

Leukotriene receptor antagonists in monotherapy or in combination with antihistamines in the treatment of chronic urticaria: a systematic review

Gabriele Di Lorenzo¹
 Alberto D'Alcamo¹
 Manfredi Rizzo¹
 Maria Stefania Leto-Barone¹
 Claudia Lo Bianco¹
 Vito Ditta¹
 Donatella Politi¹
 Francesco Castello¹
 Ilenia Pepe¹
 Gaetana Di Fede²
 Giovambattista Rini¹

¹Dipartimento di Medicina clinica e delle Patologie Emergenti;

²Dipartimento di Discipline Chirurgiche ed Oncologiche, Università degli Studi di Palermo, Italy

Abstract: In vitro and in vivo clinical and experimental data have suggested that leukotrienes play a key role in inflammatory reactions of the skin. Antileukotriene drugs, ie, leukotriene receptor antagonists and synthesis inhibitors, are a class of anti-inflammatory drugs that have shown clinical efficacy in the management of asthma and in rhinitis with asthma. We searched MEDLINE database and carried out a manual search on journals specializing in allergy and dermatology for the use of antileukotriene drugs in urticaria. Montelukast might be effective in chronic urticaria associated with aspirin (ASA) or food additive hypersensitivity or with autoreactivity to intradermal serum injection (ASST) when taken with an antihistamine but not in mild or moderate chronic idiopathic urticaria [urticaria without any possible secondary causes (ie, food additive or ASA and other NSAID hypersensitivity, or ASST)]. Evidence for the effectiveness of zafirlukast and the 5-lipoxygenase inhibitor, zileuton, in chronic urticaria is mainly anecdotal. In addition, there is anecdotal evidence of effectiveness of antileukotrienes in primary cold urticaria, delayed pressure urticaria and dermatographism. No evidence exists for other physical urticarias, including cholinergic, solar and aquagenic urticarias, vibratory angioedema, and exercise-induced anaphylaxis.

Keywords: chronic idiopathic urticaria, leukotriene receptor antagonists, montelukast, zafirlukast, antihistamine

Urticaria is a common disorder of the skin, affecting between one in four and one in six people, sometimes throughout their lives. Urticarial episodes of up to 6 weeks' duration are classified as acute, whereas those lasting longer are considered chronic. The clinical characteristic of chronic urticaria (CU) are repeated occurrences of short-lived cutaneous wheals accompanied by redness and itching exceeding 6 weeks. The individual wheals last less than 24 hours, with the exceptions of delayed pressure urticaria and urticarial vasculitis, which persist for 24 to 72 hours. Wheals are lesions ranging from a few millimeters to several centimeters in diameter. The itch of urticaria is the hallmark symptom, and it is usually worse in the evening or nighttime. CU typically follows this diurnal pattern. Angioedema (AE) accompanies 40% to 50% of the cases of chronic urticaria and 10% of the patients experience only AE without hives.¹⁻³ In these patients the treatments have focused on symptom control.

Pathogenesis of urticaria

The weal or hive is the "final pathway" involving dermal mast-cells. This pathway is activated by various trigger factors through immunological or nonimmunological mechanisms and the result is the release of preformed (eg, histamine) and newly synthesized mediators (eg, arachidonic acid metabolites), with potent effects on the micro-vasculature.²

Correspondence: Gabriele Di Lorenzo
 Dipartimento di Medicina Clinica e delle Patologie Emergenti, Via del Vespro, 141 – 90127 Palermo, Italy
 Tel +39 091 6552973
 Fax +39 091 6555995
 Email dilo601@unipa.it

The most popular theory to explain the development of CU is referred to as the autoimmune hypothesis. This notion had its origins in 1924, when Lewis and Grant improved the technique of experimentally creating histamine wheals initially described by Eppinger in 1913.⁴

