

Clinical studies with cetirizine in allergic rhinitis and chronic urticaria

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Allergic rhinitis is a common condition, affecting 10–15% of the US population. Most seasonal allergic rhinitis is caused by airborne allergens including pollens or mold spores. Major symptoms include recurrent sneezing, rhinorrhea, nasal itching, and congestion. Ocular itching, redness, and tearing may also occur; in some cases, otitis media or sinusitis may occur as a complication of allergic rhinitis. Perennial rhinitis patients may be sensitive to both seasonal allergens and dust mites or animal dander. As a result, these patients often have a constantly inflamed nasal mucosa. The symptoms are similar to those of seasonal allergic rhinitis, although nasal obstruction is often more pronounced. Treatment relies upon oral antihistamines, but many patients receiving the first-generation drugs complain of sedative and anticholinergic side-effects. Thus, patients often have had to choose between enduring their allergic symptoms or the unpleasant effects of the first-generation drugs. In recent years, the second-generation H_1 antihistamines have largely replaced the first-generation drugs, becoming a great asset in the treatment of both seasonal and perennial allergic rhinitis (1). Of the second-generation drugs available, cetirizine has been shown to be both efficacious and safe in the treatment of these conditions (2–4). Various studies have been done in the USA on the clinical effects of cetirizine in allergic rhinitis. I have selected several for review and discussion.

Studies with cetirizine have been done on both perennial and seasonal allergic rhinitis. In particular, three studies have been done in which large numbers of patients were used. Mansmann et al. (5) evaluated 215 patients in a double-blind, placebo-controlled study in which cetirizine was given over 4 weeks at two doses (10 and 20 mg once daily), and both efficacy and safety were assessed. Both doses of cetirizine were comparable in reducing symptoms in contrast to placebo, particularly in relieving postnasal discharge and sneezing. In terms

of safety, there was a small but statistically significant increase in the number of patients receiving 20 mg cetirizine reporting fatigue, but no significant increases compared to placebo in headache or somnolence were observed. The 10 mg dose afforded optimal symptomatic relief, while the 20 mg dose provided little additional benefit. A single-blind parallel study by Lockey et al. (6) compared cetirizine (10 mg four times daily) with terfenadine (60 mg twice daily) in seasonal allergic rhinitis for 1 week during the ragweed season. The drugs were compared with each other and with placebo for efficacy and safety. At days 5 and 7, cetirizine had a better clinical effect than terfenadine. Both drugs were well tolerated in terms of side-effects, and there was no significant difference in their central nervous system (CNS) side-effect profile.

The study by Falliers et al. (7) looked at the largest number of patients with seasonal allergic rhinitis ($n=419$). Placebo was compared with three doses of cetirizine (5, 10, and 20 mg) in a double-blind, parallel-controlled study over 1 week in the late summer/autumn. Once again, efficacy and safety were the main variables measured. All three cetirizine doses had a significant effect, and improvement in symptom scores was seen as early as day 1. A slight dose-response effect was observed, although this was not statistically significant. As for adverse experiences, there was a statistically significant increase at 10 and 20 mg of cetirizine in patients who had somnolence, as compared with 5 mg cetirizine or placebo. No significant increase in headache or fatigue was observed. In summary: of the effects of cetirizine in allergic rhinitis, two studies showed that cetirizine had a significant effect on symptoms, as compared with placebo. One study over 1 week showed cetirizine to be slightly superior to terfenadine at days 5 and 7, and another study found that cetirizine at 5, 10, or 20 mg daily was superior to astemizole 10 mg once daily in the treatment of seasonal allergic rhinitis (8). Several other studies have made similar obser-

vations. For example, Chaweewan et al. also found that cetirizine tended to give a greater improvement in weekly symptom scores and greater relief of rhinorrhea than astemizole (9). These investigators also found cetirizine to be superior in onset of action. A similar study found that patients considered cetirizine to be more effective than astemizole for the relief of their symptoms (10). An optimal dose for cetirizine for the treatment of allergic rhinitis, 10 mg once a day, seems ideal for balancing efficacy with potential side-effects. In only one study were adverse effects observed at 10 and 20 mg of cetirizine. These studies confirm the findings from several other studies which emphasized the efficacy and safety of cetirizine for the management of patients with allergic rhinitis (11–17). In summary, cetirizine has been shown to be both efficacious and safe for the treatment of allergic rhinitis in children (18, 19).

