

The addition of zafirlukast to cetirizine improves the treatment of chronic urticaria in patients with positive autologous serum skin test results

Scott E. Bagenstose, MD,^a Linda Levin, PhD,^b and Jonathan A. Bernstein, MD^a

Cincinnati, Ohio

Background: Because leukotrienes have potent local effects on cutaneous vasculature, leukotriene antagonists might be effective in the treatment of chronic urticaria.

Objective: A double-blinded, placebo-controlled trial comparing cetirizine 10 mg daily in combination with zafirlukast 20 mg twice a day versus cetirizine 10 mg daily and placebo was conducted to determine whether subjects with chronic urticaria benefit from add-on therapy with a leukotriene-modifying agent.

Methods: Patients 12 years or older with a history of chronic urticaria (more than 6 weeks in duration) required diary documentation of 6 or more hives on at least 2 days/week and a suboptimal response to H₁-antagonist therapy for enrollment. At baseline, all subjects were skin tested to autologous serum to assess for the potential presence of FcεRI or IgE autoantibodies. Subjects meeting the initial entry criteria were treated with cetirizine 10 mg a day and placebo twice daily for 1 week. Those patients with persistent hives were randomized to receive cetirizine 10 mg daily and zafirlukast 20 mg twice a day or cetirizine 10 mg daily and placebo. At each successive weekly visit, physician and patient treatment effectiveness score (TES) and visual analog scale (VAS) ratings were recorded. Statistical analysis used generalizing estimating equations to compare the effect of combination therapy versus monotherapy on TES and VAS ratings. Results were adjusted for baseline rating, recruiting center, and autologous serum skin test (ASST). A separate analysis evaluated patients with positive ASST results receiving combination therapy versus monotherapy.

Results: Combination therapy with zafirlukast demonstrated a modest but significantly greater improvement compared with cetirizine monotherapy in physician and patient recorded VAS ratings at visit 4 and across treatment visits 4 through 6 ($P < .05$ unless stated otherwise). Subjects with ASST positive results receiving combination therapy as compared with subjects with negative ASST results exhibited a significant improvement in

patient recorded VAS ratings across visits 4 through 6. Subgroup analysis of subjects with ASST positive results receiving combination therapy versus monotherapy showed improvement in physician recorded TES at visit 5, physician recorded VAS at visits 4 and 5 and across visits 4 through 6, as well as for patient recorded VAS at visit 5. There were no significant results for patients with ASST negative results.

Conclusion: The results of this study indicate that only patients with autoimmune (ASST positive) chronic urticaria refractory to H₁-antagonist monotherapy might benefit from the addition of the leukotriene D₄-receptor antagonist zafirlukast to their treatment regimen. These results also suggest that routine screening of patients with chronic urticaria with the ASST might be useful in formulating therapeutic algorithms in the management of chronic urticaria. (*J Allergy Clin Immunol* 2004;113:134-40.)

Key words: Chronic urticaria, autologous serum, zafirlukast, leukotriene D₄ antagonist, cetirizine, H₁ antagonist, visual analog scale, treatment effectiveness score, autoantibodies, combination therapy

Leukotrienes are potent bioactive mediators known to play important roles in asthma and allergic rhinitis.^{1,2} Leukotrienes are also known to have potent local effects on cutaneous vasculature.^{3,4} Studies in guinea pigs have suggested that leukotriene D₄ (LTD₄) functions through selective receptors in the skin.³ Intradermal reactions to LTD₄ remain unaltered despite pretreatment with H₁ antagonists, local anesthetics, or cyclooxygenase inhibitors.⁴ Soter et al⁵ demonstrated that injection of an LTD₄ agonist in human skin results in a wheal and erythema response attributable to its dilatation of microvasculature and subsequent vascular leakage.

