

EVALUATION OF CETIRIZINE HYDROCHLORIDE-BASED THERAPEUTIC STRATEGY FOR CHRONIC URTICARIA

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ABSTRACT

We investigated the suitability of cetirizine HCl (cetirizine) for the initial treatment of chronic urticaria. A secondary aim was to identify the optimal alternative treatments when switching from this drug to other drugs in patients who are dissatisfied with cetirizine. We started cetirizine at a once-daily dose of 10 mg for 2 weeks and then, depending on the course of symptoms in individual patients, it was either continued, titrated to a higher dose, or switched to other drugs (antihistamines including H₂ blockers) for a further 2 weeks. Degrees of patient satisfaction and ratings by physicians were analyzed, as were adverse events. At 2 weeks after the start of treatment, among 74 patients included in the final evaluation 55 (74.3%) expressed satisfaction with cetirizine therapy. Those not satisfied included five (6.7%) who felt drowsy after taking the drug and 14 (18.9%) in whom the drug had not demonstrated adequate efficacy. After optimizing the treatment on a per-patient basis, including switching from cetirizine to other drugs, the percentage satisfied with treatment at 4 weeks was 83.7% (62/74). In the group of patients who were satisfied with the therapy at 2 weeks, attending physicians confirmed that wheals and scratches were significantly alleviated at 2 and 4 weeks, respectively. Adverse effects were mild and uncommon. Cetirizine as an initial treatment for chronic urticaria appears effective and safe. For patients in whom cetirizine fails to satisfactorily alleviate symptoms as well as those who complain of drowsiness, switching to other antihistamine drugs may be an effective strategy.

Key Words: Urticaria, Cetirizine, Efficacy, Safety, Sedation

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INTRODUCTION

Urticaria is a commonly encountered skin disease in clinical practice. It causes repeated intense sensation and temporary wheals persistence of these clinical symptoms lasting for >1 month is usually classified as chronic urticaria.¹⁾ Regarding the mechanism of its onset, urticaria is thought to arise when mast cells proximal to dermal capillaries undergo degranulation in the presence of various stimuli and thereby release chemical mediators such as histamine that act on the histamine H₁ receptors of vascular endothelium, which increases vascular permeability resulting in the leakage of plasma components and the onset of local edema. Itching is caused when these chemical mediators simultaneously act on sensory nerves.^{1,2)}

When treating patients with chronic urticaria, ideally the pathogenic substances and factors exacerbating the disease should be identified and hence eliminated or avoided. In clinical practice, however, exciting factors precipitating this disease often remain unidentified.^{1,3,4)} Therefore antihistamines are usually prescribed as first-choice drugs to control symptoms, largely on an empirical basis. Apart from having higher clinical efficacy, the newer second-generation antihistamines including azelastine, olopatadine, and loratadine exhibit much higher selectivity for the histamine H₁-receptor, thus causing fewer anticholinergic side effects such as dry mouth than classic antihistamines (ethanolamines, piperazines, and tricyclics). Cetirizine HCl (cetirizine), a highly effective second-generation antihistamine not associated with sedation (drowsiness),⁵⁻⁷⁾ is commonly prescribed for the treatment of chronic urticaria.⁸⁾ Cetirizine was approved for the first-line treatment of chronic urticaria in Japan in 1998.

The present study was undertaken to evaluate the efficacy and safety of cetirizine as a first-line drug used for the treatment of chronic urticaria. As a secondary consideration, the study was also designed to identify the optimal methods of switching from this drug to other drugs in patients dissatisfied with its effectiveness as first-choice therapy as well as those obliged to discontinue treatment because of adverse reactions.

SUBJECTS AND METHODS

Subjects

Subjects were chronic urticaria patients aged ≥16 years who visited our department or any of the facilities affiliated with our department between January 2003 and October 2004. We excluded patients who had received oral or injected steroids within 1 week before the start of the study, were diagnosed with complications such as severe hepatic, renal, and cardiac disease, women who were pregnant, possibly pregnant, or nursing, those engaged in hazardous occupations such as automobile drivers, or were otherwise judged by their attending physician to be inappropriate subjects for the study.

