

BRIEF REVIEW

Non-sedating antihistamines in the treatment of chronic idiopathic urticaria using patient-reported outcomes

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ABSTRACT

Background: Chronic idiopathic urticaria (CIU) greatly impairs quality of life (QoL). Thus, patient-reported outcome (PRO) measures, using validated scoring instruments, are probably the most accurate tools available for assessing the efficacy of medications that treat CIU, such as second-generation antihistamines.

Research methods: A structured search of the MEDLINE database was conducted to identify English-language papers published between 1 January 1991 and 30 September 2007 on the treatment of CIU with the second-generation antihistamines cetirizine, desloratadine, fexofenadine, and levocetirizine, and their effects on patient-reported QoL. We used the following search terms alone or in combination: 'chronic idiopathic urticaria'; 'pruritus'; 'wheals'; 'hives'; 'second-generation antihistamines'; 'cetirizine'; 'desloratadine'; 'fexofenadine'; 'levocetirizine'; and 'quality of life'.

Scope: We evaluated the effects of second-generation antihistamines on the QoL of subjects with CIU using desloratadine as a treatment model. Desloratadine was selected because it is the most frequently assessed

non-sedating second-generation antihistamine in QoL studies in patients with CIU.

Findings: Desloratadine 5 mg QD improved QoL in numerous PRO studies. Treatment with desloratadine significantly ($p < 0.05$) lowered (better) scores in three studies ($n = 364$) that used validated dermatology-specific scoring instruments. Three 6-week double-blind, placebo-controlled trials ($n = 553$) found that desloratadine significantly ($p < 0.05$) improved patient-reported pruritus, sleep disruption, and interference with daily activities. Desloratadine was associated with a low incidence of adverse events and an overall tolerability profile similar to placebo.

Limitations: Limitations in this review include divergence in search practices that may lead to omission of relevant research, unintentional error in data transfer, inconsistency in quality of selected papers, and potential publication bias against papers that report results from small studies.

Conclusions: The favorable impact of second-generation antihistamines on the QoL of patients with CIU was demonstrated using desloratadine, the most frequently investigated drug in this field, as a treatment model.

Introduction

Chronic idiopathic urticaria (CIU) manifests as spontaneous, widespread pruritic wheals occurring on a daily or near-daily basis for ≥ 6 weeks¹⁻³. The lifetime prevalence of CIU is estimated at 0.5% of the population⁴.

Women are more likely to be affected than men, and the average age of onset is 40 years⁵.

The duration of CIU can be highly variable. In one study of adults, 52% reported a disease duration of 6–12 weeks, and 11% reported that the condition had lasted for > 5 years⁵. As many as 20% of patients

still manifest symptoms 20 years after the onset of the disease⁶. The bothersome itching and wheals associated with CIU lead to substantially reduced quality of life (QoL), limiting patients' daily activities and adversely affecting emotions, sleep, relaxation, and work⁷. In fact, the impact of CIU on QoL has been shown to be as severe as that of ischemic heart disease or other apparently more severe dermatologic conditions such as psoriasis^{7,8}. Thus, from the point of view of the patient, improvement of QoL is the major focus of CIU disease management.

In recent years, QoL has become increasingly more important in clinical practice in allergology. The European Academy of Allergology and Clinical Immunology (EAACI)/Global Allergy and Asthma European Network (GA²LEN)/European Dermatology Forum (EDF) joint guidelines state that assessment of QoL is no longer considered optional by physicians and researchers when evaluating treatment regimens. Moreover, QoL, which comprises both objective functioning and subjective well being, is now recognized as a primary outcome in clinical trials and population-based studies⁹.

This brief review focuses on the efficacy of second-generation antihistamines for improving QoL in patients with CIU. Desloratadine has been the most extensively studied drug in this class for treatment of CIU from the patient's perspective.

Methods

We conducted a structured search of the MEDLINE database for randomized controlled trials or open-label studies using the following search terms, alone or in combination: 'chronic urticaria'; 'chronic idiopathic urticaria'; 'pruritus'; 'wheals'; 'hives'; 'antihistamines'; 'second-generation antihistamines'; 'cetirizine'; 'desloratadine'; 'fexofenadine'; 'levocetirizine'; and 'quality of life'. To be included, papers had to be

published in English between 1 January 1991 and 30 September 2007. In addition, we reviewed bibliographies from papers fitting our parameters for additional sources. Similarly, an examination was made of recent, relevant guidelines on treatment of CIU for added resources. The literature search returned 179 articles. Studies that did not report QoL improvement or improvement in pruritus, sleep disruption, or interference with daily activities for subjects with CIU as an outcome measure or reported on trials focusing on treatments other than second-generation antihistamines for CIU were excluded. We then identified three guidelines and 24 reports from randomized controlled clinical trials or open-label studies that fit our inclusion criteria.