Leukotriene antagonists have been advocated for the treatment of chronic urticaria.⁶ Studies with leukotriene antagonists in guinea pigs showed suppression of the vascular leakage induced by intradermal injection of LTD₄ agonist.⁷ Bernstein et al⁸ previously demonstrated in a randomized, double-blinded, placebo-controlled crossover trial that zafirlukast inhibits cutaneous vascular reactivity to LTD₄ in a dose-related fashion. An earlier single-blinded, placebo-controlled study reported significant benefit of montelukast over cetirizine or placebo ($P < .001$) in the treatment of chronic urticaria induced by food additives and aspirin.⁹ More recently, a randomized, single-blinded, placebo-controlled crossover study

From the ^aDepartment of Internal Medicine, Division of Immunology, and ^bCenter for Biostatistical Services, University of Cincinnati College of Medicine.

Supported by Astra-Zeneca.

Received for publication April 15, 2003; revised September 18, 2003; accepted for publication October 2, 2003.

Reprint requests: Jonathan A. Bernstein, MD, University of Cincinnati, Division of Immunology, 231 Albert Sabin Way ML#563, Cincinnati, OH 45267-0563.

0091-6749/\$30.00

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doi:10.1016/j.jaci.2003.10.002

Abbreviations used

ASST: Autologous serum skin testing
LTD₄: Leukotriene D₄
TES: Treatment effectiveness score
VAS: Visual analog scale

demonstrated that treatment with montelukast resulted in significant decreases in urticaria activity scores compared to placebo ($P < .001$).¹⁰ However, a separate double-blinded, placebo-controlled study found that zafirlukast 20 mg twice a day had no effect as monotherapy for the treatment of chronic urticaria.¹¹

Collectively, these data support the need to conduct additional studies to determine the role, if any, of leukotriene-modifying agents in the treatment of chronic urticaria. H₁ antagonists are firmly established as first-line therapy for chronic urticaria.¹² Second-generation H₁ antagonists such as cetirizine have been shown to be as effective in controlling urticaria as the first-generation agents (which are more sedating).¹³ Thus, the role of leukotriene-modifying agents is best examined as that of an adjuvant to H₁ antagonists when the latter fails to be effective as monotherapy. This study was therefore designed to determine whether treatment with the LTD₄-receptor antagonist zafirlukast, in combination with the H₁ antagonist cetirizine, is more effective than cetirizine alone at controlling refractory chronic urticaria.

Chronic urticaria encompasses a heterogeneous group of disorders with presumably diverse etiologies. However, up to 40% of patients with chronic urticaria exhibit autoantibodies directed against either high-affinity IgE receptors (FcεRIα subunit) or IgE antibody on mast cell surfaces.¹⁴⁻¹⁷ Because these patients represent such a large proportion of the population with chronic urticaria, it is important to identify whether their response to antileukotriene therapy differs from that of the general population with chronic urticaria. Therefore, subgroup analyses were performed to determine whether individuals exhibiting a positive cutaneous response to autologous serum, previously shown to correlate with the presence of an anti-FcεRI or IgE antibody, respond preferentially to combination therapy with H₁ and LTD₄-receptor antagonists.^{14,15}

METHODS

Subjects

Patients with chronic urticaria were recruited from 7 centers. Enrollment criteria required that patients be 12 years of age or older, have a history of urticaria for at least 6 weeks' duration, and have at least 6 hives present 2 days per week. Only subjects with a history of a suboptimal response to H₁ antagonists were recruited. Therefore, a treatment effectiveness score (TES) of less than 5 while taking an H₁ antagonist (on a scale of 0 to 10) was required at the time of enrollment.

Study design

Fig 1 illustrates a flow diagram of the study. During visit 1, subjects meeting enrollment criteria signed an informed consent approved by the Western institutional review board. All subjects underwent a medical history and physical examination. Autologous

serum skin testing (ASST) was performed by epicutaneous injection of 0.02 mL autologous serum into the dorsal forearm with appropriate positive histamine (1 mg/mL) and negative saline controls.¹⁵ A wheal 3 mm or greater with erythema greater than the saline control was considered significant. All female subjects underwent a urine pregnancy test. Finally, subjects were instructed to discontinue all current urticaria medications at least 4 days before visit 2 to confirm the presence of active urticarial lesions.