Treatment

Cetirizine 10 mg (Zyrtec®, UCB Japan, Tokyo) was orally administered to each patient once daily at bedtime for 2 weeks (phase I). Based on the likelihood that at 2 weeks some patients might express dissatisfaction with the efficacy of cetirizine therapy or complain of experiencing drowsiness or other side effects, the study protocol allowed such patients to increase the dose or switch their therapy to one as considered appropriate by their physician (see next section, "Evaluation"). Therefore at the end of phase I, patients who were satisfied with the efficacy of cetirizine continued their treatment unchanged for a further 2 weeks (phase II), whereas those who were dissatisfied because of inadequate efficacy either increased the dose of cetirizine or

combined it with other drugs as add-on therapy, while those dissatisfied because of drowsiness could be switched to other antihistamine drugs at the discretion of their attending physician.

Although all existing antihistamine drugs were discontinued 1 week before the start of the study, topical steroid preparations, nonsteroidal antiinflammatory drugs, glycyrrhizin preparations, sedatives, and herbal preparations were allowed as concomitant medications.

Evaluation

At the start of the study and on each day of evaluation during treatment, physicians rated the severity of each patient's wheals on a five-grade scale according to the extent of visibility on the body as follows: level 0, absent—not visible; level 1, minimal—observable about once/week; level 2, mild—observable on about half of days; level 3, moderate—observable every day; level 4, severe—observable throughout the day.

The severity of scratches was similarly rated on a four-grade scale as follows: level 0, absent—no scratches visible; level 1, mild—visible at 1–2 sites; level 2, moderate—visible on part of the body; level 3, severe—visible on whole body.

The severity of itching and drowsiness as evaluated in the range 0–100 by a visual analogue scale (VAS) in the morning and at bedtime daily was recorded in patient diaries. Mean scores were calculated for each week and compared with a baseline (i.e., score on first day of treatment).

Safety evaluations were conducted by interviewing patients and assessing their symptoms throughout the treatment period. All adverse events appearing during the treatment period were recorded and investigated, as was any exacerbation of symptoms already noted at the start of the study.

Statistical analysis

The severity of wheals and scratches as evaluated by a physician and of itching and drowsiness self-reported by patients were compared at 2 and 4 weeks versus baseline values by the Wilcoxon signed rank test. $P < 0.05$ was regarded as statistically significant.

RESULTS

Patients

Seventy-four patients (M/F, 30/41; gender of 3 not recorded) were enrolled, all of whom completed the study. Mean (\pm SD) age was 51 ± 18 (range, 19 to 83) years. Median duration of symptoms was 3 ± 7 years (range, 1 month to 40 years). No statistically significant difference was identified among patients who completed 4 weeks of cetirizine therapy and those in whom the dose was increased or in whom cetirizine was switched to other treatments in terms of age, sex, length of disease, disease cause, and history of desensitization therapy and of allergy.

Patient satisfaction

Fig. 1 shows the results of patient satisfaction. After 2 weeks of cetirizine therapy, 55 of 74 patients (74.3%) were satisfied with treatment. Five (6.7%) were dissatisfied because of drowsiness, and 14 (18.9%) reported disappointing efficacy. In the 5 patients complaining of drowsiness, cetirizine was replaced with epinastine HCl with good results in 3, and to fexofenadine with poor results in the remaining 2. Among the 14 patients dissatisfied with the lack of efficacy, 6 of 9 whose cetirizine dose was increased to 20 mg or who received additional drugs as a combination therapy and 3 of 5 whose therapy was switched to other drugs reported satisfaction