The suggestion that chronic idiopathic urticaria (CIU) may have an autoimmune basis came from the recognition that thyroid auto-antibodies and thyroid dysfunction were observed more commonly in patients with CIU.⁴

The suggestion that a serologic factor is responsible for the pathogenesis of CIU has been a dominant theme in the literature for more than 20 years. In 1986, a serologic mediator called HRF was identified in patients with CU using an *in vivo* skin test called the autologous serum skin test (ASST).⁵

We demonstrated that both aspirin (ASA) and food additives determine a significant increase in urinary leukotriene 4 (LTE₄) levels, after oral specific challenge in patients with CU and hypersensitivity to ASA or food additives. The urinary LTE₄ levels were compared between patients with CU and hypersensitivity to ASA or food additives, patients with CU but tolerating both ASA and food additives, and healthy subjects. No difference was found at baseline between the three groups. After a specific challenge with ASA and food additives, the urinary excretion levels of LTE₄ were significantly higher in patients affected by CU and hypersensitivity to ASA or food additives than in patients with CU but without hypersensitivity to ASA or food additives and in healthy subjects.^{6,7}

Therapy of urticaria

The management of CU remains a challenge for both clinicians and patients. Primary recommendations for the management of CU include general measures such as avoidance of any aggravating stimuli, topical antipruritic emollients, reassurance and education, and specific pharmacotherapy, of which the newer selective H1-antihistamines are the preferred intervention.¹ However, the prior generation “sedating” antihistamines remain useful, efficacious first-line agents for many patients.

Some of these nonselective antihistamines have other useful receptor properties that may extend additional efficacy in certain cases. Such agents include doxepin, cyproheptadine, and ketotifen.^{8–10} The H2-antihistamines are also used in clinical practice, most often as add-on therapy, but these agents generally offer modest incremental efficacy.¹¹ In addition to combining multiple antihistamines in such a way, higher doses of antihistamines are widely recommended or

prescribed;¹² however, the evidence supporting this practice is minimal.¹³

Oral corticosteroids almost always control urticaria and are undoubtedly the most versatile and useful second-line therapy. However, the incidence of side-effects is substantial if the dose, the duration of use, or both, are too great.¹⁴ Other second-line therapies include sulphasalazine¹⁵ and thyroxine.¹⁶ While third-line, immunosuppressive therapies for severe CU are now accepted practice, there is still the problem of knowing which patients have autoimmune urticaria and are therefore most likely to respond, even if there is some evidence for the therapeutic effect of immunosuppression therapy in patients without autoimmune urticaria.¹⁷ Newer biologic and nonbiologic immunomodulatory agents, approved for other indications and in clinical development, provide potential options for this often severe CU.¹⁸

Urticaria treatment with antileukotrienes

The efficacy and, primarily, safety of the leukotriene modifiers have placed these agents at the top of the list of alternative agents, and future practice may place them alongside antihistamines as first-line therapy.¹⁹

We searched MEDLINE database and carried out a manual search on journals specializing in allergy and dermatology for the use of antileukotriene drugs in urticaria. Even though treatment with antileukotrienes in urticaria has not been recommended by manufacturers of the drugs, we found numerous anecdotal and open-series reports and some placebo-controlled studies on the treatment of urticaria with cysteinyl-leukotriene antagonists. The studies were evaluated using the parameters of Shekelle (Tables 1, 2).²⁰

Rationale of the treatment with antileukotrienes

Injected leukotriene D4 is more potent than histamine in causing a wheal and flare.²¹ Serum from patients with CIU with positive ASST or negative ASST, since patients cannot have both idiopathic and autoimmune disease, is capable of releasing leukotrienes, in addition to other mediators.²² Leukotriene-mediated urticaria is not blocked by other agents.²³

Anecdotal series and open studies

Anecdotal studies suggested therapeutic effects for antileukotrienes in the treatment of urticaria exacerbations induced by ASA²⁴ and other nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with CIU,²⁵ chronic autoimmune