Chronic idiopathic urticaria is a common clinical condition, the cause of which remains unidentified in over 90% of patients. Although rarely serious or life-threatening, it is a distressing and bothersome condition. There is a clear need for improved drugs for the symptomatic treatment of this disorder, because the underlying cause remains unknown. Histamine appears to play a role in the typical wheal-and-flare reaction of urticaria. Thus, antihistamines are often the treatment of choice. However, the sedative side-effects of the first-generation compounds make them a poor option for daytime use. The second-generation antihistamines are therefore often the most suitable agents in the treatment of chronic idiopathic urticaria and can be given as a prophylactic against the symptoms of this condition (20, 21).

Kaplan (22) examined the cellular infiltrate in the lesions of 43 patients with chronic idiopathic urticaria. The infiltrate consisted mainly of mononuclear cells with evidence of mast-cell accumulation. Although large numbers of eosinophils were absent in most of the tissues examined, the presence of major basic protein in the lesions of around 50% of the patients suggested the involvement of eosinophils in this condition. This observation may partly explain the efficacy of cetirizine, given its ability to inhibit eosinophil accumulation *in vivo* (23, 24).

I will review some studies of the efficacy and safety of cetirizine in the treatment of chronic idiopathic urticaria, and I will also present recent data from a paper by Breneman et al. which was presented at the 1992 annual meeting of the American Academy of Allergy and Clinical Immunology (25).

In a multicenter study by Kalivas et al. (26), cetirizine (5–20 mg) was compared with hydroxyzine

(25–75 mg) for efficacy and safety in a double-blind, placebo-controlled study over 4 weeks in 219 chronic urticaria patients. The patients were initially started on the lower dose of each drug, i.e., 5 mg for cetirizine and 25 mg for hydroxyzine. Patients were allowed to increase their dose to 10 or 20 mg of cetirizine, or 50 or 75 mg hydroxyzine if no benefit was obtained from the starting dose. Symptoms were scored (on a 0–3 scale) for number of lesions, separate episodes, average lesion size and duration, and degree of pruritus. For all these variables, cetirizine and hydroxyzine were equivalent in their ability to reduce symptoms. As for side-effects, as compared with placebo, only 6% of patients taking cetirizine experienced “constant” or “frequent” sedation, while 15% of hydroxyzine-treated subjects had somnolence. Anticholinergic effects, i.e., dry mouth, were seen more often in the placebo group than in the cetirizine group. The conclusion drawn from this study was that cetirizine is a more satisfactory drug because of a reduction in CNS side-effects.

In a recent study, Breneman et al. (25) compared the efficacy and safety of cetirizine and astemizole in treatment of 136 patients with chronic idiopathic urticaria. In the double-blind, randomized, and placebo-controlled study, cetirizine was given at 10 mg once daily and astemizole at 10 mg once daily over 4 weeks. Cetirizine reduced the total number of lesions on days 1 and 2. No significant effect on the number of lesions or on the other symptoms measured was seen with astemizole at this time, reflecting its significantly later onset of action. Moreover, cetirizine was statistically more effective than astemizole up to day 6, significantly reducing all five signs/symptoms within 24 h of the first dose. Cetirizine also was significantly more satisfactory in reducing the degree of pruritus than astemizole from day 1 to 5. When improvement was looked at by study week, cetirizine significantly reduced the number of lesions at weeks 1 and 4 compared to placebo. However, a significant difference between the efficacy of cetirizine and that of astemizole was seen only in week 1. Both drugs had similar effects on the mean degree of pruritus when also looked at by study week. As expected, a significant number of patients (21.3%) on placebo stopped treatment because of insufficient response. Perhaps surprisingly, a significant number (13.8%) of those taking astemizole also stopped treatment because of lack of improvement in symptoms. In contrast, only 3.3% of patients in the cetirizine group stopped taking their medication for this reason. The physicians’ overall assessment of efficacy by mean score showed significant improvements by both drugs over placebo. No statistical difference between cetirizine and astemi-

zole was noted in the physicians' overall assessment of efficacy, although a trend in favor of cetirizine was observed. Both drugs were well tolerated with no reported significant differences between the drug groups or between a drug group and the placebo group. In terms of the pattern of response over week 1, cetirizine gave significant improvement in all symptoms scored within 24 h of the first dose; therefore, it showed superior efficacy in the early stages of treatment. In contrast, astemizole showed delayed onset in its effect, with a delay of 3 or 4 days before onset of effect. After 1 week of treatment, both medications were equally effective in managing the symptoms associated with urticaria, and both were well tolerated with minimal side-effects. These results confirm those of another study which noted rapid clinical improvement in recipients of cetirizine, as compared with those receiving astemizole (27). This difference in onset of action was also significant in another instance (28).