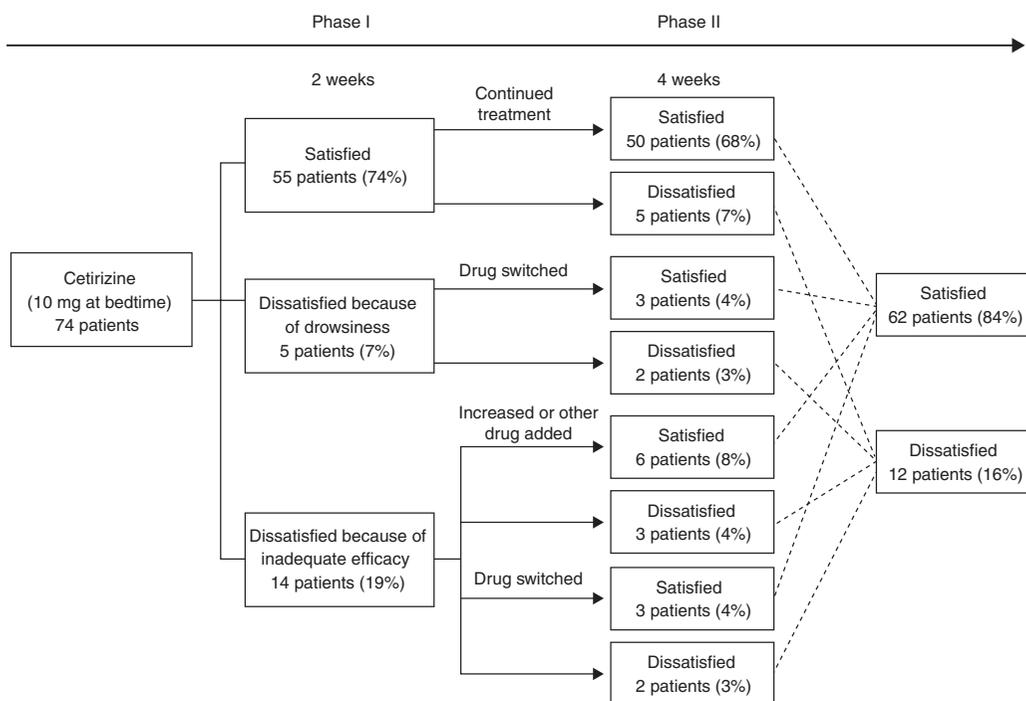


Fig. 1 Degree of patient satisfaction during phases I and II of the study.

within 4 weeks.

Fifty of the 55 patients who were satisfied after 2 weeks of treatment with cetirizine also reported satisfaction at 4 weeks. Thus the percentage of patients satisfied after 4 weeks of treatment among the entire study population was 83.7% (62/74).

Severity of wheals and scratches as evaluated by physicians

Figs. 2 and 3 show the progressive results of the severity of wheals and scratches at the start of treatment, after 2 weeks, and after 4 weeks in patients who remained on cetirizine therapy throughout the study period. In those patients, wheals were significantly ($p < 0.001$) alleviated from a mean (\pm SD) of 2.6 ± 0.7 at baseline to 0.6 ± 0.7 at 2 weeks and 0.4 ± 0.6 after 4 weeks of treatment. Furthermore, in this group, a significant ($p < 0.01$) alleviation of wheals was seen after 4 weeks versus only 2 weeks of treatment (Fig. 2). In those same patients, the severity of scratches also significantly ($p < 0.001$) decreased from 1.1 ± 0.6 at baseline to 0.1 ± 0.2 at 2 weeks and 0.2 ± 0.4 at 4 weeks (Fig. 3). Furthermore, whereas at baseline 32 of 54 patients (59%) were evaluated as having moderate-to-severe wheals, only 1 exhibited wheals of this severity at 2 weeks, and none of the patients had moderate-to-severe wheals at 4 weeks (2 weeks: no wheals, 50%; minimal, 37%; mild, 11%; moderate, 2%; 4 weeks: no wheals, 65%; slight, 28%; mild, 7%). Similarly for scratching, whereas at baseline all except 7 of the 54 patients were assessed as having mild (65%), moderate (20%), or severe (2%) symptoms, scratching was assessed as either none (91%) or mild (9%) in all patients at 2 weeks, and as none (85%), mild (13%), or moderate (2%) in all patients at 4 weeks.

In the 5 patients who were switched to other drugs because of drowsiness, wheals were

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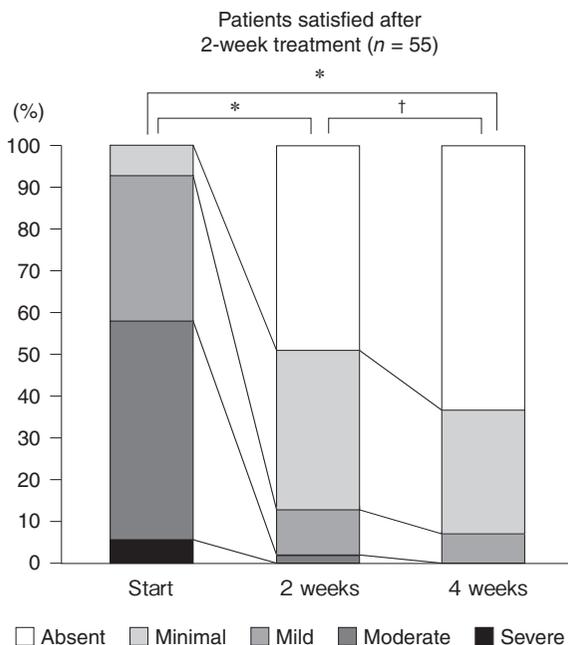


Fig. 2 Wheals in patients satisfied after 2-week treatment with cetirizine 10 mg once daily ($n = 55$) and who remained on treatment for 4 weeks. The percentage of patients with wheals as rated on a five-point scale of severity is shown. $*P < 0.001$; $†P < 0.01$ (Wilcoxon signed rank test).

