Pharmacology and therapeutics

Once-daily desloratadine improves the signs and symptoms of chronic idiopathic urticaria: a randomized, double-blind, placebo-controlled study

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Abstract

Background Chronic idiopathic urticaria (CIU) is the most common type of chronic urticaria, and pruritus is the most prominent symptom. Antihistamines are the first-line treatment for CIU. Sedation and anticholinergic adverse effects are often experienced with the first-generation antihistamines and there is a risk of cardiovascular adverse effects and drug interactions with some second-generation agents. Hence, new treatment options are needed. Desloratadine is a new, potent, nonsedating antihistamine that has an excellent cardiovascular safety profile.

Methods This was a multicenter, randomized, double-blind, placebo-controlled study designed to determine the efficacy and safety of desloratadine in the treatment of moderate-to-severe CIU. A total of 190 patients, aged 12–79 years, with at least a 6-week history of CIU and who were currently experiencing a flare of at least moderate severity, were randomly assigned to therapy with desloratadine 5 mg or placebo once daily for 6 weeks. Twice daily, patients rated the severity of CIU symptoms (pruritus, number of hives, and size of largest hive), as well as the impact of CIU symptoms on sleep and daily activity. Patients and investigators jointly evaluated therapeutic response and overall condition. Safety evaluations included the incidence of treatment-emergent adverse events, discontinuations due to adverse events, and changes from baseline in vital signs, laboratory parameters, and ECG intervals.

Results Desloratadine was superior to placebo in controlling pruritus and total symptoms after the first dose and maintained this superiority to the end of the study. Measures of sleep, daily activity, therapeutic response, and global CIU status were also significantly better with desloratadine after the first dose; these clinical benefits were also maintained throughout the 6-week study. No significant adverse events occured.

Conclusions Desloratadine 5 mg daily is a safe and effective treatment for CIU with significant benefits within 24 h and maintained through the treatment period.

Introduction

Urticaria is a very common disorder, affecting as many as 23% of the US population.[1] In patients with chronic idiopathic urticaria (CIU), the most common form of chronic urticaria, characteristic wheals or hives occur for more than 6 weeks without a detectable allergic, physical, or environmental cause. The symptoms of CIU, such as pruritus, are mediated primarily by histamine, and antihistamines are the first-line therapy in CIU.[2]

Desloratadine is a new, nonsedating antihistamine with potent peripheral H_1 receptor blockade.[3] A multicenter,

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placebo-controlled, randomized, parallel-group study of 5 mg desloratadine daily in patients with moderate-to-severe CIU was performed to determine the efficacy and safety of this new H_1-receptor antagonist.

Materials and methods

Study design

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Patients completed a screening period of 3–14 days prior to treatment randomization, during which inclusion and exclusion criteria were assessed and CIU severity was measured. After screening, suitable patients were randomized (using a computer-generated schedule) to receive either desloratadine 5 mg daily or a matched placebo. Study medications were administered for 6 weeks. Efficacy and safety assessments were performed at visits to the study centers on Days 1 (baseline) and 4, and at Weeks 1, 2, 4, and 6.

Inclusion/exclusion criteria

Men and women aged ⩾ 12 years were eligible for enrolment if they had a minimum 6-week history of CIU and were experiencing an active flare. CIU had to be active for more than 3 weeks prior to screening, with wheals visible for ⩾ 3 days per week. In addition, patients had to have at least an overall moderate disease severity at screening and baseline, as well as at least moderate pruritus and the presence of wheals at screening. At baseline, patients also had to have a total reflective pruritus score of ⩾ 14 (at least moderate) over the previous 3 days and the morning of the baseline visit. Results of standard laboratory biochemistry, hematology, and urinalysis tests, as well as electrocardiograms (ECG), obtained at screening had to be within clinically acceptable limits as assessed by the investigator.

Patients with significant concomitant illnesses (e.g. malignancy) or those taking pharmacological agents that could interfere with the study drug or interpretation of efficacy parameters were excluded, including patients with asthma using leukotriene inhibitors or those requiring chronic inhaled or systemic corticosteroid therapy. Sufficient washout time was required for previous CIU treatments (especially long-acting antihistamines and corticosteroids) before the study drug was administered.

Study medication

Each dose of study medication was administered orally in the morning, after completion of the diary, without regard to the timing of meals. Compliance was checked by referral to the daily study diary, questioning of patients, and by performing a tablet count.