At visit 2, all subjects satisfying entry criteria were started on cetirizine 10 mg at bedtime and zafirlukast placebo tablets morning and evening for 1 week (run-in period). At visit 3, patients with persistent urticaria (TES less than 5) were randomized to receive cetirizine 10 mg at bedtime and zafirlukast 20 mg twice a day or cetirizine 10 mg at bedtime and zafirlukast placebo twice a day. Enough medication was provided for 3 weeks with weekly follow-up visits (visits 4, 5, and 6). All subjects were provided diphenhydramine-HCl 25 mg tablets as rescue medication for use up to 50 mg four times a day on an as-needed basis.

Monitoring

Both the physician and patient rated hives at visits 2 through 6 by using both a 10-cm visual analog scale (VAS) and an 11-point TES illustrated in Fig 2. Similar rating systems have been used in other studies assessing treatment efficacy of chronic urticaria.¹⁸⁻²³ The VAS rating indicates the number and size of lesions, whereas the TES reflects the effectiveness of therapy. Lower VAS ratings correlate with a reduction of urticarial lesions, whereas higher TES ratings signify therapeutic efficacy in alleviating urticaria-related symptoms. Physician ratings with both scales were based on overall estimations, taking into account both historical features and objective findings. Every effort was taken to ensure that the same physician recorded the VAS and TES ratings for each patient. In addition, patients recorded any adverse events throughout the study.

Blood was collected at visits 2 and 6 from each subject to exclude an underlying cause for hives and to monitor for any adverse events, respectively. Laboratory studies assessed at both visits included complete blood count with differential, sedimentation rate, serum electrolytes, renal and liver function tests. Thyroid-stimulating hormone, antinuclear antibody, and hepatitis B and C viral profiles were only evaluated at visit 2.

Statistical analysis

Data were analyzed by using a modified intent-to-treat population, which included only those subjects who responded poorly to cetirizine during the 1-week antihistamine monotherapy run-in period (between visits 2 and 3). Analysis compared drug and placebo ratings of TES and VAS in 95 patients recorded by the physician and patient at 3 different visits. Multiple ratings on the same patient at visits 4, 5, and 6 were analyzed; results were adjusted for several factors including baseline rating of the respective outcome, ASST status of the patient, and recruiting center. Interactions were modeled to test for differences in treatments between each visit, subject ASST status, and recruiting center. TES scores ranging from 0 to 10 were modeled as count data assuming a log transformation with a Poisson link. VAS scores ranging from 0 to 96 were modeled continuously. Analyses were carried out by using the method of generalized estimating equations, which takes into account the correlation between repeated measurements on the same subject. Analyses comparing monotherapy versus combination therapy were performed for the entire subject population ($n = 95$); differences between subjects with ASST positive and negative results in each treatment group were evaluated by including interaction effects between treatment group and ASST status. Separate analyses were carried out for subjects with ASST positive results ($n = 22$) and subjects with ASST negative

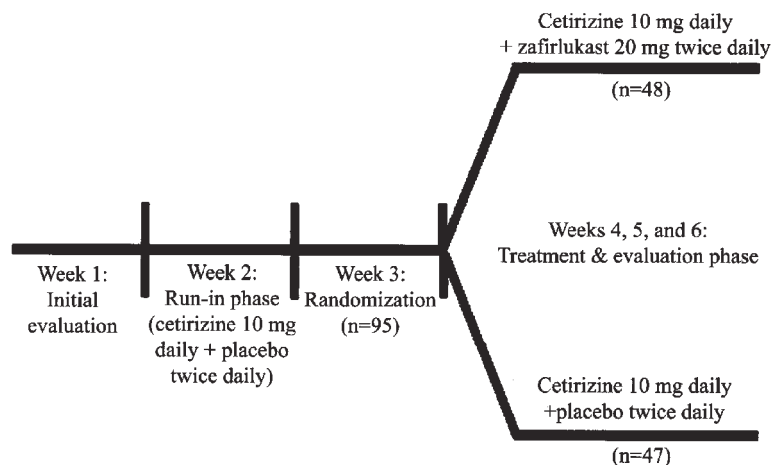


FIG 1. Study flow diagram.

