

Montelukast reduces symptom severity and frequency in patients with angioedema-predominant chronic spontaneous urticaria



Ayobami T. Akenroye, MD, MPH, Conor McEwan, BS, and Sarbjit S. Saini, MD

Clinical Implications

- In patients with angioedema-predominant chronic spontaneous urticaria, the addition of a leukotriene receptor antagonist to background daily antihistamine therapy improved symptoms in a significant proportion of patients and led to disease resolution in about two-thirds of patients.

TO THE EDITOR:

In chronic spontaneous urticaria (CSU), 50% of patients report mainly urticaria, about 40% have concomitant angioedema with urticaria, whereas 10% of patients mainly suffer from angioedema.¹ Following exclusion of other causes of angioedema such as hereditary angioedema and angiotensin-converting enzyme inhibitor-induced angioedema, the management of angioedema-predominant patients, that is, patients with CSU who primarily have angioedema with or without concomitant hives, is similar to that of patients with CSU. Therapy includes a stepwise approach, using antihistamines up to 4-fold standard dose, followed by the use of omalizumab in antihistamine-refractory cases.² However, less than half of patients with CSU respond optimally to antihistamines, which are the first line of treatment.^{3,4} Leukotriene receptor antagonists (LTRAs) are well tolerated, and thus are an attractive option for additional therapy in antihistamine-refractory CSU.⁵ However, the reported effectiveness of LTRAs in CSU is mixed,⁵⁻⁸ and in the 2018 World Allergy Organizations consensus statement, evidence supporting LTRA use was considered too weak for a clear recommendation.² Previous studies of LTRAs for CSU have included patients with CSU but have not selectively studied patients with angioedema-predominant CSU. In patients with CSU, the presence of angioedema contributes to a lower quality of life and less productivity, and increases health care resource utilization.^{3,9} In this study, we assessed the response of patients with angioedema-predominant CSU to montelukast, the most prescribed LTRA in our center, as an add-on therapy to antihistamines.

We conducted a retrospective chart review of 49 patients who had been evaluated in our clinic for angioedema-predominant CSU between 2008 and 2017. Of these, 11 patients were lost to follow-up and response to treatment could not be assessed. All subjects were determined not to have hereditary angioedema, acquired C1 inhibitor deficiency, underlying thyroid disease, or angiotensin-converting enzyme inhibitor-induced angioedema. Autoimmune diseases and malignancies were excluded as appropriate. Of the 38 patients included, 24 received montelukast as part of their regimen while 14 did not receive

montelukast or any other LTRA. All these patients were on 4 times the usual dose of antihistamines except in few instances when this dose could not be tolerated. None had received omalizumab before montelukast therapy. Montelukast was given at a dose of 10 mg daily. We graded the severity of each patient's disease using an 8-point Likert scale, with a higher number depicting worse disease (see footnote in Table 1). The scale was applied at the time of initial clinical encounter, at peak disease state, and at follow-up visits when applicable or after a change in medication regimen. For patients who received montelukast, we assessed disease severity and frequency of episodes from before to after montelukast prescription. For patients who did not use montelukast, we compared symptoms from the initial visit when other add-on therapies such as doxepin and daily steroids were initiated to after the initiation of these therapies. We also assessed whether the patient had "no improvement," "some improvement" (meaning any decrease in disease severity or frequency but without complete resolution), or "complete resolution" of disease. We used Wilcoxon-Mann-Whitney test for continuous variables, Fisher exact test for categorical variables, and nonparametric Wilcoxon signed rank test for paired analyses. We used a significance level of less than .05.

Both groups were similar in age, sex, duration, and severity of disease at the initial visit (Table 1). A total of 22 (92%) of the 24 patients on montelukast had some improvement in their symptoms following the addition of montelukast compared with 7 (50%; $P = .006$) of the 14 patients who did not receive montelukast. The 14 patients who did not receive montelukast were on various other regimens that included antihistamines (all the 14 patients), doxepin (given in addition to other antihistamines in 4 patients), and 2 patients on daily prednisone. A higher percentage of patients who received montelukast also experienced complete resolution of disease in the follow-up period ranging from 4 months to 3 years (Figure 1, A). There was a significant improvement in within-individual disease severity and frequency in the group that received montelukast (Figure 1, B). More than 70% of patients who noted improvement in symptoms experienced this improvement within the first 6 months of therapy although 2 patients reported improvement following 12 months of therapy.

One of the 2 patients with no response to montelukast had a good response to doxepin, whereas the other was placed on omalizumab therapy with favorable response. All patients tolerated montelukast except 1 patient who reported nightmares on therapy.

