

Is there a role for antileukotrienes in urticaria?

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Summary

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, i.e. leukotriene receptor antagonists and synthesis inhibitors, are a new class of anti-inflammatory drugs that have shown clinical efficacy in the management of asthma. We searched the 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 or food additive hypersensitivity or with autoreactivity to intradermal serum injection when taken with an antihistamine but not in moderate chronic idiopathic urticaria. 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 dermographism. No evidence exists for other physical urticarias, including cholinergic, solar and aquagenic urticarias, vibratory angio-oedema, and exercise-induced anaphylaxis.

Introduction

Urticaria is a common disorder of the skin, affecting between one in four and one in six people, sometimes throughout their lives. Individual lesions usually last for minutes or a few hours and rarely for up to 48 h or occasionally even longer, when severe. Urticarial episodes of up to 6 weeks' duration are classified as acute, whereas those lasting longer are considered chronic. Furthermore, chronic urticaria (CU) may persist for at least 1 year in more than 50% and for more than 20 years in 20% of those affected.^{1–3}

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Pathogenesis of urticaria

The common element of urticaria appears to be the hive or weal, i.e. 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 (e.g. histamine) and newly synthesized mediators (e.g. arachidonic acid metabolites), with potent effects on the microvasculature. Activated mast cells may also release other substances, such as chemotactic factors, cytokines, enzymes and neuropeptides, which recruit and activate various inflammatory cells, such as lymphocytes and polymorphonuclear cells (e.g. neutrophils and eosinophils).⁴ Various investigators have found increased levels of inflammatory mediators and/or factors in the different types of urticaria (Table 1).^{1–3} More recently, CU has also been proposed to be an autoimmune disorder, as approximately 30–50% of these patients present a positive autologous serum skin test (ASST), with circulating IgG antibodies directed against

Table 1 Type of urticaria, mediators and factors.

Type of urticaria	Mediators and factors
Dermographism	Histamine, tryptase, ECP, NP
Pressure urticaria	Histamine, LTs, ECP, MBP, IL-3, IL-6, TNF- α
Cold urticaria	Histamine, LTs, kinins, PAF, PGD ₂ , ECP, IL-3, IL-6, TNF- α , ECF, NCF
Solar or cholinergic urticaria	Histamine, tryptase, ECP, MBP, ECF
Chronic urticaria	Histamine, LTs, ECP, MBP, IL-3, TNF- α

ECP, eosinophil cationic protein; NP, neuropeptides; LTs, leukotrienes; MBP, major basic protein; IL, interleukin; TNF- α , tumour necrosis factor- α ; PAF, platelet-activating factor; PGD₂, prostaglandin D₂; ECF, eosinophil cationic factor; NCF, neutrophil chemotactic factor.

the α -subunit of the high-affinity IgE receptor (Fc ϵ RI) or against IgE, which activate basophils and mast cells to release histamine.⁴

In our recent study, 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.⁵

Therapy for urticaria

For most patients, first-line therapy is with H₁ antihistamines. Nonsedating antihistamines, such as cetirizine, levocetirizine, loratadine, desloratadine and fexofenadine, alleviate pruritus and decrease the incidence of weals in patients with mild CU. If nonsedating H₁ blockers are only partially effective, the therapeutic options are: increase the dose of nonsedating H₁ blockers or combine these with a sedative H₁ antihistamines (hydroxyzine or diphenhydramine or chlorpheniramine), taken at night, or add an H₂ antihistamine blocker. The response to the latter option is often modest.^{6,7}

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.⁸ Other second-line therapies include sulphasalazine⁹ and thyroxine.¹⁰

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.¹¹

Urticaria treatment with antileukotrienes

We searched the 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 (Table 2). The studies were evaluated using the Scottish Intercollegiate Guidelines Network (SIGN) coding.¹²

Anecdotal series and open studies

Anecdotal studies suggested therapeutic effects for antileukotrienes in the treatment of urticaria exacerbations induced by ASA¹³ and other nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with CU,¹⁴ chronic autoimmune urticaria,¹⁵ acquired cold urticaria,^{16,17} delayed-pressure urticaria (DPU),¹⁸ and intractable CU.¹⁹ A single negative study reported a pranlukast-evoked urticaria in patients affected by ASA-induced urticaria;²⁰ however, this molecule is not marketed in Europe.

Other open studies, with more patients, suggested a beneficial effect for antileukotrienes in the treatment of DPU,²¹ steroid-dependent urticaria^{22,23} chronic idiopathic urticaria,^{24,25} and dermatographism.²⁴ Patients with allergic urticaria showed less benefit.²⁴

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.²⁶

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

Table 2 Urticaria. treatment with antileukotrienes.