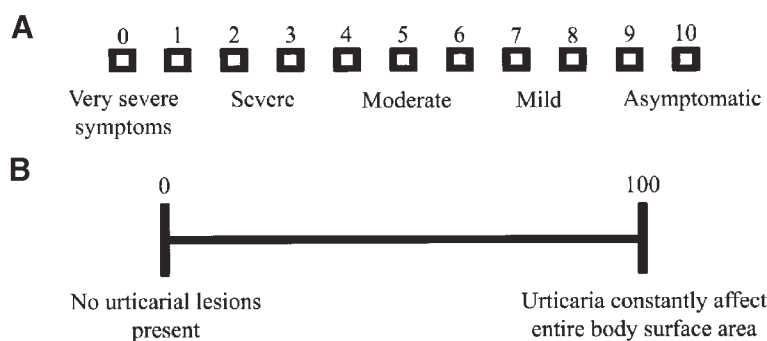


FIG 2. Monitoring instruments: A, TES; B, VAS.

results ($n = 73$). Similar regression models were assumed except for the exclusion of recruiting center because of the small sample size. A P value less than .05 was considered significant.

RESULTS

Table I summarizes the demographic characteristics of the population studied and displays the baseline (post-randomization) TES and VAS scores. There were no statistically significant differences between the groups. A total of 95 patients were enrolled with 86 completing the study. Numbers of patients at visits 4, 5, and 6 were 95, 90, and 86, respectively. There were 3 and 6 patients in the combination and monotherapy groups, respectively, who did not complete the study. Those who dropped from the study either had inadequate control of their hives or were lost to follow-up. Because this was an intent-to-treat analysis, the last evaluable data point of all subjects (including dropouts) was included in all analyses. ASST results were positive in 22 subjects. There were no significant adverse treatment effects or abnormal laboratory results reported throughout the study for any subject in either treatment group. Mean physician and patient VAS scores were lower, whereas mean physician and patient TES ratings were higher at each visit among

subjects receiving combination therapy compared with those on monotherapy. Significance was reached in both the physician and patient VAS when all visits were combined and at visit 4 in the physician VAS (Table II).

To investigate whether ASST has therapeutic relevance, subjects with ASST positive and ASST negative results who received combination therapy were compared. There was a significant improvement in average physician TES ($P < .01$) and patient VAS ($P < .02$) scores among subjects with ASST positive results compared with subjects with ASST negative results for subjects receiving zafirlukast (Table III). ASST status was not associated with significant benefit among patients assigned to the placebo group.

In a separate analysis of 22 subjects with ASST positive results, physician and patient VAS ratings were lower at each visit for subjects receiving combination therapy compared with those receiving monotherapy (Table IV). The addition of zafirlukast resulted in significant improvements in physician recorded VAS at visit 4 ($P = .04$), visit 5 ($P < .01$), and across treatment visits 4 through 6 ($P = .04$). Subjects receiving zafirlukast also exhibited a significantly improved mean patient VAS score at visit 5 ($P = .02$) and mean physician recorded

TABLE I. Demographic characteristics of 95 subjects; mean values (SD) of the baseline TES and VAS according to treatment group

	Cetirizine + zafirlukast (n = 48)	Cetirizine + placebo (n = 47)	P value
Male/female (% female)	6/42 (88%)	10/37 (73%)	.25
Mean age (y) (SD)	41.2 (12.6)	43.5 (13.3)	.39
Positive ASST (% n)	13 (27%)	9 (19%)	.36
Physician TES	3.6 (1.6)	3.7 (1.2)	.79
Patient TES	4.0 (1.6)	3.8 (1.4)	.73
Physician VAS	54.6 (15.5)	56.9 (17.8)	.50
Patient VAS	53.9 (18.6)	52.9 (19.0)	.79

TABLE II. Physician and patient TES and VAS mean values [95% CI], *t* statistics, and *P* values comparing cetirizine + zafirlukast group and cetirizine + placebo group at each visit and across visits 4-6*

