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Rupatadine effective in the treatment of chronic spontaneous urticaria in children aged 2-11 years: a randomized, double blind, placebo and desloratadine controlled study.

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Abstract

Recommendations in current guidelines for the treatment of Chronic Spontaneous Urticaria (CSU) in infants and children is mostly based on extrapolation of data obtained in adults. This study report on the efficacy and safety of Rupatadine, an oral H1 and PAF antagonist recently authorised in Europe for children with rhinitis in children with CSU.

Methods: A double-blind, randomized, parallel group, multicentre, placebo controlled compared with desloratadine was carried out in children aged 2 to 11 years with CSU, with or without angioedema. Patients received either rupatadine (1 mg/ml), or desloratadine (0.5 mg/ml) or placebo once daily over 6 weeks. A modified Urticaria Activity Score (UAS) was employed as the primary end point. **Results:** The absolute change of UAS7 at 42 days, showed statistical significant differences between active treatments vs placebo (-5.5 ± 7.5 placebo, -11.7 ± 8.7 rupatadine and -10.5 ± 9.6 desloratadine; $p < 0.001$). There was a 55.8% decrease for rupatadine followed by desloratadine (-48.4%) and placebo (-30.3%). Active treatments also showed a statistically better improvement in children's quality of life compared with placebo. Adverse events were uncommon and non-serious in both active groups.

Conclusion: This is the first study to use a modified UAS to assess severity and outcome in CSU in children. Rupatadine is effective in the relief of urticaria symptoms and quality of life over 6 weeks in children with chronic spontaneous urticaria.

Introduction

There are very few studies of efficacy of new antihistamines in the management of children with chronic spontaneous urticaria. Urticaria is characterized by the rapid appearance of wheals and pruritus and/or angioedema. Urticaria which occurs within the superficial dermis, is characterized by an oedema and dilatation of the postcapillary venules and lymphatic vessels. *Chronic spontaneous urticarial (CSU) is defined as the appearance of wheals on a recurrent basis, over 6 consecutive weeks and usually more than twice a week (1).* In the general population, the prevalence of CSU has been reported to occur in 0.1-3% of the population in Europe and the United States of America. It has been estimated that its worldwide prevalence is approximately 0.5% and does not vary significantly within different populations (2). According to a population-based study (3), the prevalence of CSU in Spain is about 0.6% of the general population. Approximately 25% of children will achieve remission within the first 3 years of presentation (4), but studies of the long term outcome for children with urticaria are lacking.

According to the most recent international EAACI/GA(2)LEN/EDF/WAO guideline (5), H1 antihistamines remain the first line of treatment (grade of recommendation=A) for CSU for both adults and children. Pharmacological treatment should be started with a standard dose, but higher than normal doses of antihistamines may be required to control severe urticaria/angioedema (grade of recommendation=B). Almost all symptoms of urticaria are mediated by H1-receptors and therefore H1-receptor antagonists are the mainstay of treatment. Second-generation antihistamines are regarded as the first-line treatment for urticaria. If this is insufficient, higher doses (up to a four-fold increase) are recommended.

Most of the therapeutic evidence with antihistamines has been obtained from studies performed in adults. This situation is unsatisfactory and does not comply with criteria for the optimal medical care (6). Furthermore for chronic spontaneous urticaria the clinical evidence for paediatric patients is weak and only a few efficacy studies (7-9) have been reported.

Rupatadine is a compound that shows both antihistamine and anti-PAF effects through its interaction with specific receptors, rather than physiological antagonism (10). A new oral solution of rupatadine (1mg/ml) has been recently authorised in Europe for children with allergic rhinitis between 2-11 years. The study objective was to evaluate the efficacy and safety of rupatadine in the treatment of children with chronic spontaneous urticaria (CSU) symptoms over a 6-week treatment period, compared to placebo and desloratadine.

Methods

Design

This was a 42-day double-blind, randomized, three arm, parallel group, multicentre, placebo and desloratadine controlled study to assess the efficacy and the safety of rupatadine oral solution in children aged 2 to 11 years with CSU. To be enrolled in the study, children weighing ≥ 10 kg had to have a documented history of CSU, with or without angioedema, of at least 6 weeks before the selection visit, according to the EAACI/GA2LEN/EDF guidelines Urticaria Activity Score (UAS) was defined as the sum of the scores (0-3) of the two symptoms assessed (pruritus and number of wheals) on a daily basis. Patients with a 7 days cumulative score ≥ 12 points in the adapted UAS7 before Visit 0. Were eligible A 12 lead ECG obtained was conducted at screening, QTc interval values (msec) after Fridericia's correction had to be normal (< 450 msec).