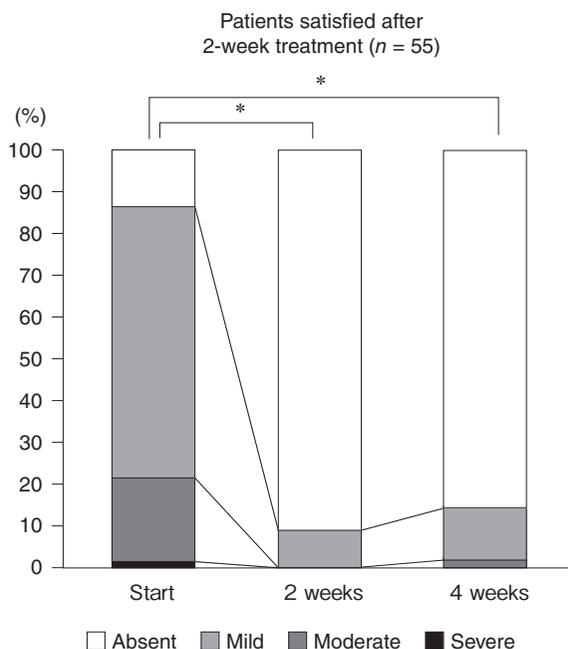


Fig. 3 Scratching in patients satisfied after 2-week treatment with cetirizine 10 mg once daily ($n = 55$) and who remained on treatment for 4 weeks. The percentage of patients with scratching as rated on a five-point scale of severity is shown. $*P < 0.001$ (Wilcoxon signed rank test).

somewhat alleviated at 2 weeks of initial therapy—2 of the 5 whose wheals were assessed as moderate at baseline both exhibited mild symptoms at 2 weeks and 1 went on to achieve only a minimal decrease in wheals at 4 weeks. A similar trend was noted with scratching scores after 2 weeks of initial therapy and 2 weeks of successive therapy, with 2 of the 5 exhibiting mild scratching at baseline, while none complained of scratching thereafter.

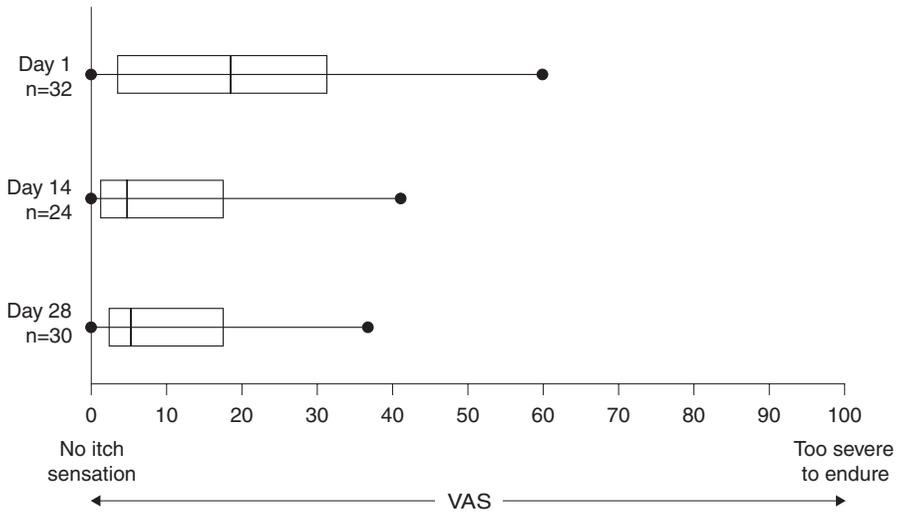


Fig. 4 Box-and whisker plots showing itching as evaluated by patients using a visual analog scale (VAS) among those satisfied after a 2-week treatment with cetirizine 10 mg once daily ($n = 22$) and who remained on treatment for 4 weeks. $*P < 0.05$ (Wilcoxon signed rank test).