	Visit			All visits, 4-6
	4	5	6	
Physician TES				
Zafirlukast (n = 48)	6.1 [5.4-6.8]	6.5 [5.8-7.4]	6.1 [5.3-7.0]	6.2 [5.6-6.9]
Placebo (n = 47)	5.1 [4.4-6.0]	5.9 [5.1-6.8]	6.1 [5.1-7.2]	5.7 [5.0-6.5]
Zafirlukast vs placebo <i>t</i> statistic (<i>P</i> value)	1.63 (.10)	1.06 (.29)	0.00 (.96)	0.97 (.33)
Patient TES				
Zafirlukast (n = 48)	5.5 [4.9-6.3]	6.0 [5.3-6.8]	5.7 [5.0-6.5]	5.7 [5.1-6.5]
Placebo (n = 47)	5.0 [4.3-5.8]	5.6 [5.0-6.3]	5.8 [4.9-6.8]	5.5 [4.8-6.2]
Zafirlukast vs placebo <i>t</i> statistic (<i>P</i> value)	0.96 (.34)	0.69 (.49)	-0.10 (.92)	0.57 (.57)
Physician VAS				
Zafirlukast (n = 48)	36.4 [28.8-44.0]	33.0 [24.5-41.5]	33.5 [25.1-42.0]	34.3 [27.0-41.6]
Placebo (n = 47)	49.1 [41.6-56.5]	43.9 [36.8-51.1]	42.8 [34.1-51.4]	45.3 [38.8-51.7]
Zafirlukast vs placebo <i>t</i> statistic (<i>P</i> value)	2.29 (.02)	1.91 (.06)	0.41 (.14)	2.16 (.03)
Patient VAS				
Zafirlukast (n = 48)	36.0 [27.7-44.2]	33.6 [24.8-42.3]	32.7 [23.9-41.5]	34.1 [26.3-41.9]
Placebo (n = 47)	47.6 [40.0-55.2]	43.7 [36.8-50.7]	42.2 [33.1-51.3]	44.5 [37.6-51.4]
Zafirlukast vs placebo <i>t</i> statistic (<i>P</i> value)	2.05 (.04)	1.78 (.07)	1.47 (.14)	1.97 (.05)

*Results obtained from repeated measures analysis at each visit adjusted for baseline scores, ASST status, recruiting center, and interactions between treatment and visit, ASST status, and recruiting center. Results of TES are obtained from the analyses of log-transformed data; results are shown on the original scale.

TABLE III. Physician and patient TES and VAS mean values [95% CI] and *P* values comparing subjects with ASST positive and negative results in each treatment group across visits 4-6*

Treatment	ASST	Mean	95% CI	P value
Physician TES				
Zafirlukast (n = 48)	+ (n = 13)	7.4	[6.0-9.1]	<.01
	- (n = 35)	5.2	[4.6-5.9]	
Placebo (n = 47)	+ (n = 9)	5.9	[4.1-8.5]	.68
	- (n = 38)	5.5	[4.9-6.2]	
Patient TES				
Zafirlukast (n = 48)	+ (n = 13)	6.2	[4.9-7.9]	.20
	- (n = 35)	5.3	[4.7-6.0]	
Placebo (n = 47)	+ (n = 9)	5.3	[3.7-7.4]	.69
	- (n = 38)	5.7	[5.0-6.4]	
Physician VAS				
Zafirlukast (n = 48)	+ (n = 13)	28.7	[14.3-43.1]	.14
	- (n = 35)	39.9	[32.4-47.4]	
Placebo (n = 47)	+ (n = 9)	45.8	[28.0-63.6]	.92
	- (n = 38)	44.7	[37.4-52.0]	
Patient VAS				
Zafirlukast (n = 48)	+ (n = 13)	25.3	[10.4-40.2]	.02
	- (n = 35)	42.8	[35.4-50.2]	
Placebo (n = 47)	+ (n = 9)	39.7	[21.0-58.4]	.35
	- (n = 38)	49.3	[42.6-56.0]	

*Results of TES are obtained from the analyses of log-transformed data; results are shown on the original scale.