Second-generation antihistamines in CIU

Because histamine is a prominent mediator of CIU, non-sedating second-generation antihistamines are widely advocated as first-line therapy for this disease⁹. While first-generation antihistamines (e.g., diphenhydramine and hydroxyzine) are efficacious, these agents often produce drowsiness/somnolence and anticholinergic effects (although these effects may be desired in situations such as sleep difficulties)^{9,10}. Second-generation agents (i.e., cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine) ameliorate symptoms with few or no adverse effects² and have been shown to improve QoL in patients with CIU¹¹⁻¹⁶. There have been few well-controlled studies directly comparing second-generation antihistamines in urticaria¹⁷. A 2005 review by Monroe¹⁷ assessed the efficacy and safety of currently available first- and second-generation antihistamines using a 0 (no effect) to 3 (strong effect) scale; results are presented in Table 1.

Table 1. Efficacy and safety of H₁ antihistamines in chronic idiopathic urticaria

Antihistamine	Efficacy	Anticholinergic effect	Drowsiness		Impairment	
			Recommended dose	>Recommended dose	Recommended dose	>Recommended dose
Cetirizine	+++	0	+	+	+	+
Chlorpheniramine	+++/+++	+++	++	+++	++	+++
Desloratadine	+++	0	0	+	0	+
Diphenhydramine	+++	+++	+++	+++	+++	+++
Fexofenadine	+++	0	0	0	0	0
Loratadine	+++	0	0	+	0	+

0 = none; + = mild, ++ = moderate, +++ = strong

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Other medications recommended as second-line agents or adjunctive therapy for refractory CIU include H₂ antihistamines, the tricyclic antidepressant doxepin, leukotriene modifiers (e.g., montelukast, zafirlukast), and cyclosporine^{18,19}. Brief courses of oral corticosteroid therapy may also be beneficial, but corticosteroids are not appropriate for long-term use^{20,21}. Efficacy with these treatments has been demonstrated, but their impact on QoL has not been systematically studied, and they have been found to be very sedating²².

Impact of treatments for CIU using patient-reported outcomes

Quality-of-life tools

The beneficial impact of treatments can be assessed by their respective effects on separate factors that negatively affect QoL, such as patient-reported pruritus and interference with sleep and daily activities. However, validated, dermatology-specific scoring instruments such as the Dermatology Life Quality Index (DLQI) and the VQ-Dermato are by far more relevant to assessing the overall impact on patients. The DLQI evaluates the effect of skin disorders on patients' lives using 10 equally weighted items: itchiness/soreness/pain, embarrassment, interference with shopping, choice of clothing, social leisure, difficulty playing sports, difficulty with work or study, problems with partner, sexual difficulties, and problems at home caused by treatment. Each item is scored from 0 (least impairment) to 3 (worst impairment). Total DLQI scores range from 0–30 and are rated as follows: 0–1 = no effect; 2–5 = small effect; 6–10 = moderate effect; 11–20 = very large effect; 21–30 = extremely large effect²³. The VQ-Dermato questionnaire (the only validated French-language QoL instrument) consists of 28 items in seven domains: self-perception, daily living activity, mood state, social functioning, leisure activity, treatment-induced restriction, and physical discomfort. Each item is scored on a scale of 0–4. Total VQ-Dermato scores range from 0 (least serious effect) to 112 (worst effect) and are then converted to a 0–100 linear scale⁸.

Effects of second-generation antihistamines on patient-reported outcomes in patients with CIU

In two clinical efficacy trials of identical design, subjects ($n = 325$) aged 12–65 years with moderate-to-severe CIU receiving fexofenadine 60 mg twice daily for 4–6 weeks showed significant improvement compared with

placebo ($p = 0.0002$) in five of six DLQI domains¹⁴. Similarly, in a 4-week efficacy trial of subjects ($n = 254$) ≥ 12 years with CIU and a history of wheals for ≥ 3 days/week for 6 consecutive weeks, those receiving fexofenadine 180 mg once a day showed significant improvement from baseline to Week 4 compared with placebo in mean total DLQI score ($p < 0.03$) and in the individual domains of symptoms/feelings ($p < 0.01$) and personal relationships ($p = 0.01$)²⁴. A multicenter, randomized, placebo-controlled trial evaluating levocetirizine 5 mg in CIU reported a similar improvement in QoL following antihistamine treatment; subjects ($n = 81$) receiving levocetirizine showed 24% improvement in DLQI scores versus 8% improvement in those taking placebo ($n = 85$)¹⁶. The levocetirizine group also showed a comparable increase in work productivity.