Quality of evidence	Type of urticaria	No. of patients studied	Drugs	Results	Outcome	Methodological quality*	Level of evidence	Grade of recommendation	Reference
Anecdotal	Severe CU with aspirin hypersensitivity	1	Zafirlukast 20 mg twice daily vs. zileuton 600 mg 4 times daily	Zileuton is more effective than zafirlukast	Favourable	No RCT	3	D	13
Anecdotal	Severe CU with aspirin hypersensitivity	1	Zileuton 600 mg 4 times daily	Marked improvement	Favourable	No RCT	3	D	13
Anecdotal	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	Favourable	No RCT	3	D	14
Anecdotal	NSAID-induced exacerbation of CU	1	Zafirlukast 20 mg twice daily	Complete resolution of urticaria without relapse after a course of injected piroxicam	Favourable	No RCT	3	D	14
Anecdotal	Chronic autoimmune urticaria	1	Montelukast 10 mg once a day	Fundamental improvement	Favourable	No RCT	3	D	15
Anecdotal	Cold urticaria refractory to histamine receptor blockers	1	Montelukast 10 mg once a day	Fundamental improvement	Favourable	No RCT	3	D	16
Anecdotal	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	Favourable	No RCT	3	D	17
Anecdotal	Delayed pressure urticaria	1	Montelukast 10 mg a day	Symptom-free under treatment but discontinuation not possible	Favourable	No RCT	3	D	18
Anecdotal	Intractable CU	1	Zafirlukast 20 mg twice daily	Remission of symptoms	Favourable	No RCT	3	D	19
Anecdotal	Intractable CU	1	Zileuton 600 mg 4 times daily	Remission of symptoms	Favourable	No RCT	3	D	19
Anecdotal	ASA-induced urticaria	2	Pranlukast 112.5 mg once a day	Provocation urticaria	Unfavourable	No RCT	3	D	20
Open series	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	Favourable	+	2-	D	21
Open series	Steroid-dependent chronic idiopathic urticaria	15	Montelukast 10 mg once a day, zafirlukast 20 mg twice daily	Marked improvement in some patients	Favourable	No RCT	3	D	22

Table 2 Continued.

Quality of evidence	Type of urticaria	No. of patients studied	Drugs	Results	Outcome	Methodological quality*	Level of evidence	Grade of recommendation	Reference
Open series	Unremitting steroid-dependent urticaria	12	Montelukast 10 mg once a day, zafirlukast 20 mg twice daily	Nearly total remission in some of the patients	Favourable	No RCT	3	D	23
Open series	Chronic idiopathic urticaria	6	Zafirlukast 20 mg twice daily	Marked improvement	Favourable	No RCT	3	D	24
Open series	Dermographism	2	Zafirlukast 20 mg twice daily	Marked improvement	Favourable	No RCT	3	D	24
Open series	Allergic urticaria	7	Zafirlukast 20 mg twice daily	Less benefit	Unfavourable	No RCT	3	D	24
Open series	Chronic idiopathic urticaria	7	Montelukast 10 mg once a day, zafirlukast 20 mg twice daily	Marked improvement	Favourable	No RCT	3	D	25
Controlled study	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	Favourable	-	2-	D	26
Controlled study	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	Favourable	+	2-	D	27
Controlled study	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	Favourable	-	2-	D	28
Controlled study	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	Favourable	-	2-	D	29
Controlled study	Refractory chronic idiopathic urticaria	30	Montelukast 10 mg once a day vs. placebo using cetirizine 10 mg as needed	Montelukast controls urticaria symptoms better than placebo	Favourable	+	2-	D	30
Controlled study	Heterogeneous population of CU	52	Zafirlukast 20 mg twice daily vs. placebo	No significant effect for any of the efficacy measures	Unfavourable	++	2+	D	31

Table 2 Continued.

Quality of evidence	Type of urticaria	No. of patients studied	Drugs	Results	Outcome	Methodological quality*	Level of evidence	Grade of recommendation	Reference
Controlled study	Mild CU	76	Desloratadine 5 mg once a day vs. desloratadine 5 mg once a day plus montelukast 10 mg once a day vs. placebo	Combination therapy (desloratadine plus montelukast) better than desloratadine alone and placebo	Favourable	+	2-	D	32
Controlled study	Moderate chronic idiopathic urticaria	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	Unfavourable	++	2+	D	33