TABLE IV. Subgroup analyses of patients with ASST positive results ($n = 22$): physician and patient TES and VAS mean values [95% CI] and P values comparing cetirizine + zafirlukast and cetirizine + placebo groups at each visit and across visits 4-6*

	Visit			All visits, 4-6
	4	5	6	
Physician TES				
Zafirlukast ($n = 13$)	5.8 [4.7-7.1]	6.9 [5.8-8.1]	6.0 [4.6-7.9]	6.2 [5.1-7.6]
Placebo ($n = 9$)	4.5 [3.4-5.8]	4.3 [3.3-5.7]	6.1 [4.8-7.9]	4.9 [3.9-6.2]
Zafirlukast vs placebo P value	.13	<.01	.90	.14
Patient TES				
Zafirlukast ($n = 13$)	4.9 [3.9-6.2]	5.8 [4.4-7.7]	5.2 [3.9-6.8]	5.3 [4.2-6.7]
Placebo ($n = 9$)	4.8 [3.7-6.3]	4.7 [3.7-6.1]	6.4 [4.8-8.6]	5.3 [4.2-6.6]
Zafirlukast vs placebo P value	.89	.31	.31	.97
Physician VAS				
Zafirlukast ($n = 13$)	34.4 [21.8-47.1]	24.6 [13.4-35.8]	28.5 [14.9-42.2]	29.2 [19.0-39.5]
Placebo ($n = 9$)	54.8 [42.6-67.0]	47.6 [37.8-57.5]	34.8 [22.2-47.3]	45.7 [36.0-55.4]
Zafirlukast vs placebo P value	.04	<.01	.53	.04
Patient VAS				
Zafirlukast ($n = 13$)	36.2 [25.7-46.7]	26.5 [15.3-37.8]	30.5 [18.4-42.7]	31.1 [21.3-40.9]
Placebo ($n = 9$)	48.5 [35.3-61.8]	48.6 [34.2-63.0]	35.2 [16.6-53.8]	44.1 [31.9-56.3]
Zafirlukast vs placebo P value	.17	.02	.68	.12

*Results of TES are obtained from the analyses of log-transformed data; results are shown on the original scale.

TES at visit 5 ($P < .01$). A similar analysis involving patients with ASST negative results showed no significant differences in response to combination therapy over cetirizine monotherapy (data not shown).

DISCUSSION

Leukotrienes have been identified as potentially important bioactive mediators that participate in the pathogenesis of chronic urticaria.²⁴ The purpose of this study was to determine whether blocking LTD₄ receptors with a leukotriene receptor antagonist (zafirlukast) in combination with an H₁ antagonist was more effective than an H₁ antagonist alone in the treatment of refractory chronic urticaria. We found that patients with chronic urticaria exhibiting an incomplete response to H₁-antagonist therapy derived benefit from the addition of zafirlukast to their treatment regimen. Our findings of an additional therapeutic effect of zafirlukast when used in combination with an H₁ antagonist is consistent with the fact that chronic urticaria involves multiple mast cell mediators including histamine and leukotrienes.¹¹ Interestingly, subjects who had ASST positive results were more likely than subjects with ASST negative results to improve with combination therapy by using an LTD₄-receptor antagonist.

ASST was performed according to the protocol described by Sabroe et al¹⁵ and Gratton et al,²⁵ with the exception that tests were read at 30 minutes. It is recognized that the ASST has limited sensitivity (65% to 71%) and specificity (78% to 81%) in that a positive test result does not distinguish between the presence of FcεRI autoantibodies, anti-IgE antibodies, or histamine-releasing factors.^{15,26} However, despite these limitations, its low cost and simplicity make it a practical screening tool

for detecting the possible presence of autoantibodies. The clinical relevance of these autoantibodies has been demonstrated in a recent case of a woman with ASST positive result with corticosteroid-dependent urticaria who had complete long-term remission of her hives after treatment with intravenous cyclophosphamide.²⁶ The post-treatment ASST result was negative, suggesting that this treatment was successful in eliminating B-lymphocyte clones responsible for producing FcεRI autoantibodies.²⁶