Disease activity and therapeutic response assessment

Patients assessed disease activity during the screening period and the course of the trial using a system of scores for signs and symptoms. The scores were recorded on daily diary cards. CIU symptom scores were evaluated using 4-point scales under the following headings: pruritus, number of hives, and size of largest hive; the sum of these individual scores was the total symptom score (TSS). Other symptom scores recorded interference with sleep and interference with daily activities. The patients scored pruritus, hive number, and size of largest hive symptom severity over the preceding 12 h (reflective) and immediately at the time of assessment (instantaneous) on all study days. This was done upon awakening (predose) and 12 h later, providing a total of four symptom severity scores – two morning (reflective/instantaneous) and two evening (reflective/instantaneous). Reflective scores over the previous 12 h were recorded for interference with sleep (am) and interference with daily activities (pm).

CIU severity was assessed jointly by the investigator and the patient/guardian, after the diaries were reviewed on Days 1 and 4 and Weeks 1, 2, 4, and 6, using another 4-point scale: 0 (none) to 3 (severe). The therapeutic response to study medication was also assessed jointly by the investigator and patient/guardian and was determined at Day 4 and Weeks 1, 2, 4, and 6. A 5-point scale was used: 1 (complete relief) to 5 (treatment failure).

Safety assessments

Vital signs were recorded at every visit. Laboratory evaluations and ECGs were performed at screening and at the end of the study. All adverse events were recorded and graded with respect to severity and potential relation to study medication.

Efficacy and safety variables

The change in average reflective am/pm pruritus symptom score from baseline over the first seven days of treatment, as recorded in the patient diaries, was the primary efficacy variable. The secondary efficacy outcomes were: reflective average am/pm scores for the number of hives, size of largest hive, and TSS. Average individual am/pm instantaneous, am reflective, pm reflective, and pm instantaneous scores for pruritus, number of hives, size of largest hive, and TSS were also secondary outcomes as were interference with sleep (am reflective) and interference with daily activities (pm reflective). All variables were assessed individually at the primary time point (first seven days), for Days 1–4 of treatment, and also as averages for all weeks of the study up to Week 6. Joint patient/investigator assessment of change in overall condition of CIU from baseline and therapeutic response were also secondary efficacy outcomes.

Safety evaluations included the incidence of treatment-emergent adverse events, discontinuations due to adverse events, and changes from baseline in vital signs, laboratory parameters, and ECG intervals.

Statistical analysis

The study was designed to enroll 200 patients (sample size of 100 patients per treatment group). This figure was chosen to

detect, with 90% power and at a 5% significance level, a mean intergroup difference of ⩾0.5 units in the mean change from the reflective baseline pruritus score, assuming a standard deviation of 1.0.

The consistency of efficacy results across centers was assessed with a two-way analysis of variance (ANOVA) extracting variations due to treatment, center, and treatment-by-center. The primary and secondary efficacy variables in the combined data were also analysed using two-way ANOVA. Analyses were performed primarily on the randomized population (intention-to-treat, ITT), but were also confirmed in the subset of patients in whom a full set of efficacy data were available (efficacy-evaluable population). To prevent misinterpretation of differences between active treatment and placebo due to the large numbers of dropouts in the placebo group for lack of efficacy, results were also analysed by 'endpoint week,' which used the last week for which sufficient efficacy data were available for the specific patient as the final endpoint.

Results

Demographics

A total of 190 patients were randomized (ITT population), 95 in each group. At baseline, the two groups were balanced for age, sex, race, duration of CIU symptoms, and baseline symptom severity scores (Table 1). Nineteen patients in the desloratadine group and 32 patients in the placebo group discontinued treatment early (Table 2). The efficacy-evaluable population consisted of all patients for whom complete valid efficacy data sets were collected. In the desloratadine and placebo groups, 13 and 15 patients, respectively, were excluded from the efficacy-evaluable subset due to failure to meet all entrance criteria, use of unacceptable concomitant medications, noncompliance with the protocol, or insufficient reported efficacy data.

Efficacy analysis

Desloratadine was superior to placebo on the basis of the primary efficacy parameter, reducing the average mean am/pm reflective pruritus score over the first seven days by 56.0% (–1.22), compared with a 21.5% reduction (–0.49) in placebo-treated patients ($P < 0.001$). Compared with the placebo group, am/pm reflective pruritus scores were also significantly lower in the desloratadine group on Day 2, approximately 36 h after administration of the first dose (–45.2% vs. –14.0%, $P < 0.001$). The superior effect of desloratadine on this efficacy parameter was maintained throughout the trial: at Week 6 there was a 74.0% reduction in pruritus with desloratadine and a 48.7% reduction with placebo ($P < 0.001$) (Fig. 1). Similar results were obtained in the efficacy-evaluable subgroup and when endpoint week analyses were performed. No sex, race, age-subgroup, or treatment site effects were apparent.

