

# Comparison of Acrivastine, Loratadine and Cetirizine Monotherapies, and Co-Administration with Famotidine in the Treatment of Chronic Idiopathic Urticaria

## KRONİK İDYOPATİK ÜRTİKER TEDAVİSİNDE AKRİVASTİN, LORATADİN VE SETİRİZİN MONOTERAPİLERİ İLE FAMOTİDİN KOMBİNASYONLARININ KARŞILAŞTIRILMASI

Nilgün BİLEN\*, Rebiya APAYDIN\*, Dilek BAYRAMGÜRLER\*\*, Şeniz DÖKMECİ\*\*\*

\* Yrd.Doç.Dr., Kocaeli Üniversitesi Tıp Fakültesi Dermatoloji AD,

\*\* Uz.Dr., Kocaeli Üniversitesi Tıp Fakültesi Dermatoloji AD,

\*\*\* Arş.Gör.Dr., Kocaeli Üniversitesi Tıp Fakültesi Dermatoloji AD, İZMİT

### Summary

Some studies about chronic idiopathic urticaria show advantages in combining H1 and H2 receptor antagonists. In this randomized single-blind study, 59 patients with chronic idiopathic urticaria were allocated into 6 study groups and the first 3 groups received acrivastine (8 mg, t.i.d), loratadine (10 mg, once a day), cetirizine (10 mg, once a day) respectively. The other 3 groups received combination of the aforementioned antihistamines with famotidine (40 mg, once a day). The patients were evaluated for the severity of the signs and symptoms of urticaria at the 15th day of the therapy, and results were described as effective and ineffective. Comparison of the incidence in 6 groups were done by Fischer's exact Chi-square test and the differences between groups were not statistically significant. Any H1 receptor antagonist was not more effective than others.

We have found no evidence of additional benefit of co-administration of famotidine with acrivastine, cetirizine, and loratadine in the treatment of chronic idiopathic urticaria.

**Key Words:** Chronic urticaria, Famotidine, Acrivastine, Loratadine, Cetirizine

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**Yazışma Adresi:** Dr. Nilgün BİLEN  
Yahya Kaptan Konutları  
Fil Blok Daire: 18  
P.K. 41050, İzmit, TURKEY

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### Özet

Bazı çalışmalarda kronik idyopatik ürtiker tedavisinde H1 ve H2 reseptör antagonistleri kombinasyonunun yararlı olduğu gösterilmiştir. Bu randomize tek-kör çalışmada kronik idyopatik ürtikerli 59 hasta, 6 gruba ayrılarak; ilk 3 gruba sırasıyla akrivaslin (3X8 mg/gün), loratadin (10 mg/gün) ve setirizin (10 mg/gün) verilmiştir. Diğer 3 gruba ise adı geçen antihistaminiklerle, famotidin (40 mg/gün) kombine edilerek verilmiştir. Hastalar tedavinin 15. gününde kronik idyopatik ürtikere ait ve belirti ve semptomlar yönünden etkili ve etkisiz olarak değerlendirilmiştir. Fischer kesin ki-kare testi ile yapılan değerlendirmede bütün gruplar arasında istatistiksel bir farklılık saptanmadı. Herhangi bir H1 reseptör antagonistinin diğerlerine üstünlüğü yoktu. Kronik idyopatik ürtiker tedavisinde akrivastin, loratadin ve setirizinle kombine edilen famotidin ek bir yarar sağlamadığı sonucuna varıldı.

**Anahtar Kelimeler:** Kronik ürtiker, Famotidin, Acrivastin, Loratadin, Setirizin

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Urticaria is characterized by transient itchy wheals (1), mainly produced by histamine (2). Histamine binds to H1 and H2 receptors on cutaneous blood vessels, causing vasodilatation and increased vascular permeability which are being manifest as erythema and edema, respectively (2). Recurrent episodes of urticaria of more than 6

weeks' duration are considered to be chronic (3,4). Most chronic urticarias are idiopathic (1). The mainstay of treatment for chronic idiopathic urticaria (CIU) continues to be H1 receptor antagonists and the combination of H1 and H2 receptor antagonists may produce additional benefits in some patients (5).