A 4-week, multicenter randomized trial compared efficacy and safety of cetirizine 10 mg once daily, the first-generation antihistamine hydroxyzine 25 mg three times daily, and placebo in CIU subjects ≥ 12 years ($n = 188$)²⁵. Subjects reported more sedation with cetirizine (21%) and hydroxyzine (30%) than with placebo (11%). Somnolence was reported by 14 (22%) patients taking hydroxyzine, 9 (15%) taking cetirizine, and 3 (5%) taking placebo.

Focus on desloratadine and quality of life

Desloratadine as a model

Desloratadine has been involved in more clinical trials studying QoL in CIU than any other antihistamine^{26–32} and, thus, constitutes the best model for assessing the kind of benefit second-generation antihistamines can provide from the point of view of patients with CIU.

Desloratadine

Desloratadine is a highly selective peripheral H₁-receptor antagonist^{33–35} indicated for the relief of symptoms related to allergic rhinitis and CIU. The recommended dosage of desloratadine for adults and adolescents with CIU is one 5 mg tablet/day. In children, the recommended dosages are 1.25 mg of syrup/day for those aged 1–5 years and 2.5 mg of syrup/day for those aged 6–11 years³⁶. Desloratadine acts rapidly, is quickly absorbed, and is non-sedating because it does not readily penetrate the blood-brain barrier³⁶. In controlled clinical trials, subjects given desloratadine 5 mg daily did not experience increased somnolence compared with those receiving placebo^{36,37}. Co-administration of desloratadine with alcohol does not potentiate impairment or drowsiness, and the drug can be taken with or without food^{37,38}. In CIU studies, the incidence and types of treatment-emergent adverse events (AEs) were comparable between desloratadine

and placebo groups^{11–13}. Further data from a post-marketing safety study of nearly 78 000 subjects with CIU and allergic rhinitis confirm a low incidence of AEs with desloratadine; most were mild to moderate, did not require dose adjustment, and improved as therapy continued³⁹. No AE occurred at a frequency of >0.1%, and nearly all subjects (98.5%) rated treatment tolerability as excellent or good.

Quality of life assessments with desloratadine

Grob *et al.*²⁷ compared the effects of 6 weeks of desloratadine treatment versus placebo on QoL and CIU-induced disturbances of sleep and daily activities in 137 subjects using both the DLQI and the VQ-Dermato. By the end of the study, significant improvements were seen in DLQI ($p<0.001$) and VQ-Dermato scores ($p=0.0009$) in subjects taking desloratadine compared with placebo (Table 2). This benefit was also significant for several individual dimensions of VQ-Dermato: social life ($p=0.005$), mood ($p=0.027$), physical pain ($p=0.006$), and daily activities ($p=0.001$). At Day 1 of treatment, the mean sleep disruption and daily activity disruption scores were lower for subjects taking desloratadine compared with those taking placebo ($p<0.05$), and this effect was sustained throughout the study²⁷.

Several open-label studies have also used the DLQI to assess the effect of desloratadine on QoL. In one such study of 121 subjects, total DLQI scores significantly decreased with desloratadine therapy ($p<0.0001$ vs. placebo at Days 7 and 42)³¹, representing a change from a moderate to a small impact of the disease on QoL²⁹.

Another study that used the VQ-Dermato to measure QoL compared continuous desloratadine treatment with as-needed (PRN) dosing following

4 weeks of daily therapy ($n=106$)²⁸. The first 4 weeks of continuous daily desloratadine therapy led to considerable improvement in QoL; subjects continuing with daily desloratadine reported greater reductions in total and all individual VQ-Dermato scores compared with subjects on the PRN regimen. VQ-Dermato scores for subjects receiving desloratadine PRN improved at 28, 60, and 90 days; however, scores were significantly higher (worse) than those of daily desloratadine at 60 and 90 days ($p=0.001$ and $p=0.016$, respectively).