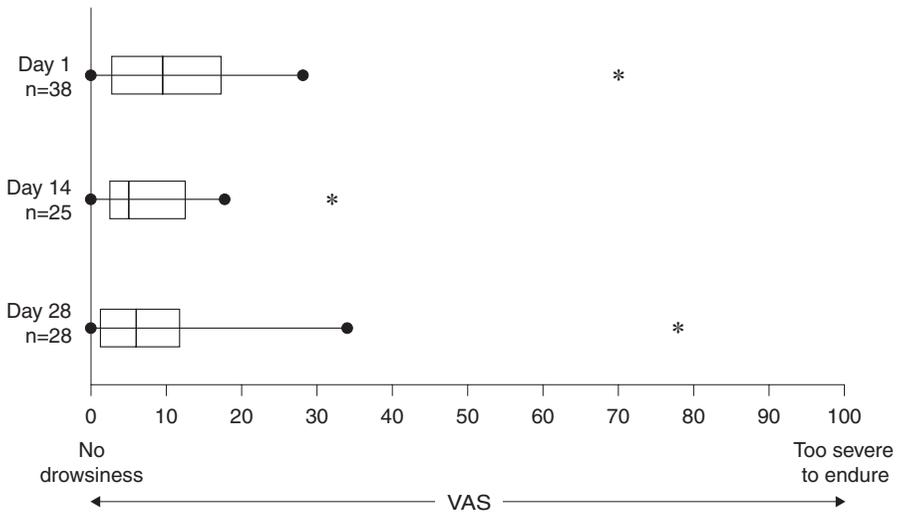


Fig. 5 Box-and-whisker plots showing drowsiness as evaluated by patients using a visual analog scale (VAS) among those satisfied after a 2-week treatment with cetirizine 10 mg once daily ($n = 18$) and who remained on treatment for 4 weeks.

In patients who were switched to other therapies because of inadequate efficacy after 2 weeks of cetirizine, wheals were significantly alleviated from a mean (\pm SD) of 2.79 ± 0.70 at baseline to 2.07 ± 0.62 at 2 weeks, and 1.23 ± 1.01 at 4 weeks ($p < 0.01$ and < 0.001 , respectively). Furthermore, wheals were more significantly ($p < 0.01$) alleviated at 4 than at 2 weeks. In this group, the severity of scratching was significantly ($p < 0.05$) alleviated from 1.29 ± 0.61 at baseline to 0.62 ± 0.77 at 4 weeks.

Itching and drowsiness as evaluated by patients

Among patients who continued taking cetirizine for 4 weeks, the median score of itching versus baseline was significantly ($p < 0.05$) reduced after 2 weeks of treatment, and remained almost at that reduced level for 4 weeks (Fig. 4). In patients switched to other treatments because of inadequate efficacy at 2 weeks, itching scores decreased over time and were significantly ($p < 0.05$) lower than baseline value at 4 weeks. In patients who were switched because of drowsiness, the itching score decreased during the first 2 weeks of treatment then rose only slightly at 4 weeks.

The time-course of drowsiness in patients taking cetirizine for 4 weeks is shown in Fig. 5. Their median VAS score of drowsiness remained almost unchanged at about 10 during the treatment period (range at baseline range, 0–70; 2 weeks, 0–32; 4 weeks, 0–78). In those switched because of drowsiness at 2 weeks, their VAS scores subsequently declined after switching from approximately 54 (range, 45–64) at 2 weeks to approximately 20 (range, 5–44) at the end of the study, though this change was not significant. In patients switched at 2 weeks because of inadequate efficacy, the VAS score for drowsiness was not significantly changed at 4 weeks (2 weeks, mean [range, 0–76] 18; n=11; 4 weeks, mean [range, 5–85] 26; n=6).

Adverse reactions

Other than drowsiness reported by 5 patients, malaise and headache in 1 patient and systemic erythema and hand swelling in a second were noted as adverse reactions to taking cetirizine. Once the first patient was switched to loxoprofen, the side effects disappeared; the second patient dropped out of the study and was lost to follow-up.

DISCUSSION

The second-generation of antihistamines has been amply demonstrated as at least as effective as older antihistamine drugs such as chlorpheniramine and hydroxyzine while causing significantly less sedation.^{8–12} Cetirizine is a second-generation antihistamine drug that exerts potent antihistamine action while only infrequently causing adverse drug reactions such as drowsiness.⁷ Several reports have demonstrated the usefulness of this drug in the treatment of chronic urticaria.^{13–15} Usually, about three fourths of patients with urticaria respond to antihistamine therapy. However, treatment is difficult in patients who are not satisfied with the results after a 2–4-week course. We routinely encounter such patients who do not want to continue taking antihistamines because of their inadequate efficacy or the drowsiness they cause.