The aim of this study was to compare the clinical efficacies of acrivastine, loratadine, and cetirizine monotherapies which are considered as new non-scdating H1 receptor antagonists and co-administration of these antihistamines with famotidine in the treatment of CIU.

### Patients and Methods

A total of 72 adult patients with CIU were selected for the study. In this randomized single-blind study, the therapeutical effects of acrivastine, cetirizine, loratadine alone; acrivastine plus famotidine, loratadine plus famotidine, and cetirizine plus famotidine in the CIU were investigated in six groups. All our subjects had chronic urticaria lasting for more than 6 weeks. The previous treatments (antihistamines, immunosuppressants or steroids) were withdrawn one month before the study. The patients were investigated for the causes of chronic urticaria by history and laboratory tests. Physical urticarias and urticarial vasculitis excluded. Prior and after the treatment the following laboratory tests were carried out: complete blood cell count; full serum and urine chemistry panel.

Ethical approval was granted in this study and all patients gave informed consent to the procedures performed. After informed consent had been obtained, patients were randomly allocated into six study groups. The first group received acrivastine

orally (8 mg, t.i.d), the second group received cetirizine (10 mg, once daily), the third group received loratadine (10 mg, once daily), the fourth group received acrivastine (8 mg, t.i.d) plus famotidine (40 mg, once daily), the fifth group received cetirizine (10 mg, once daily) plus famotidine (40 mg, once daily) and the sixth group received loratadine (10 mg, once daily) plus famotidine (40 mg, once daily). The duration of the treatment was 15 days for each group.

Oral drugs used were acrivastine (Semprex, Pfizer), cetirizine (Zyrtec,UCB), loratadine (Claritine, Schering-Plough), and famotidine (Famodin, İlsan-İltaş).

We evaluated the patients for the severity of the signs and symptoms of urticaria on the 15<sup>th</sup> day of the therapy and noted as effective and ineffective. The efficacy was defined by asking the patients whether they had improved or cleared and by the absence of wheals throughout the treatment period.

Statistical analysis was performed using the Fischer's exact Chi-square test.

### Results

#### Patient population

Of the 72 patients enrolled, 59 (81,9%) patients (15 males and 44 females) completed the study. The range of age was 15 to 60 years (mean 35.0). A total of 12 patients were lost to follow up and one female patient gave up the study due to a serious headache. There were no significant differences among treatment groups in the study population with regards to age, sex, and duration of the disease. Characteristics of 59 patients who completed the study are listed in Table 1.

**Table 1.** General characteristics of 59 patients

Group	(n)	Age (years)	Sex (M/F)	Duration of disease (months)
Acrivastine (A)	10	Mean 32,7 (range 21-56)	4/6	Mean 3,5 (range 1,5-5)
Cetirizine (C)	10	Mean 35,4 (range 15-60)	2/8	Mean 3,2 (range 2-4)
Loratadine (L)	11	Mean 38,6 (range 30-50)	2/9	Mean 3,8 (range 2-4,5)
(A)+Famotidine	8	Mean 34,6 (range 21-51)	1/7	Mean 3,6 (range 2-4)
(C)+Famotidine	12	Mean 33,4 (range 20-49)	4/8	Mean 3,5 (range 1,5-4)
(L)+Famotidine	8	Mean 35,7 (range 33-48)	2/6	Mean 3,8 (range 2-4,5)
Total	59	Mean 35 (range 15-60)	15/44	Mean 3,5 (range 1,5-5)

**Table 2.** The therapeutical results of acrivastine, cetirizine, loratadine, acrivastine plus famotidine, loratadine plus famotidine, and cetirizine plus famotidine in the CIU on the 15<sup>th</sup> day of the therapy

Group	Effective	(%)	Ineffective	(%)	Total	(%)
Acrivastine (A)	8	(80)	2	(20)	10	(100)
Cetirizine (C)	10	(100)	-	-	10	(100)
Loratadine (L)	9	(81,8)	2	(18,2)	11	(100)
(A)+Famotidine	7	(87,5)	1	(12,5)	8	(100)
(C)-i Famotidine	10	(83,3)	2	(16,7)	12	(100)
(L)+Famotidine	8	(100)	-	-	8	(100)
Total	52		7		59	

### Evaluation of therapeutical efficacies

Fifty nine patients were evaluated for existence of the signs and symptoms of urticaria on the 15<sup>th</sup> day of the therapy.

