Rupatadine fast onset of action.
Pruritus and number of wheals relieve in patients suffering from Chronic Urticaria, a pooled analysis

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Background

Rupatadine is a once-daily, nonsedating, selective and long-acting histamine H1-receptor inverse agonist (H1 antihistamine). Rupatadine has been shown to have higher affinity for the H1-receptor than fexofenadine and levocetirizine.[1] Although some antihistamines have shown PAF antagonist properties, [2] these effects cannot be attributed to specific interactions with PAF receptors. Rupatadine has shown both antihistamine and anti-PAF effects through its interaction with specific receptors and not due to physiological antagonism.[3] (Fig.1)

Rupatadine is currently approved in 22 European contries as a once daily dose of 10 mg for the treatment of chronic idiopathic urticaria (CIU) [4, 5] and allergic rhinitis [3]. Rupatadine has a fast onset of action, and its long-lasting effect (> 24 h) permits once-daily dose.

Chronic urticaria is defined by spontaneous wheals long-lasting more than six weeks.[6] If any apparent etiology was considered, chronic urticaria is categorized as idiopathic (CIU). Non-sedating H_1 antihistamines have been recommended by the EAACI / GA^2LEN / EDF guideline as first line of treatment.[7]

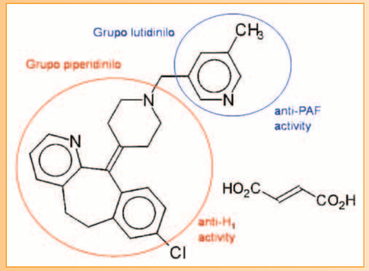


Fig.1 Rupatadine fumarate chemical structure

Aims

To assess at which time point rupatadine 10 and 20 mg effectively relieves the pruritus and the number of wheals following the first dose when we treated moderate to severe Chronic Idiopathic Urticaria.

Material and methods

The pooled data from two randomised, double blind and placebo controlled multicenter studies were used for this analysis. The first was a dose-ranging study comparing the efficacy and safety of placebo or rupatadine 5 mg, 10 mg and 20 mg once daily in 248 CIU patients [4]. The second study compared the efficacy of placebo or rupatadine 10 mg and 20 mg once daily in 334 CIU patients [5]. Efficacy and safety profile was evaluated over 6 weeks of treatment.

The randomized patients in both studies suffered from moderate to severe CIU. Active CIU (score ≥ 2 labelled as moderate pruritus) for at least 3 days (not necessarily consecutive days) in the week before inclusion with a total score of active CIU ≥ 6 labelled as moderate pruritus for these 3 days. Documented history of active CIU (urticaria wheals) with or without an associated angioedema for at least three days per week over the last 6 weeks prior to Screening Visit. (Fig.2) Efficacy was evaluated using as primary outcome measure Mean Pruritus Score (MPS) and as secondary outcome measure: Mean Number of Wheals (MNW), Mean Number of Total symptoms (MTSS), DLQI [8], VAS and the overall investigator assessment.

At the Screening visit, patients were instructed by the investigator to self-evaluate their scores in the daily diary twice each day, first at the morning (AM evaluation) and approximately 12 hours later, during the evening (PM evaluation). Patient had to record the symptoms severity retrospectively (over the previous 12 hours). Patients who did not collaborate, did not attend to scheduled visits or did not keep the diaries were withdrawal from the study. (Fig.3)

The first symptom assessment following the first drug intake was twelve hours after (first PM score) and the second one was 24 hours after (first AM score), before the second drug administration. The first seven days AM and PM score from MPS, MNW and MTSS were also analyzed.

Efficacy analysis was performed on the Intent-to-Treat (ITT) population. The analyses employed a mixed-effect model 3,4 by means of individual data from main efficacy variable and similar numbers of patients. The model for the main efficacy variable analysed the effects for study, treatment and study-by-treatment interactions, with study and study-by-treatment being random and treatment fixed. Furthermore, we studied the effects of covariates. Model extracted effects for study, treatment, sex, age, sex-by-treatment, and age-by treatment interactions, study and study-by-treatment being random, and the other effects fixed. The chi-square test was performed on the responders' patient rates.