In this study we investigated the percentage of patients who reported satisfaction with cetirizine therapy at 2 and 4 weeks, and attempted to improve the level of satisfaction in those who were dissatisfied at 2 weeks by empirically modifying their treatment and reassessing the results at 4 weeks.

Our data imply that patients' acceptance rates of their initial treatment were relatively high, with 74.3% of those receiving cetirizine 10 mg reporting satisfaction at 2 weeks, and most

(67.5% overall) continued to be satisfied at 4 weeks. Evaluation by physicians revealed significant decreases of urticaria symptoms (wheals and scratching) in patients who received cetirizine throughout the entire 4-week study period. Since very few adverse events were reported, cetirizine therefore seems efficacious and well tolerated when given as the initial treatment for chronic urticaria. A multicenter double blind study of the clinical efficacy and safety of cetirizine versus ketotifen was conducted in Japanese subjects with perennial allergic rhinitis. Among 110 such subjects in the cetirizine arm, 2 reported mild drowsiness and another 2 moderate drowsiness (total incidence rate, 3.6%) versus 17 of 101 subjects (16.8%) in the ketotifen arm, including 5 cases of severe drowsiness.¹⁶⁾ In our study, 6.7% of patients reported drowsiness associated with taking cetirizine, a slightly higher but comparable percentage to that in the earlier report. Overall, therefore, cetirizine seems safe and unlikely to cause drowsiness, although patients should be adequately warned about this potential side effect.

VAS self-evaluations of itching severity by patients who expressed satisfaction with their initial treatment with cetirizine appear to reflect this perceived efficacy, with a lower rate of itching severity reported at 2 weeks and throughout phase II of treatment versus baseline.

A secondary aim of this study was to identify the optimal methods of switching patients to other treatments who express dissatisfaction with cetirizine at 2 weeks of initial therapy. That is, the protocol allowed those who were dissatisfied because of inadequate efficacy either to increase the dose of cetirizine or to combine cetirizine with other drugs, while those who were dissatisfied because of drowsiness could be switched to other antihistamine drugs at the discretion of their attending physician. Among our patients, 14 (18.9%) complained of inadequate efficacy; after altering their therapy (up-titrating, combining cetirizine with other agents, or switching the drug) 9 were satisfied. Among the 5 patients (6.7%) dissatisfied because of drowsiness, cetirizine was replaced by other antihistamines with mixed outcomes regarding satisfaction. In light of these results, it seems that, to improve efficacy, increasing the dose of cetirizine or combining it with other drugs may prove to be a reasonable strategy, whereas to avoid drowsiness, switching cetirizine to other antihistamines might not ameliorate this side effect. Although our study subjects were very few in numbers, we observed that patients who were switched to epinastine found relief from their drowsiness, whereas those who switched to fexofenadine remained dissatisfied. In the absence of comparative clinical data and with few available alternative treatments for patients with urticaria, the question of how best to switch patients who experience drowsiness on cetirizine to other medications remains.

In patients who switched to other treatments because of their disappointment with the efficacy of cetirizine at 2 weeks, itching scores decreased to significantly lower levels during phase II. However, a subanalysis of those patients revealed a nonsignificant trend towards higher VAS scores for itching than at the start of the study. According to UK diagnostic and management guidelines for urticaria and angioedema¹⁷⁾ as well as recently published Japanese urticaria guidelines,¹⁾ it may be better to consider administering antihistamine drugs at higher doses in patients with more severe symptoms. Because at 2 weeks in our study only 1 patient was switched to high-dose cetirizine (20 mg) our data are insufficient to either support or refute this recommendation.

In patients who switched the initial treatment because of drowsiness, VAS itching scores decreased slightly during phase I but appeared to gradually increase during phase II when they switched to alternative drugs (fexofenadine 60 mg bid or epinastine HCl 20 mg qd). Although such changes were not statistically significant, the trends in the data suggest that switching to alternative medications did not prove effective against itching.

This study has some limitations. First, since the study was uncontrolled, neither the investigators nor the patients were blinded to the treatment. Another limitation was the fairly small sample

size ($n = 74$). That having been said, the following conclusions may be drawn: 1) 55 of 74 patients (74.3%) were satisfied with cetirizine 10 mg as the initial treatment for chronic urticaria; 2) cetirizine appears safe as an initial treatment for chronic urticaria; and 3) after switching the initial therapy of patients dissatisfied at 2 weeks to other treatments tailored on an individual basis, the overall percentage of patients satisfied with treatment rose to 83.7% (62/74) at 4 weeks, suggesting that such individuals may be effectively and safely switched from cetirizine to other antihistamine drugs.

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