In summary, two studies have shown cetirizine to be superior to placebo in urticaria treatment, and another study found the efficacy of cetirizine to be equal to that of hydroxyzine, but cetirizine did not cause the CNS side-effects associated with that drug. In the most recent study, cetirizine and astemizole had comparable efficacy, but the former had a more rapid onset of action, particularly in week 1 of treatment (25). Various other studies have confirmed the usefulness of cetirizine, as compared with other second-generation antihistamines, in the treatment of chronic urticaria (29–32).

Round-table discussion

Simons: With regard to the study by Breneman et al. (25), do you think that if it had been performed for longer, the results in, say, the 8th or 12th week may have been different?

Broide: That is always possible. The differences between cetirizine and astemizole were only seen in the first week and by week 4 both gave comparable effects. It's possible that a difference might have been seen over a longer time period, but the only way to answer that would be to perform such a study.

Juhlin: I was surprised by the statistics in the Falliers et al. study (7) of cetirizine in allergic rhinitis. It seems strange that somnolence was seen in 23 patients in one group, compared with 25 in the other. This difference seems too small to be significant.

Broide: Significant somnolence scores were only seen in the groups taking 10 or 20 mg of cetirizine (23/106 and 25/104 patients, respectively) when compared with placebo (6/103 patients). Cetirizine given at a dose of 5 mg did not cause significant somnolence (9/102 patients). No significant differences were seen between the 10 and 20 mg cetirizine doses in terms of somnolence.

Meltzer: It's clear that the Falliers et al. study is the only one to show a statistical difference with regard to cetirizine and somnolence, but the other studies do show a trend for cetirizine to cause some somnolence and fatigue.

Rihoux: In some studies, it's somnolence that's significant; in some, it's fatigue. What is the difference between the two?

Broide: That depends on how the question is phrased to the patient and how the patient perceives the question. In one study, they asked the patients whether they felt somnolence at that specific time or throughout the day. They had different answers depending on whether they tried to quantify tiredness over a brief period or over 24 h. One hopes that in such studies one person would phrase the questions, but all of these studies are multicenter. This raises the question as to whether one center is inquiring about symptoms in exactly the same manner as another center. Do the positive somnolence answers tend to come from one center, or are they evenly distributed among centers?

Walsh: One study in the UK suggests that the latter scenario is possible. Backhouse et al. (33) compared cetirizine with terfenadine for efficacy and safety in seasonal allergic rhinitis in a double-blind, double-dummy, randomized, controlled, multicenter study. Adverse effects, mainly drowsiness, were only reported by 12% of patients in the study. Of these, 13 patients reported adverse effects from one center, 11 patients from another, while three centers reported no adverse effects at all.

Hindmarch: Could somnolence reflect patients reporting the underlying condition which may have not been adequately treated?

Broide: We all see patients with allergic rhinitis who have fatigue as one of their symptoms, and, if the rhinitis is not treated properly, this would continue, so I think your question is a valid one. However, it would be unusual if fatigue, in the absence of other significant ongoing allergic symptoms, was the sole symptom of allergy.

Simons: But surely such symptoms would be similar in both placebo and treatment groups if somnolence is caused by the underlying disease?

De Vos: It depends. If you have sleep problems caused by, for example, pruritus or a blocked nose and you then have relief of symptoms after treatment with the medication, you may have patients who sleep better as well as feel better.

Simons: So you are saying that a patient might be more sleepy because of a bad night caused by badly controlled symptoms?

De Vos: Yes.

Simons: But surely the patients in the placebo group would be more sleepy during the day because of uncontrolled symptoms. This is a circular argument, but I think what everyone is trying to say is that in the clinical studies which look at patients with disease the situation is quite different from looking at normal volunteers in the laboratory situation.

Hindmarch: I am worried about the whole question of sedation by antihistamines. We have reviewed virtually every clinical paper we can find on sedation by antihistamines which use rating scales for somnolence. We can find no evidence of differences in rates of sedation between the various antihistamines. There was no consistency in the clinical studies when a subjective rating or questionnaire was used to measure sedation.

Simons: When you say antihistamines, do you mean first- or second-generation drugs?

Hindmarch: Whichever antihistamines you look at, the lack of consistency in measurement of fatigue is a major problem. Although more patients complain of somnolence after taking older-generation antihistamines, the measurement of fatigue in these studies was done using subjective criteria, and I think this is a major problem. Also one would have thought that the patients taking placebo in these studies would be even more fatigued than those on medication.

Simons: Because they would be up all night scratching or sneezing.

Hindmarch: That's right.

Simons: You would think if that were so, they would feel tired the next day and this would be reflected in the score.

Hindmarch: Maybe the patients decide that because they were up all night scratching they do not need to mention it to the doctor, since they know why they are tired the next day. This is a big problem because we cannot get patients to behave with antihistamines along the lines we can show with normal volunteers in the laboratory situation.

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