Table 1 Categories of evidence

Categories of evidence	
Ia	Meta-analysis of randomized controlled trials (RTC)
Ib	At least one RTC
IIa	At least one controlled study without randomization
IIb	At least one other type of study
III	Non-experimental descriptive studies
IV	Expert committee reports or opinions or clinical experience of respected authorities

urticaria,²⁶ acquired cold urticaria,^{27,28} delayed-pressure urticaria (DPU),²⁹ and intractable CIU.³⁰ A single negative study reported a pranlukast-evoked urticaria in patients affected by ASA-induced urticaria.³¹ However, this molecule is not marketed in Europe and in US (Table 3).

Other open studies, with more patients, suggested a beneficial effect for antileukotrienes in the treatment of DPU,³² steroid-dependent urticaria,^{33,34} chronic idiopathic urticaria,^{35,36} and dermatographism.³⁵ Patients with allergic urticaria showed less benefit.³⁵ Nettis et al treated patients affected by chronic idiopathic urticaria with montelukast or fexofenadine. They demonstrated that montelukast had a better therapeutic effects compared with fexofenadine. The majority of the patients presented a positive ASST and, after therapy with montelukast, were unreactive to autologous serum.³⁷

A case report suggested a beneficial effect for antileukotrienes in the treatment of urticaria exacerbation induced by a COX-2 selective inhibitors.³⁸ Another study demonstrated in 22/25 patients the effect of antileukotrienes in the treatment of urticaria exacerbation induced by ASA or NSAIDs.³⁹ Finally, a comparison between montelukast and cetirizine demonstrated that cetirizine is better than montelukast in monotherapy.⁴⁰

Table 2 Strength of evidence

Strength of evidence	
A	Category I evidence
B	Category II evidence or extrapolated recommendation from category I evidence
C	Category III evidence or extrapolated recommendation from category I or II evidence
D	Category IV evidence or extrapolated recommendation from category I or II or III evidence

Controlled studies

A double-blind, placebo-controlled study demonstrated a better therapeutic effect of montelukast vs cetirizine and placebo in patients with ASA and/or food additive-induced urticaria.⁴¹

Perez et al demonstrated that in individuals with histories of recurrent episodes of urticaria and/or angioedema after the administration of different NSAIDs, pretreatment with montelukast before a single-blind oral challenge with NSAIDs, completely or partially prevented the reaction in most of those patients.⁴² In a double-blind, placebo-controlled trial comparing cetirizine plus zafirlukast vs cetirizine plus placebo in patients affected by CU refractory to H1-antagonist monotherapy, Bagenstose et al demonstrated that only patients with autoreactive (positive ASST) CU might benefit from the addition of the leukotriene receptor antagonist zafirlukast to their treatment regimen.⁴³

A randomized, single-blind, placebo-controlled, crossover study with montelukast vs placebo, using a nonsedating H1-antihistamine when needed, demonstrated that montelukast might be an effective and safe therapeutic agent in the treatment of patients with refractory chronic idiopathic urticaria, including patients with intolerance to NSAIDs and positivity to ASST.⁴⁴

Reimers et al in a double-blind, placebo-controlled, crossover study, treated with zafirlukast a heterogeneous population of patients with CU. In comparison with placebo, treatment with zafirlukast resulted in no significant positive effect for any of the efficacy measures, but it may be relevant that a high proportion of patients had dermatographism.⁴⁵

Nettis et al reported on another randomized, double-blind, placebo-controlled study conducted on patients with a diagnosis of mild CU, randomized to receive once daily: (a) oral desloratadine plus placebo; (b) desloratadine plus montelukast; or (c) oral placebo alone. In this study, the combination of desloratadine plus montelukast was effective in the treatment of CU.⁴⁶ Di Lorenzo et al treated 160 patients affected by chronic idiopathic urticaria with montelukast alone or in combination with a nonsedating antihistamine (desloratadine), or only with nonsedating antihistamine, or with matched placebo. In this study, we evaluated only patients affected by moderate chronic idiopathic urticaria.