Children with dermatological conditions such as hereditary angio-oedema, isolated dermographism, physical urticaria, urticaria caused by the ingestion of any drug or food, or any infection, contact urticaria, urticaria caused by vasculitis and/or collagenosis were not eligible. Patients with any parasitic infestations able to cause urticaria (i.e. discarians, anisakiasis, strongyloidiasis, etc.) were not eligible. Children were not permitted to take systemic or topical medication for CSU for a wash-out period as follows: Oral/topical H1-receptor antagonists (7 days prior to inclusion)(except occasional use of cetirizine taken as rescue medication); H2-receptor antagonists (10 days prior to inclusion); H1- and H2- receptor antagonists: doxepin (7 days prior to inclusion); leukotriene antagonists (4 days prior to inclusion), anticholinergics (3 days); oral corticosteroids (28 days prior to inclusion); tricyclic antidepressants (30 days prior to inclusion) and/or any drug interacting with

or any potential inhibitor of CYP3A4 (cytochrome P450). Regular schedule at allergen immunotherapy was permitted throughout the study but was disallowed from 24h prior to 24h after first study dosing. Patients with ascertained of presumptive hypersensitivity to the active principle and/or formulation ingredients of the tested compounds e.g. lactose intolerance were not eligible for participation.

After informed consent was signed from the patient's parent or guardian at the initial screening visit, there was a screening period during which diary cards were completed, to assess the severity of the child's symptoms. If children did not reach the UAS7 adapted score necessary to be randomized from a minimum of 14 days to a maximum of 18 days, they were excluded.

The study consisted of a total of 5 visits: a screening (Screening Visit), a baseline (Visit 0), treatment day 21 (Visit 1), final visit after 42 days (Visit 2), and an additional non treatment safety follow-up Visit at week 12 (Visit 3). Daily assessments were made by the child or caregiver/guardian using a Patient Diary Card 'reflective' (24 h) based on a 4-grade scale ranging: (0)= symptom is absent; (1)= mild:(1-<10 wheals/24 h); (2)= moderate: (10-30 wheals/24 h) and (3)= intense: (>30 wheals/24 h or large confluent areas of wheals) for wheals and (0) = symptom is absent; (1) = mild: present but not annoying or troublesome; (2)= moderate: troublesome, but does not interfere with normal daily activity, or sleep (3)= intense: severe pruritus, which is sufficiently troublesome to interfere with normal activity or sleep) for pruritus. Children fulfilling all the inclusion and exclusion criteria as well as the symptom severity criteria [cumulative score ≥ 12 points adapted UAS7) (max. 42) over 7 complete days (consecutive or not)] were randomized at Visit 0 (day 0) to either rupatadine oral solution 1 mg/ml, desloratadine 0.5 mg/ml oral solution or matching placebo.

Baseline data were obtained and the patients were provided with the first bottle of the study medication and another diary card to assess CSU symptoms for the following 21 days. At Visit 1 (day 21). Patients were provided with a second bottle of study medication and a final diary card for the remaining study period, until visit 2(day 42). Drug compliance was checked throughout the study based on returned medication, which was weighed and measured, and diary card entries. A physical examination was performed at each visit throughout

the study and adverse events and/or concomitant medication was also recorded.

Rupatadine 1mg/ml oral solution was given at a dose of 2.5 ml in children with a body weight ≥ 10 Kg up to < 25 Kg and at a dose of 5 ml in children ≥ 25 Kg body weight. The same dosing was used for the active comparator desloratadine 0.5 mg/ml oral solution. Medication was properly blinded to ensure a double blind study and was dispensed in child-resistant packaging. The medication was provided in two bottles, each one containing 120 mL. A syringe of 5 mL with a 0.2 mL of pinpoint accuracy was also provided for the dosing according to body weight. The use of rescue medication was only allowed if the patients had a daily UAS score of 6 (maximum severity) and they took second generation antihistamines (only cetirizine) as rescue medication. The following day was not counted for the UAS7, due to carry-over effects of the antihistamine; and so seven valid individual days was calculated, counting backwards.

The primary efficacy end-point consisted of comparing the adapted UAS7 prior to Visit 0 (baseline) with the cumulative adapted UAS in the 7 days prior to Visit 2 (42 days end of treatment), according to the following formula: $\text{Change UAS7} = \text{UAS7 at baseline} - \text{UAS7 at Visit 2}$. This change was also calculated in terms of a percentage. Secondary outcome measurements were: Changes from baseline over the 42-day treatment period in the mean adapted number of wheals (MNW score) and the Changes from baseline over the 42-day treatment period in the mean pruritus score (MPS score), based on symptoms on the diary card assessed by child or patient's parents.