Morning instantaneous scores assess the effect of treatment 24 h after the most recent dose, providing an indication of an agent's 24-h efficacy. Patients treated with desloratadine had a significantly greater mean percent reduction from baseline in am instantaneous pruritus score

Table 1 Baseline demographic characteristics

Characteristics	Desloratadine 5 mg (*n* = 95)	Placebo (*n* = 95)
Mean age (years)	38.9	42.0
Age subgroup, *n* (%)		
12 to < 18 years	6 (6)	3 (3)
18 to < 65 years	86 (91)	86 (91)
⩾ 65 years	3 (3)	6 (6)
Men/women (*n*)	27/68	21/75
Race, *n* (%)		
White	81 (85)	85 (89)
Black	5 (5)	4 (4)
Asian	3 (3)	1 (1)
Hispanic	4 (4)	5 (5)
American Indian	1 (1)	0
Other	1 (1)	0
Duration of CIU (years)		
Mean	4.3	6.4
Median	1.8	1.5
Range	0–49	0–46
Reflective am/pm pruritus score		
Least-square mean	2.24	2.22
Reflective am/pm total symptom score		
Least-square mean	6.65	6.51

Table 2 Patient disposition

	Desloratadine 5 mg	Placebo
Number randomized	95	95
Number (%) completed	76 (80.0)	63 (66.3)
Number (%) discontinued	19 (20.0)	32 (33.7)
Reason for discontinuation		
Treatment failure	13 (13.7)	21 (22.1)
Noncompliance	3 (3.2)	6 (6.3)
Adverse event	3 (3.2)	2 (2.1)
Lost to follow-up	0	2 (2.1)
Did not wish to continue	0	1 (1.1)

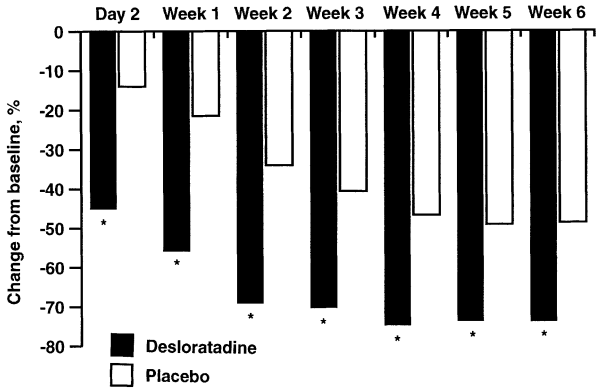

Figure 1 Change from baseline am/pm pruritus score. *$P < 0.001$.

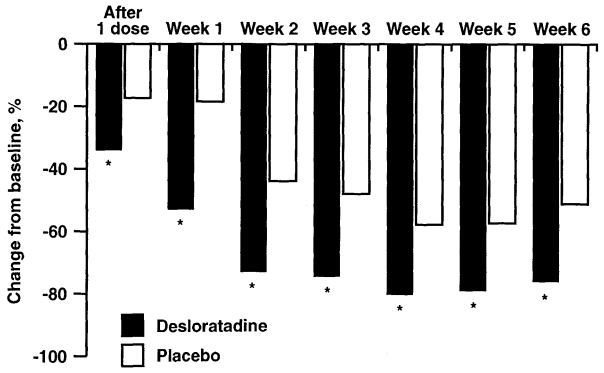

Figure 3 Interference with sleep. *$P \leq 0.030$.

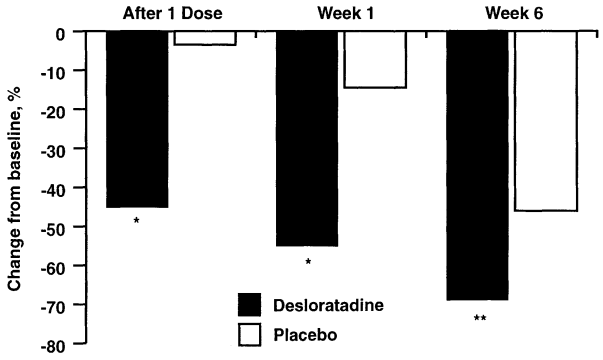

Figure 2 Pruritus am instantaneous. *$P < 0.001$, **$P = 0.033$.

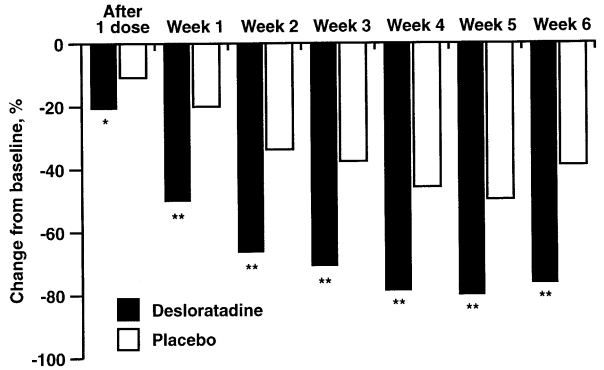

Figure 4 Interference with daily activities. *$P = 0.02$, **$P < 0.001$.

than placebo patients 24 h after the first dose of study medication (−45.1% vs. −3.5%, $P < 0.001$). Desloratadine treatment was also associated with a greater reduction from baseline over the first week of therapy (−55.1% vs. −14.5%, $P < 0.001$). This effect was maintained through the end of the trial (Fig. 2): at Week 6 there was a 68.9% reduction with desloratadine and a 46% reduction with placebo ($P = 0.033$).