Short duration chronic urticaria studies of this type inherently have several shortcomings that require cautious interpretation of the results. In this study, the 3-week treatment period might not have been long enough to discern the complete therapeutic effect of combination therapy. Because the course of chronic urticaria is often quite variable, it is not surprising that significant results are not reported consistently at every visit. Furthermore, most patients with chronic urticaria who achieve an incomplete response to drug therapy continue to itch and urticate. Although there might be a reduction in their symptoms, they might be more likely to record an "all or none" response and less apt to report a partial response to treatment accurately. For this reason, the VAS is likely a more reliable indicator of treatment response in short duration studies. Another potential limitation in these types of studies is the utility of the physician's treatment response assessment. Physician ratings are often less reliable than patient ratings, because physician assessments are typically cross-sectional in nature and do not independently capture the dynamic, evanescent course of this chronic disease. Physician ratings are also subject to interrater differences, an unavoidable factor in a multicenter trial such as this one. Nevertheless, both patient and physician VAS ratings were significantly decreased across the treatment

phase among those treated with combination therapy. Given the small sample size and the short duration of this study, these results are quite remarkable and strongly indicate there is an overall benefit of combination therapy in patients with ASST positive results.

Although the results of this study require confirmation in larger trials, these findings might be germane for physicians who treat patients with chronic urticaria. Currently, H₁ and H₂ antagonists are considered first-line agents for treatment of this disorder. Secondary therapeutic choices are often based on physician anecdotal experience and are often not supported by scientific evidence-based clinical trials. This study provides a rationale for the selection of LTD₄-receptor antagonists as a second-line "add-on" therapy for the treatment of chronic urticaria. These results also suggest that the ASST might be of value in the assessment of patients with chronic urticaria because these individuals exhibited an improved response to combination therapy with zafirlukast. This is in contrast to a previous investigation, which found that treatment response of chronic urticaria to cyclosporine did not correlate with the presence of a positive ASST result.²⁷

Further delineation of the mechanism(s) through which patients with ASST positive results manifest an enhanced response to zafirlukast would broaden our understanding of the pathogenesis of chronic urticaria. Our results might be explained by differences in mast cell activation and differential expression of cytokine and bioactive mediator release between patients with and without FcεRI or IgE autoantibodies. It is possible to speculate that the presence of FcεRI or IgE autoantibodies could result in the more vigorous activation of connective tissue mast cells present in the skin, leading to increased expression and release of cytokines. Earlier studies have demonstrated discrete differences in activation and mediator release between connective tissue and mucosal mast cell subsets.^{28,29} A number of cytokines including IL-2, IL-3, and IL-4 have been demonstrated to have a pro-inflammatory effect on connective tissue mast cells by enhancing anti-IgE-mediated histamine release.³⁰ It has further been demonstrated that connective tissue mast cells, cultured with stem cell factor and IL-4, release increased amounts of leukotriene C₄ after stimulation with nonimmunologic factors such as substance P.³¹ Therefore, it can be postulated that the presence of increased localized cytokine expression enhances the release of mast cell-derived leukotriene mediators, explaining why leukotriene receptor antagonists might be more effective in the treatment of patients with ASST positive results and chronic urticaria.

In summary, the leukotriene receptor antagonist zafirlukast demonstrates modest efficacy as an adjunct to an H₁ antagonist in the treatment of patients with ASST positive chronic urticaria refractory to H₁-antagonist monotherapy. Because treatment effectiveness is limited only to patients with a positive ASST result, consideration should be given to ASST screening before initiation of therapy to identify potential responders. Further investigation is necessary to

determine the basis for the preferential therapeutic response in patients with ASST positive results and to better explain the complex mechanisms of mast cell activation in the presence of FcεRI or IgE autoantibodies.

Investigator sites included Hal Nelson, Anjuli Nayak, Theodore Chu, Sheldon Spector, Jonathan Corren, and Albert Finn.

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