Off-Label Drug Uses

Montelukast: Chronic Urticaria

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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. The approaches to consider when treating urticaria 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 chronic urticaria is identification of a treatable cause, a cause may not be identified. Conventional treatment (eg, histamine H₁ antagonists) is not effective in all patients. As leukotrienes are thought to 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: 10 mg daily.^{3,4}

DISCUSSION

Results from trials evaluating the use of montelukast (mostly in combination with an H₁ antihistamine) in the management of CU are inconsistent, and trials are of short duration. Guidelines find only weak support for the use of leukotriene antagonists in combination with an H₁ antihistamine in patients who do not respond to conventional treatment.

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 (JTFPP) 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

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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

World Allergy Organization

World Allergy Organization guidelines for the diagnosis and treatment of urticaria and angioedema state that second-generation nonsedating H₁ 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 changed 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), H₂-antihistamines (moderate-quality evidence; weak recommendation), dapsone (low-quality evidence; weak recommendation), anti-IgE (low-quality evidence; weak recommendation).²

Controlled Trials

Combination Therapy with Antihistamines

In a single-blind, placebo-controlled trial, 120 patients with chronic idiopathic urticarial (CIU) completed a 1-week washout period and then randomized to 4 weeks of therapy with (a) oral hydroxyzine (25 mg daily) with cetirizine (5 mg twice daily), (b) oral hydroxyzine (25 mg daily) with famotidine (20 mg twice daily), (c) oral hydroxyzine (25 mg twice daily) with montelukast (5 mg twice daily), or (d) oral placebo twice daily. Possible weekly urticaria activity scores (UAS) ranged from 0 to 42 and were based on daily patient recording of number of wheals (0 = <10 wheals to 3 = covered with wheals) and relative severity of itching (0 = none to 3 = severe). Treatment

response was defined as a reduction of weekly UAS to less than 25% of baseline. Relapse was defined as greater than 75% of baseline UAS. The dropout rate in the placebo group was high (43.3%) and was related to a lack of therapeutic benefit after 1 to 2 weeks. In the remaining patients in the placebo group, there was no change in the mean UAS after 4 weeks of treatment compared to baseline (31.2) and no patients experienced therapeutic response. A total of 23.3%, 63.3%, and 53.3% of the patients achieved therapeutic response in groups A, B, and C, respectively. The combination of a histamine-2 receptor antagonist with a histamine-1 receptor antagonist (group B) was similar to a leukotriene receptor antagonist combined with a histamine-1 receptor antagonist (group C). Hydroxyzine-related sedation was the most commonly cited adverse event.⁵

In a double-blind, placebo-controlled trial, 81 patients with CU were randomized to receive oral desloratadine (5 mg daily) with placebo, desloratadine (5 mg daily) with montelukast (10 mg daily), or placebo alone. The 8-week study was initiated with a single-blind, 1-week placebo baseline period and ended with a 1-week, single-blind, placebo washout period. A total of 76 patients completed the study. Desloratadine alone and desloratadine in combination with montelukast demonstrated significant improvement in total symptom score (maximum score, 12) based on the severity of pruritus, number and size of wheals, and number of separate urticarial episodes. Patients also self-rated the overall severity of urticaria based on a 10-cm visual analog scale. At the end of the study, mean total symptom score decreased from baseline by 88.5% in the combination group and by 69% in the desloratadine monotherapy group. Total relief from symptoms was documented in 73% and 16% of the 2 groups, respectively. At the end of the washout period, positive effects persisted, with a total resolution of symptoms recorded in 19.2% and 8% of the groups, respectively. The authors concluded that the combination of desloratadine and montelukast is effective in the management of CU.³

In a double-blind, placebo-controlled, double-dummy, parallel group study, 160 adult patients with moderate CIU were randomized to 6 weeks treatment with desloratadine (5 mg daily) or montelukast (10 mg nightly) as monotherapy, desloratadine and montelukast combination therapy, or placebo. Efficacy was based on cutaneous symptoms (eg, pruritus, number of hives, size of hives) and interference with sleep and daily activities. Most patients in the montelukast monother-

apy and placebo groups failed to complete the study (67.5% and 87.5%, respectively). All patients treated with desloratidine monotherapy or in combination therapy completed the trial. When compared to the placebo control group, all treatment groups showed significant differences in total symptom score (TSS), number of hives, and size of largest hive. For pruritus symptoms, only desloratidine monotherapy or combination therapy showed significant differences compared to placebo. There was no difference in all parameters between the desloratidine monotherapy group and the combination therapy group. Adverse events were mild and similar in all groups, with the exception of urticaria exacerbation in patients treated with montelukast monotherapy or placebo monotherapy. The authors concluded that desloratidine monotherapy is effective in the management of CIU and that the addition of montelukast offers no additional benefit.⁴

RISK/BENEFIT CONSIDERATIONS

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

In the limited studies reviewed, no adverse reactions were reported during the course of therapy.

THERAPEUTIC CONSIDERATION

Data from controlled, double-blind trials are conflicting regarding the use of montelukast in

combination with antihistamines for the management of CU.³⁻⁵

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

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