This is an important difference compared with some of the previous reports, in which patients were selected without precise characteristics.^{33,34,46} In patients with moderate chronic idiopathic urticaria, the role of leukotrienes is probably rather insignificant.^{6,43} In this study, montelukast alone

Table 3 Anecdotal case and open series: chronic urticaria (CU) treated with antileukotrienes

Type of CU	Patients treated	Drugs	Results	Outcome	Study	Category of evidence	Grade of recommendation	Reference
Severe CU with ASA intolerance	1	zafirlukast 20 mg twice daily vs zileuton 600 mg 4 times daily	zileuton better than zafirlukast	Favorable	NA	III	D	24
Severe CU with ASA intolerance	1	zileuton 600 mg 4 times daily	Marked improvement	Favorable	NA	III	D	24
NSAID-induced exacerbation of CU	1	montelukast 10 mg once a day	Complete resolution of urticaria but relapse after a single dose of oral piroxicam	Favorable	NA	III	D	25
NSAID-induced exacerbation of CU	1	zafirlukast 20 mg twice daily	Complete resolution of urticaria without relapse after a course of injected piroxicam	Favorable	NA	III	D	25
Chronic autoimmune urticaria	1	montelukast 10 mg once a day	Improvement of CU	Favorable	NA	III	D	26
Cold urticaria refractory to H1-antihistamine	1	montelukast 10 mg once a day	Improvement of cold urticaria	Favorable	NA	III	D	27
Acquired cold urticaria	2	zafirlukast 20 mg twice daily vs cetirizine 10 mg once a day vs zafirlukast plus cetirizine	Combination therapy (zafirlukast plus cetirizine) better than monotherapy	Favorable	NA	III	D	28
Delayed pressure urticaria	1	montelukast 10 mg a day	Symptom-free under treatment but discontinuation not possible	Favorable	NA	III	D	29
Intractable CU	1	zafirlukast 20 mg twice daily	Remission of symptoms	Favorable	NA	III	D	30
Intractable CU	1	zileuton 600 mg 4 times daily	Remission of symptoms	Favorable	NA	III	D	30
ASA-induced urticaria	2	pranlukast 112.5 mg once a day	Relapse of urticaria	Unfavorable	NA	III	D	31
Delayed pressure urticaria	20	loratadine 10 mg once a day alone vs loratadine 10 mg once a day plus montelukast 10 mg once a day	Combination therapy (loratadine plus montelukast) better than loratadine alone	Favorable	No reported the randomized	IIb	C	32

Steroid-dependent chronic idiopathic urticaria	15	montelukast 10 mg once a day zafirlukast 20 mg twice daily	Improvement in some patients	Favorable	No RTC	IIb	C	33
Unrelenting steroid-dependent urticaria	12	montelukast 10 mg once a day zafirlukast 20 mg twice daily	Nearly total remission in some of the patients	Favorable	No RTC	IIb	C	34
Chronic idiopathic	6	Zafirlukast 20 mg twice daily	Marked improvement	Favorable	No RTC	IIb	C	35
Dermographism	2	Zafirlukast 20 mg twice daily	Marked improvement	Favorable	No RTC	IIb	C	35
Allergic urticaria	7	Zafirlukast 20 mg twice daily	Less benefit	Uncertain	No RTC	IIb	C	35
Chronic idiopathic	7	montelukast 10 mg once a day zafirlukast 20 mg twice daily	Marked improvement	Favorable	No RTC	IIb	C	36
Chronic idiopathic urticaria (majority of patients with positive ASST)	27	Montelukast 10 mg once a day vs fexofenadine 180 mg once a day	Montelukast had better therapeutic effects compared to fexofenadine	Favorable	No RTC	III	D	37
COX-2 selective inhibitors exacerbation of CU	1	montelukast 10 mg once a day	Marked improvement	Favorable	NA	III	D	38
ASA and NSAID-induced exacerbation of CU	25	montelukast 10 mg once a day	Marked improvement in 22 patients	Favorable	No RTC	III	D	39
Chronic idiopathic	20	montelukast 10 mg once a day or cetirizine 10 mg once a day	Cetirizine better of montelukast monotherapy	Unfavorable	Randomized without placebo	III	D	40