Table 2 summarizes the therapeutical efficacies in six groups. Comparisons of the incidence in six groups were done by Fischer's exact Chi-square test and the differences were not statistically significant. The level of the significance was set up at  $p < 0,05$  level.

Comparison of the incidence of therapeutical efficacies in the groups of antihistamines alone was done by Fischer's exact Chi-square test and the differences were not statistically significant.

Comparisons of the incidence of therapeutical efficacies in the groups of antihistamines plus famotidine were done by Fischer's exact Chi-square test and the differences were not statistically significant.

### Side-effects

No patient experienced any local or systemic side effect except one female patient who was on acrivastine treatment reported a serious headache. For this reason, she gave up the study. All the laboratory parameters monitored at the beginning of the study were remained normal throughout the study.

### Discussion

If a specific cause can not be determined by history or laboratory investigation, the primary therapy includes an H1 antihistaminic agent in the treatment of CIU. Addition of H2 receptor antagonists has sometimes been referred as beneficial (5).

H2 receptor antagonists, such as cimetidine, ranitidine, and famotidine have specific actions relevant to the treatment of allergic and immunologic disorders and may be involved in feedback control of histamine release (6). There is a speculation as to how H2 antagonists work, possibly through H2 receptors on local vasculature, suppression of T-suppressor cells, or effects on the peripheral and central nervous system (7).

It has been reported that the combination of H1 and H2 receptor antagonists may produce an additional benefit. Bleehen et al (5). found that the addition of cimetidine to chlorphenamine significantly was better than chlorphenamine alone in 40 patients with CIU. Hydroxyzine given with cimetidine was found to be more effective than hydroxyzine alone (even though the difference was not statistically significant) (6) or cimetidine alone (8). Co-administration of hydroxyzine with cimetidine significantly increased serum hydroxyzine concentrations (6) which might account for its apparent benefit (9). When cetirizine was administered with cimetidine, no enhancement of wheal and flare suppression was observed (6).

For treatment of acute urticaria, the combination of cimetidine and diphenhydramine is more effective than diphenhydramine alone (10). Yuki et al (11) reported that cimetidine (3-300 mg/kg, p.o) dose dependency potentiated the inhibitory effects of chlorpheniramine in guinea pigs. Famotidine and ranitidine did not alter the response to chlorpheniramine in a forementioned study.

In a study of 45 patients with CIU, ranitidine 300 mg/day further reduced itching and whealing when combined with terfenadine while ranitidine

monotherapy was ineffective (12). In symptomatic dermatographism, the combination of H1 and H2 receptor antagonists showed some promise in small studies (13) and a single patient with cold contact urticaria was reported to have shown a dramatic response to H1 and H2 receptor antagonists combined (14).

There is a sparse evidence that H2 receptor antagonists alone are beneficial in urticaria. Furthermore, a case of solar urticaria has been reported to respond to cimetidine alone (15).

Vidovich et al (16) reported an abatement of urticaria and normalization of vital signs soon after intravenous famotidine given in a patient with urokinase-related anaphylactoid reaction. On the other hand, Pontasch et al (17) suggested that patients receiving diphenhydramine were more satisfied with their treatment than those of receiving famotidine or cromolyn sodium in the treatment of urticaria.

However, the additional effect of H2 receptor antagonists was not thought to be clinically worthwhile in dermatographic urticaria (18). Moreover, famotidine-induced symptomatic dermatographism was reported (19).

Evaluation of therapeutic results was carried out in our study and we found no evidence of additional benefit of co-administration of famotidine (40 mg, p.o) with acrivastine, cetirizine, and loratadine in the treatment of CIU. It must be taken into consideration that urticaria is a self-limiting disease and there was no placebo control in our study to assess the effects of the drugs on the psyche of these patients.

To best of our knowledge, we did not encounter a similar study in the literature with the concomitant administration of acrivastine, loratadine, and cetirizine which are new non-sedating H1 antagonists with famotidine in the treatment of CIU. We observed that co-administration of famotidine with acrivastine, loratadine, and cetirizine has no any additional benefit in the treatment of CIU on the 15th day of the therapy.

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