Fig.2 Primary and secondary efficacy measures. Pruritus and number of wheals score

- **Pruritus score:**
  0= None
  1= Mild, not annoying or troublesome
  2= Moderate, annoying or troublesome
  3= Severe, very annoying, substantially interfering with sleep and daily activities
  4= Very severe, warranting physician visit
- **Number of wheals:**
  0= no wheals
  1= 1 - 5 wheals
  2= 6 - 15 wheals
  3= 16 - 25 wheals
  4= > 25.

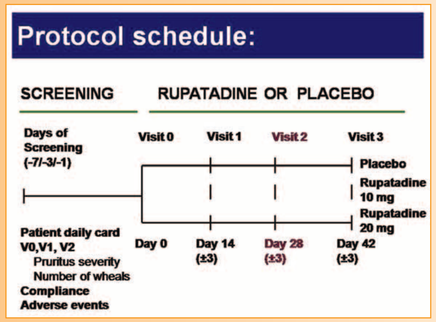


Fig.3 Protocol schedule

Discussion

It is important to emphasize that the pruritus severity and the number of wheals was reported by the patients two times per day during all the treatment. In the absence of specific measures for pruritus severity, the assessment of this symptom in the present study was reliant on a subjective evaluation. This fact is common with other similar studies that use pruritus as an outcome of treatment efficacy. The symptoms were evaluated from patient´s perspective in a valuable subjective way reproducing the exact patient feeling. Patient compliance was good.

Significant decreases in the primary outcome measure, and indeed the secondary outcome measures assessing symptoms were shown with rupatadine early, just 12 and 24 hours after the first dose. This improvement was maintained at seven day and over a period of 6 weeks.

Results

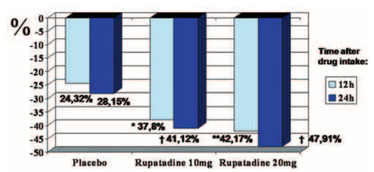
Demographic data is shown in Table 1.

Considering the percentage of MPS, MNW and MTSS reduction at 12 and 24 hours, 10 and 20 mg of rupatadine showed an effective relieve of CIU symptoms after the first dose of treatment. Significant differences between the placebo group and both groups treated with 10 and 20 mg of rupatadine were observed at 12 and 24 hours for MPS, MNW and MTSS. (Figs. 4, 5, 6) This clinical improvement was maintained during the first week until the end of the study (6 weeks).

Table I. Pooled CIU Demographic data (ITT population)

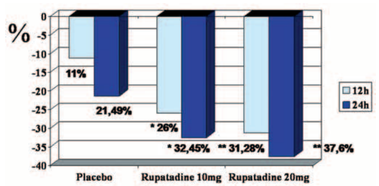
		Treatment				All
		Placebo	Rupatadine 5 mg	Rupatadine 10 mg	Rupatadine 20 mg	
Gender						
Male	N	58	19	52	54	183
	%	31.87	27.14	27.96	30.17	29.66
Female	N	124	51	134	125	434
	%	68.13	72.86	72.04	69.83	70.34
Age (years)		36.31	39.1	40.1	37.8	38
All	N	182	70	186	179	617

Fig 4. Mean Pruritus Score reduction after 12h (first PM score) and 24h (first AM score) of treatment



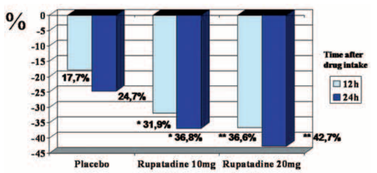
*p< 0,01 pruritus score reduction from baseline after 12 h with 10 mg ruptadine
**p< 0,001 pruritus score reduction from baseline after 12 h with 20 mg ruptadine
†p < 0,01 and p<0.001 respectively after 24 h with 10 and 20 mg versus placebo

Fig 5. Mean Number of Wheals, reduction after 12h (first PM score) and 24h (first AM score) of treatment



*p< 0,01 **p< 0,001
Wheal reduction from baseline after 12 / 24 h with 10 and 20 mg rupatadine treatment

Fig 6. Mean Total Score Symptoms MPS + MNW reduction after 12h (first PM score) and 24h (first AM score) of treatment



*p< 0,05 ** p< 0,001
Pruritus and Wheal reduction from baseline after 12/24 h with 10 and 20 mg rupatadine treatment

Conclusion

This analysis clearly demonstrate that rupatadine 10 and 20 mg are effective in providing fast and long-lasting relief from pruritus which is the most troublesome symptom of CIU, itch or pruritus. We demonstrate also a significant reduction in the number of wheals, the most important urticaria's sign.

Acknowlegements

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