Table 4 Randomized controlled trials with antileukotrienes

Type of CU	Patients treated	Drugs	Results	Outcome	Study	Category of evidence	Grade of recommendation	Reference
ASA- and/or food additives-induced urticaria	51	Montelukast 10 mg once a day vs cetirizine 10 mg once a day vs placebo	Montelukast controls urticaria symptoms better than cetirizine and placebo	Favorable	RTC	IIb	C	41
Healthy subjects affected by COX inhibitor-induced urticaria	10	Montelukast 10 mg once a day vs placebo before the challenge with ibuprofen	A complete blockade reaction in 3 patients; a partial blockade in 6, no effect in 1	Favorable	RTC	IIb	C	42
CU refractory to H1 antagonist monotherapy	95	Cetirizine 10 mg once a day plus zafirlukast 20 mg twice daily vs cetirizine 10 mg once a day plus placebo	Combination therapy (cetirizine plus zafirlukast) better than cetirizine plus placebo only in ASST-positive patients	Favorable	RTC	IIb	C	43
CU refractory	30	Montelukast 10 mg once a day vs placebo using cetirizine 10 mg as needed	montelukast controls urticaria symptoms better than placebo	Favorable	RTC	IIb	C	44
Heterogeneous population of CU	52	zafirlukast 20 mg twice daily vs placebo	No significant effect for any of the efficacy measures	Unfavorable	RTC	IIb	C	45
Mild CU	76	Desloratadine 5 mg once a day vs desloratadine 5 mg once a day plus montelukast 10 mg a day vs placebo	Combination therapy (desloratadine plus montelukast) better than desloratadine alone and placebo	Favorable	RTC	IIb	C	46
Moderate CIU	160	montelukast 10 mg once a day vs montelukast 10 mg once a day plus desloratadine 5 mg once a day vs desloratadine 5 mg once a day vs placebo	montelukast alone less effective than the combination with desloratadine and not useful in controlling urticaria compared with desloratadine alone	Unfavorable	RTC	IIb	C	47

was less effective than the combination with nonsedating antihistamine and appeared not to be useful in controlling the symptoms of urticaria compared with nonsedating antihistamine alone. Therefore, the expected synergistic interaction between antileukotrienes and antihistamines was not confirmed in mild chronic idiopathic urticaria.⁴⁷ This result is in accordance with another noncontrolled study⁴⁰ (Table 4).

Conclusions

Leukotriene receptor antagonists are currently the best-studied group of drugs after the antihistamines, in the therapy of CU. However, the leukotriene receptor antagonists aren't alternative agents to antihistamines. The excellent safety, absence of required monitoring in the case of montelukast and zafirlukast, and wide availability make leukotriene receptor antagonists the preferred supplementary agents to try with antihistamines. Although one study suggested persistent drug-free remission,⁴⁴ most experience argues against such a disease-modifying effect. Leukotriene receptor antagonists appear to be useful as both monotherapy and add-on therapy but are not likely to displace antihistamines from their role as first-line therapy.

In our review, leukotriene receptor antagonists may provide improvement in patients with food additive hypersensitivity or ASA and other NSAID-exacerbated CIU^{24,25,31,38,39,41,42} and in patients with positive ASST results.^{26,37,44} In other words, in the type of chronic urticaria without any associated cause, very idiopathic urticaria, the use of leukotriene receptor antagonists demonstrates lack of advantage if administered both in monotherapy and combined with antihistamines.

Disclosures

The authors have no conflicts of interest to disclose.

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