Results obtained for am/pm reflective TSS with desloratadine again showed early superiority over placebo after the first dose (−41.6% vs. −10.6%; $P < 0.001$) as well as over Week 1 (−51.6% vs. −19.3%, $P < 0.001$). The effect was maintained for the duration of the study; statistically significant reductions from baseline were sustained throughout the full 6 weeks of the study ($P < 0.001$). Desloratadine improved sleep (am reflective) (Fig. 3) and daily activity (pm reflective) individual symptom scores (Fig. 4) significantly more than the placebo with the first dose ($P = 0.012$ and 0.02, respectively), during the first week of treatment (both $P < 0.001$), and during each remaining week of the study.

Over the first week of therapy, desloratadine produced a statistically greater reduction in the number of hives when compared with the placebo and the difference was highly statistically significant ($P < 0.001$) whether the am/pm reflective, am reflective, pm reflective, am/pm instantaneous, am instantaneous, or pm instantaneous evaluation was analysed. Compared with the placebo, the number of hives was significantly reduced from baseline with desloratadine over the entire 6-week study (am/pm reflective: $P = 0.011$ to $P < 0.001$). Similarly, the size of the largest hive over the first week was also reduced with desloratadine when compared with placebo and again the difference was highly significant ($P < 0.001$) irrespective of the evaluation. Reduction of the size of the largest hive (am/pm reflective: all $P < 0.01$ vs. placebo) was also maintained for the entire study period.

The overall condition of CIU was similar in the two groups at baseline. Patients treated with desloratadine experienced a significant improvement in overall CIU condition compared with placebo at all study visits ($P = 0.002$) and this effect was maintained in the endpoint

week analysis. The assessment of therapeutic response was also significantly in favor of desloratadine at all study visits and in the endpoint week analysis.

Safety analysis

Treatment-emergent adverse events occured in 53 (55.8%) desloratadine-treated patients and in 41 (43.2%) placebo-treated patients. The most frequent adverse events in desloratadine patients were headache (12.6%), fatigue (8.4%), viral infection (7.4%), pharyngitis (6.3%), upper respiratory tract infection (5.3%), and dizziness (5.3%). The corresponding incidences with placebo were headache (16.8%), fatigue (0), viral infection (8.4%), pharyngitis (3.2%), upper respiratory tract infection (4.2%), and dizziness (2.1%). Three patients treated with desloratadine and two treated with placebo discontinued the study due to an adverse event unrelated to study treatment. No deaths or life-threatening or treatment-related serious adverse events occured during the trial. No clinically significant changes vs. baseline in vital signs, laboratory parameters, or ECG criteria occured during the study in either of the treatment groups.

Comment

CIU is the most common form of chronic urticaria. Because patients may suffer from CIU for many years, it is imperative that CIU therapy have rapid and enduring effects on symptoms. Antihistamines are the primary treatment for most CIU patients, but sedation with some agents (such as diphenhydramine) and potentially cardiotoxic effects of others (terfenadine and astemizole) have given patients and practitioners cause for concern.[4] Desloratadine has potent antihistaminic effects but is nonsedating and had no clinically relevant prolongation of QT_c interval in healthy volunteers when taken in combination with erythromycin or ketoconazole,[5,6] agents that are known to interact with terfenadine and promote the emergence of torsades de pointes. The onset of action of desloratadine was rapid, with significant reductions in all efficacy measures after one dose of desloratadine including improvements in sleep, daily activity, and physical appearance of the urticarial lesions. All improvements in efficacy measures with desloratadine were maintained for the duration of treatment in both the ITT group and the more restrictive efficacy-evaluable subpopulation.

No patients discontinued due to treatment-related adverse events in the desloratadine group. In addition, after 6 weeks of therapy with desloratadine, no clinically significant changes in ECG parameters occured, further supporting results of other studies demonstrating the cardiovascular safety of desloratadine.[7]

Conclusions

Desloratadine 5 mg daily is safe and well tolerated in patients with CIU treated for up to 6 weeks. Clinical benefits in terms of symptom reduction, improvement in physical severity of urticarial lesions, and better sleep and daily activity functions were seen as early as after the first dose and persisted throughout the full 6-week treatment period.

Acknowledgments

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