The children's Quality of Life (QoL) using the validated Children Dermatology Life Quality Index (CDLQI) for children aged ≥ 4 years old was also utilised. It is designed to be self-administered to children aged 4 to 14 years old, with or without their parents' assistance, so children aged 2 and 3 years old did not perform any quality of life assessment (11). The questionnaire was completed both at baseline and the end of treatment (Visit 2), the change in overall score from baseline to Visit 2 was evaluated. The following six domains were evaluated by the children in this QoL questionnaire: symptoms/feelings, daily activities, school/holiday

activities, personal relations, sleep and treatment. The final score at Visit 2 of these six domains was also compared among treatment groups.

Progression of the adapted UAS, and progression of each individual symptom score (wheals and pruritus) over the 42 day treatment period were also determined. This was evaluated week by week by adding the corresponding daily scores of the last 7 days, without taking into account the use of rescue medication. The time at which statistically significant differences versus placebo are seen for first time was also assessed (onset of action). Additional analyses of efficacy including primary and secondary outcomes was performed, based on age and two subgroups: very young children 2-5 years and children 6-11 years.

The safety assessment was based on adverse events reported by the patient, assessing mainly seriousness and causal relationship to the study drug. Laboratory blood tests and ECGs were scheduled at baseline and after treatment completion. Physical examination and vital signs were monitored at every study visit throughout the study.

Based on previous studies with rupatadine and taking into account the final primary endpoint, it was estimated that allowing for a 20% drop-out rate, a total of 192 patients needed to be randomized in order to demonstrate a difference of 5% in the mean adapted UAS, between the rupatadine and the placebo group, with 80% power at the 5% level of significance, assuming a common standard deviation of 0.9. The main efficacy analysis was the intention to treat modified (mITT), defined as: patients that taken at least one dose of the study medication and with a one complete UAS7. Descriptive statistics were used, with mean, standard deviation, minimum and maximum for quantitative variables, and frequencies for qualitative variables. UAS7, MNW and MPS efficacy parameters were assessed by ANCOVA, with baseline value as cofactor. For QoL and other assessments comparison an ANOVA was performed. Statistical analysis was carried out using SAS software version 9.2

This study was performed in strict compliance with the Declaration of Helsinki and its last revision (Seoul, October 2008). Additionally, the study was conducted in compliance with the International Conference on Harmonization (ICH) principles of Good Clinical Practice (GCP), and the applicable regulations of the country in which the study was conducted. The present study completes the clinical development program of rupatadine (Paediatric investigation plan number: EMEA-000582-PIP01-09-M01) for paediatric patients (2-11 years old).

Results

The study was planned in 30 centres (Germany (5), Romania (4), Hungary (8) and South Africa (13)). Finally, Germany and Romania was not considered ethically acceptable to include placebo-treatment in children and refused their participation.

A total of 257 patients were screened, of which 51 patients were not included in the study due to meet major Inclusion Criteria (UAS adapted scores ≤ 12). Two hundred six subjects were randomized (80.2%) from these in seven cases it was not possible to determine the primary endpoint and they were thus not included in the assessment of efficacy. The main demographic and baseline characteristics of the study population (mITT) are shown in Table 1. No differences among treatment groups were detected in terms of demographic data. The most frequent concomitant diseases were allergic rhinitis and asthma 26% and a 16% respectively in the screened patients. Baseline values for UAS7, MNW, MPS and CDLQI scores were similar for the three treatment groups,

Compliance, measured as the percentage of the number of days with treatment according to parents/guardian divided by the total number of days, showed a percentage of 99.07% in rupatadine group, 98.98% in placebo group and 98.11% in desloratadine treatment group.

Efficacy

The absolute change of UAS7 at 42 days, showed statistical significant differences in active treatments vs placebo (-5.5 ± 7.5 placebo, -11.7 ± 8.7 rupatadine and -10.5 ± 9.6 desloratadine; $p < 0.001$). No statistically

significant differences were found between active treatments. As percentage of change of UAS7 there was also a statistically significant difference between active treatments and placebo ($p=0.001$), the largest main change observed with rupatadine (-55.8%), followed by desloratadine (-48.4%) and placebo (-30.3%). (See figure 2A).