The clinical response of patients with CSU to LTRA in past studies is variable.⁵⁻⁸ In this study, we found that an overwhelming proportion of patients with angioedema-predominant CSU noted a significant improvement in disease severity and frequency. Although LTRAs are reported to be specifically helpful in patients with nonsteroidal anti-inflammatory drug-sensitive CSU,⁸ we found that the effect of montelukast in these angioedema-predominant patients was independent of nonsteroidal anti-inflammatory drug sensitivity. The mechanisms underlying the effect of montelukast in these patients remain to be determined but suggests a more significant role of leukotrienes in the pathogenesis of angioedema in contrast to patients with CSU with urticaria alone or a mixed urticaria/angioedema phenotype. In the 2014 American Academy of

TABLE I. Demographic and clinical characteristics of participants

Characteristic	Received montelukast	Did not receive montelukast	P value
N	24	14	
Age (y), mean $\pm$ SD	58.4 $\pm$ 14.0	50.1 $\pm$ 15.0	0.10
Female sex, n (%)	14 (58)	6 (43)	0.50
Disease duration (y), median (IQR)	4 (3-12)	6 (3-10)	0.12
NSAID sensitivity, n (%)	5 (21)	3 (21)	1.00
Doxepin, n (%)	3 (12.5)	4 (28.6)	0.39
Disease frequency and severity			
Annual frequency of episodes at baseline, median (IQR)	12 (8-36)	16.5 (11-36)	0.61
Severity of episodes at baseline, median (IQR)*	6 (6-6)	6 (5-6)	0.19
History of endotracheal intubation at baseline, n (%)	2 (8)	2 (14)	0.62

IQR, Interquartile range; NSAID, nonsteroidal anti-inflammatory drug.

*Severity Scale: 0 = no swelling and no medications; 1 = minimal swelling and antihistamine only as needed; 2 = minimal swelling + steroids only as needed; 3 = no swelling, well controlled on daily medications (3A: daily antihistamine, 3B: daily montelukast + antihistamine, 3C: daily doxepin); 4 = minimal swelling on daily program; no additional medications beyond daily regimen (antihistamines $\pm$ montelukast); 5 = moderate swelling on daily program with use of additional antihistamines beyond daily regimen; 6 = moderate to severe swelling on daily program with use of steroids; 7 = severe swelling requiring immediate medical attention; 8 = critical swelling requiring endotracheal intubation.

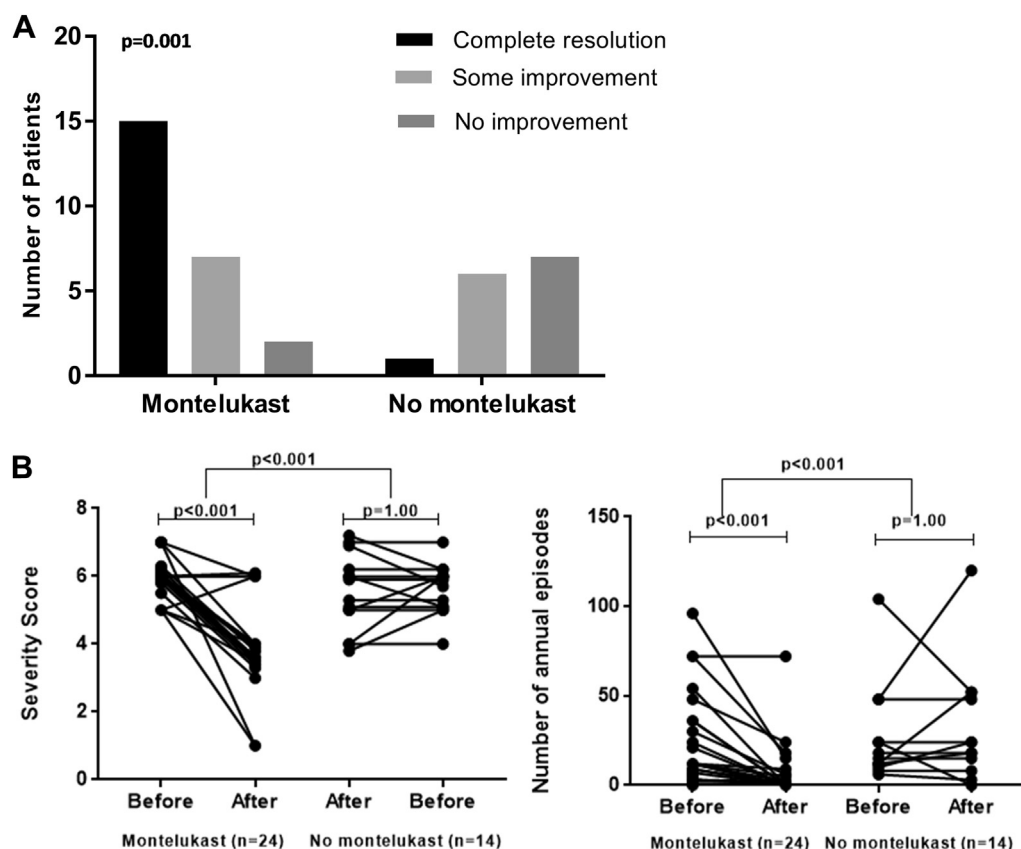


FIGURE 1. A, Number of patients with complete resolution, some improvement, or no improvement. B, Changes in (1) severity score and (2) frequency of episodes from the initial visit to the last visit.