A few studies with desloratadine also provide PRO other than QoL, by assessing directly pruritus, sleeping, and daily activities. In three randomized, double-blind, placebo-controlled, 6-week clinical trials ($n=553$), desloratadine significantly reduced reflective pruritus scores^{11–13}. Ring *et al.*¹¹ found that treatment with desloratadine led to a 56.0% reduction in mean AM/PM reflective pruritus score during Week 1 ($p<0.001$); by the end of the trial, there was a 74.0% reduction in pruritus in subjects given desloratadine versus a 48.7% reduction in subjects given placebo. The largest of the three trials, by Monroe *et al.*¹², found that desloratadine therapy led to significant lessening of pruritus as early as the first day of treatment (40.3% vs. 13.8% for placebo; $p<0.001$), and this benefit was maintained throughout the trial. A more recent study conducted in France confirmed these findings; treatment with desloratadine led to statistically significant improvements in reflective pruritus scores by Day 1 ($p<0.001$ vs. placebo) and for the study duration ($p<0.005$ at Week 6) (Figure 1)¹³. Four open-label studies also corroborate these data^{26,29,32,40}.

The study by Ring *et al.*¹¹ also showed an early and sustained reduction in interference with sleep

Table 2. Improvement in QoL from baseline

	Desloratadine	Placebo	<i>p</i> -value
DLQI score $\pm$ SD			
Baseline	9.7 $\pm$ 5.9	8.8 $\pm$ 5.2	0.373
Day 42	3.9 $\pm$ 5.5	7.5 $\pm$ 7.5	0.003
Change from baseline	–6.0 $\pm$ 6.2	–2.2 $\pm$ 5.1	<0.001
VQ-Dermato score $\pm$ SD			
Baseline	35.2 $\pm$ 18.8	35.0 $\pm$ 20.2	0.687
Day 42	18.5 $\pm$ 17.5	29.1 $\pm$ 23.9	0.009
Change from baseline	–15.0 $\pm$ 17.7	–8.0 $\pm$ 18.8	0.035

DLQI = Dermatology Life Quality Index; QoL = quality of life; SD = standard deviation

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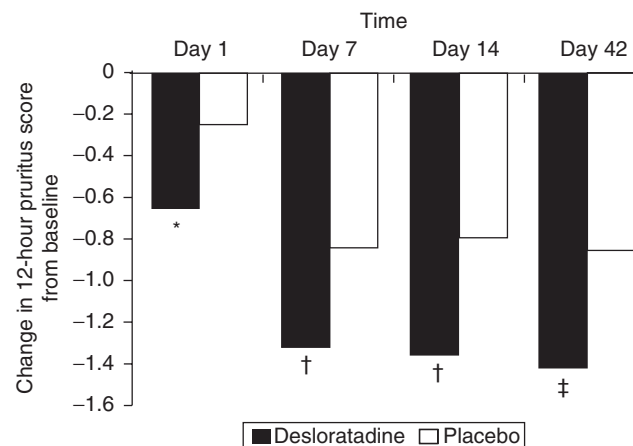


Figure 1. Mean change in 12-hour reflective pruritus score from baseline with desloratadine 5 mg. Reprinted with permission from Ortonne *et al.*¹³. * $p<0.01$; † $p<0.001$; ‡ $p<0.005$

($p \leq 0.03$) and daily activities ($p < 0.001$) following 6 weeks of desloratadine therapy. In fact, sleep and daily activities were both significantly improved in subjects receiving desloratadine by the first week of treatment ($p < 0.001$ vs. placebo). In the Monroe *et al.* study¹², interference with sleep at Week 1 improved by 44.0% in the desloratadine group compared with 17.2% in the placebo group ($p = 0.007$). Similar improvements were seen in interference with activities of daily living (46.9% with desloratadine vs. 17.2% with placebo at Week 1; $p = 0.001$), and in an open-label study conducted in Canada, subjects reported significant reductions in interference by CIU with sleep and daily activities at 1 and 2 weeks of treatment compared with baseline through daily desloratadine therapy ($p < 0.0001$)³². Subjects also reported significant improvements relevant to QoL including self-consciousness regarding skin, problems with partner, and interference by CIU with outdoor activity, sport, leisure, work/study, and sexual activity ($p < 0.0001$).

Limitations of this review include potential publication bias against papers that report results from small studies, divergence in search practices that may lead to omission of relevant research, and inconsistency in quality of selected papers. In addition, there is a paucity of QoL studies, particularly those that report results from second-generation antihistamines other than desloratadine.

Conclusion

CIU affects QoL as greatly as apparently more severe skin conditions (e.g., atopic dermatitis, psoriasis) and non-dermatologic disorders. The main goal of treatment for patients with CIU is to relieve discomfort, and, therefore, measuring effect using validated QoL tools is particularly relevant. Among the second-generation antihistamines, desloratadine has been the most extensively studied using QoL instruments and, thus, constitutes a good model for assessing the benefit obtained from the patient's perspective by treatment with second-generation antihistamines. Using the desloratadine model, this benefit is demonstrated through the improved QoL of patients with CIU.

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