1768. ■