Allergy, Asthma & Immunology update on the diagnosis and management of acute and chronic urticaria,⁵ montelukast is one of the optional add-on therapies for patients without adequate response to antihistamines. This study supports that it may be beneficial to consider montelukast an appropriate second-line agent in patients with angioedema-predominant disease. It however has several limitations. First, it is a retrospective study

and details are limited by the comprehensiveness and accuracy of documentation. However, these patients were all from a single provider's clinic with a standard template for obtaining histories from patients. It is therefore unlikely that documentation accuracy would differ between patients who received montelukast and those who did not. Second, this is a single-site study and our referral practice might differ from other practices. For instance,

montelukast is the main LTRA used, whereas other centers may prefer to use zafirlukast or the 5-lipoxygenase inhibitor zileuton. Given varying side-effect profiles, we cannot extend our findings to other therapies in this class of medication. Finally, we had relatively low patient numbers. However, because low sample sizes would affect the power of the study to a greater extent than would the type 1 error rate, it is quite interesting that we were still able to observe significant differences between the groups at the $P < .05$ significance level. We also do not know whether the effects of montelukast observed are durable but the patients in this study had a minimum of 3 months observation time after the initiation of therapy. Despite these limitations, this study could stimulate future prospective studies looking specifically at montelukast (and possibly other LTRAs or zileuton) and its effect on patients with angioedema-predominant CSU.

Department of Medicine, Division of Allergy and Clinical Immunology, Johns Hopkins Asthma and Allergy Center, Baltimore, Md

The authors received no funding for this study. S.S.S. is supported by the National Institutes of Health grant (grant no. R01AI116658).

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication March 13, 2018; revised April 26, 2018; accepted for publication April 27, 2018.

Available online May 5, 2018.

Corresponding author: Ayobami T. Akenroye, MD, MPH, Johns Hopkins Asthma and Allergy Center, 5501 Hopkins Bayview Circle 2B.80, Baltimore, MD 21224.

E-mail: ayobami.akenroye@jhmi.edu.

2213-2198

© 2018 American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaip.2018.04.026>

REFERENCES

1. Sánchez-Borges M, Asero R, Ansotegui IJ, Baiardini I, Bernstein JA, Canonica GW, et al. Diagnosis and treatment of urticaria and angioedema: a worldwide perspective. *World Allergy Organ J* 2012;5:125-47.
2. Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B, et al. The EAACI/GA²LEN/EDF/WAO Guideline for the Definition, Classification, Diagnosis and Management of Urticaria. The 2017 Revision and Update [published online ahead of print January 15, 2018]. *Allergy*. <https://doi.org/10.1111/all.13397>.
3. Maurer M, Weller K, Bindslev-Jensen C, Gimenez-Arnau A, Bousquet PJ, Bousquet J, et al. Unmet clinical needs in chronic spontaneous urticaria. A GA(2)LEN task force report. *Allergy* 2011;66:317-30.
4. Vestergaard C, Toubi E, Maurer M, Triggiani M, Ballmer-Weber B, Marsland A, et al. Treatment of chronic spontaneous urticaria with an inadequate response to H1-antihistamines: an expert opinion. *Eur J Dermatol* 2017;27:10-9.
5. Bernstein JA, Lang DM, Khan DA, Craig T, Dreyfus D, Hsieh F, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. *J Allergy Clin Immunol* 2014;133:1270-7.
6. Di Lorenzo G, Pacor ML, Pellitteri ME, Morici G, Di Gregoli A, Lo Bianco C, et al. Randomized placebo-controlled trial comparing fluticasone aqueous nasal spray in mono-therapy, fluticasone plus cetirizine, fluticasone plus montelukast and cetirizine plus montelukast for seasonal allergic rhinitis. *Clin Exp Allergy* 2004;34:259-67.
7. Nettis E, Dambra P, D'Oronzio L, Loria MP, Ferrannini A, Tursi A. Comparison of montelukast and fexofenadine for chronic idiopathic urticaria. *Arch Dermatol* 2001;137:99-100.
8. Pacor ML, Di Lorenzo G, Corrocher R. Efficacy of leukotriene receptor antagonist in chronic urticaria: a double-blind, placebo-controlled comparison of treatment with montelukast and cetirizine in patients with chronic urticaria with intolerance to food additive and/or acetylsalicylic acid. *Clin Exp Allergy* 2001;31:1607-14.
9. Sussman G, Abuzakouk M, Berard F, Canonica W, Oude Elberink H, Gimenez-Arnau A, et al. Angioedema in chronic spontaneous urticaria is underdiagnosed and has a substantial impact: analyses from ASSURE-CSU [published online ahead of print February 20, 2018]. *Allergy*. <https://doi.org/10.1111/all.13430>.

Reproduced with permission of copyright owner. Further reproduction prohibited without permission.