*Rating of methodological quality of the study or review according to the Methodology Checklist 2: Randomized Controlled Trials of the Scottish Intercollegiate Guidelines Network (SIGN).¹² ++, All or most of the criteria have been fulfilled. Where they have not been fulfilled, the conclusions of the study or review are thought very unlikely to alter; +, Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or adequately described are thought unlikely to alter the conclusions -, Few or no criteria have been fulfilled. The conclusions of the study are thought likely or very likely to alter. The grade of recommendation according to SIGN criteria: 1++, high-quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias; 1+, well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias; 1-, meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias; 2++, high-quality systematic reviews of case-control or cohort studies, high-quality case-control or cohort studies with a very low risk of confounding, bias, or chance and high probability that the relationship is causal; 2+, well-conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal; 2-, case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal; 3, non-analytical studies, e.g. case reports, case series; 4, expert opinion. The level of evidence provided by the study is derived from the code allocated for the methodological quality and the type of study, according to the methodology checklist 2: randomized controlled trials of the Scottish Intercollegiate Guidelines Network: A, at least one meta-analysis, systematic review, or RCT rated as 1⁺⁺, and directly applicable to the target population, or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1⁺ directly applicable to the target population, and demonstrating overall consistency of results; B, A body of evidence including studies rated as 2⁺⁺, directly applicable to the target population, and demonstrating overall consistency of results, or extrapolated evidence from studies rated as 1⁺⁺ or 1⁺; C, A body of evidence including studies rated as 2⁺, directly applicable to the target population and demonstrating overall consistency of results, or extrapolated evidence from studies rated as 2⁺⁺; D, Evidence level 3 or 4, or extrapolated evidence from studies rated as 2⁺.

oral challenge with NSAIDs, completely or partially prevented the reaction in most of those patients.²⁷

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.²⁸

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.²⁹

A randomized, single-blind, placebo-controlled, crossover study with montelukast vs. placebo, using a non-sedating 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.³⁰

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 dermographism.³¹

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: (i) oral desloratadine plus placebo; (ii) desloratadine plus montelukast; or (iii) oral placebo alone. In this study, the combination of desloratadine plus montelukast was effective in the treatment of CU.³²

We have treated 160 patients affected by chronic idiopathic urticaria with montelukast alone or in combination with a non-sedating antihistamine (desloratadine), or only with non-sedating 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.^{22,23,31} In patients with moderate chronic idiopathic urticaria, the role of leukotrienes is probably rather insignificant.^{5,29} In this study, montelukast alone was less effective than the combination with non-sedating

antihistamine and appeared not to be useful in controlling the symptoms of urticaria compared with non-sedating antihistamine alone. Therefore, the expected synergistic interaction between antileukotrienes and antihistamines was not confirmed in chronic idiopathic urticaria.³³

Conclusions

Research into the cause of urticaria is important for disease management. Clinically, this is important for the choice of therapy in these patients, considering that particular subgroups of patients affected by CU with ASA or food additive hypersensitivity, or IgG antibodies directed against the α -subunit of the high-affinity IgE receptor or IgE,²⁵ do not all respond to H₁ antihistamines.^{17,22}

Considering the results of the open series and of the few available controlled studies on the use of antileukotrienes in the treatment of CU, it is now possible to affirm that, in patients with no known cause of urticaria without ASA or food additive hypersensitivity, and those without positive ASST, the use of leukotriene receptor antagonists in combined therapy with a H₁ antihistamine does not produce a substantial benefit for urticaria symptoms compared with antihistamine administered as monotherapy.^{29,33,34} Combined therapy may be useful in control of urticaria induced by ASA or food additives urticaria or in patients with a positive ASST, or those affected by acquired cold urticaria and DPU.

Studies on the use of antileukotrienes in the treatment of chronic urticaria show different results in patients with ASA and/or NSAIDs,^{13,14,26,27,30} and/or in patients with food additive hypersensitivity,²⁶ and in patients with positive ASST.^{14,15,23,28–30} However, in many studies, challenge with ASA^{15,19,22–25,28,29,31,32} and/or ASST^{13,19,22,24–27,31,32} have not been reported or performed. Finally, many patients were affected by physical urticaria.^{16–18,21}

The most common adverse effects observed in randomized controlled clinical trials on asthmatic patients treated with antileukotrienes were headache, pharyngitis, cough, abdominal pain and dyspepsia. However, only two case reports also described generalized urticaria induced by antileukotriene treatment in ASA-induced urticaria²¹ and in asthmatic patients.³⁵ Thus, the results of the controlled studies and clinical experience indicate that these agents are generally safe and well-tolerated, with an incidence of adverse effects generally comparable with placebo.^{26–33}

Learning points

- *In vitro* and *in vivo* clinical and experimental data have suggested that leukotrienes play a key role in inflammatory reactions of the skin.
- Leukotriene receptor antagonists and synthesis inhibitors are a new class of anti-inflammatory drugs that have shown clinical efficacy in the management of asthma.
- The MedLine database was searched and a manual search on journals specializing in allergy and dermatology was carried out for the use of antileukotriene drugs in urticaria.
- The studies were evaluated using the SIGN (Scottish Intercollegiate Guidelines Network) coding.
- Montelukast may be effective in chronic urticaria associated with hypersensitivity to aspirin or food additives or with autoreactivity to intradermal serum injection when taken with an antihistamine, but not in moderate chronic idiopathic urticaria.
- Evidence for 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 dermographism. No evidence exists for other physical urticarias, including cholinergic, solar and aquagenic urticaria, vibratory angio-oedema, and exercise-induced anaphylaxis.
- The results of the controlled studies and clinical experience indicate that these agents are generally safe and well-tolerated, with an incidence of adverse effects generally comparable with placebo.

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