A sub-analysis of efficacy performed based on patients' age and weight (see figures 2B), represented the percentage change of efficacy variables in children of less than 6 years (with a body weight $\geq 10\text{Kg}$ up to $<25\text{Kg}$). There were no statistical significant differences in the efficacy variables investigated. However, rupatadine (-11.4 ± 9.2) and desloratadine (-10.5 ± 9.3) showed a trend to have a higher effect than placebo (-6 ± 8.5). In contrast, the analysis in the group of patients ≥ 6 years with body weight $\geq 25\text{Kg}$ (See figure 2C) showed statistically significant differences observed for both efficacy variables evaluated, absolute change UAS7 (-4.7 ± 5.1 placebo; -12.6 ± 7.7 rupatadine and -10.6 ± 10.3 ; $p=0.003$) and percentage of reduction UAS7, rupatadine (-63.6%) and desloratadine (-45.5%) being better than placebo (-27.2%) in decreasing urticaria symptoms ($p>0.001$).

Rupatadine and desloratadine were superior to placebo, both for absolute change MNW (-5.8 ± 5 , -5.1 ± 5.3 and -2.3 ± 4 respectively; $p<0.001$) and % Change MNW (-56.7%, -49.4% and -22.7% respectively, $p<0.001$). Rupatadine effect was superior to placebo, for the absolute change MPS (-5.9 ± 4.6 vs -3.25 ± 4.1 respectively; $p=0.001$) and percentage change MPS (-56.8% vs -33.4% respectively; $p=0.005$). However desloratadine, only showed statistical significant differences vs placebo in the absolute change MPS (-5.4 ± 5.1 ; $p=0.008$).

Adapted UAS7 scores presented statistically significant differences in the treatment group during the entire treatment period, from the first week until the end of the treatment (day 42), with rupatadine and desloratadine scores always lower than placebo. The progression of the UAS7 score is also shown in figure 3.

In order to know the responder population of children that respond to standard doses, we have also analysed the proportion of patients ('responders') that experimented a 50% decrease of the adapted UAS7 score at the end of the treatment for each treatment group. The percentage of responders achieving this 50%

improvement was 61% for rupatadine, 54% for desloratadine and 36 % for placebo group. When the cut off value of a good response was set at 75%, good responders were 40 % for rupatadine, 34% for desloratadine and 16 % for placebo group.

Quality of life

The overall domain of CDLQI was statistically better for rupatadine and desloratadine in comparison with placebo (-6.9 ± 5 , -6.2 ± 4 and -3.3 ± 6 ; respectively $p = 0.006$) and also percentage change (-58.6% , -64.5% and -26.7% ; respectively $p = 0.001$) (see figure 4). When absolute changes of the six domains comprised in the CDLQI questionnaire were individually analysed, statistical differences were only found in “school/holidays activities” and “daily activities” domains. Personal relationships sleep and treatment domains did not show statistically differences. However, a trend of superiority of active treatments over placebo was seen in all domains.

Safety

There were 128 adverse events reported in 40 patients (61%) in the rupatadine group, 126 adverse events reported in 37 patients (54%) in the placebo group and 147 in 46 patients (65%) in the desloratadine group. Only 10 Adverse Drug Reactions (ADRs) were considered to be related to the treatment administered. The number of ADRs at each of the treatment groups was 1 for rupatadine (1.5%), 5 for placebo (7.2%) and 4 for desloratadine (5.6%) (see table 2). Headache was the only ADR in rupatadine group. For placebo, one patient had four ADRs, which were decreased appetite, dizziness, headache and nausea. One patient in placebo group suffered constipation. In the desloratadine treatment group, there were four ADRs: blood alkaline phosphatase increase, lower abdominal pain, upper abdominal pain, and constipation, in four different patients.

Discussion

This study confirms that rupatadine, in CSU, is better than placebo in reducing the UAS7 score. To our knowledge, this trial is the first one to evaluate CSU in children between 2-12 years old in a placebo-controlled, comparative clinical trial using the adapted UAS7 of adults in children. This score, as in adults, is a patient-reported measure that captures the intensity of pruritus (0-3 range score) and the average number of wheals (0-3 range score). The score is based on the UAS7 for adults, only the numbers of wheals were reduced in each category to adapt to the body surface of children. The mean greatest change was obtained with rupatadine (-56%), followed by desloratadine (-48%) and placebo (-30%). In the same way, the secondary variables number of wheals (MNW) and pruritus (MPS) were found superior for both active treatments in comparison with placebo. The mean greatest change of MNW was obtained with rupatadine (-56.7%), followed by desloratadine (-49.4%), both significantly superior than placebo (-22.7%). Only rupatadine treatment (-56.8%) was statistically superior than placebo (-33.4%) for MPS, while desloratadine (-46.7%) did not reach a significant level in comparison with placebo. As expected, a marked placebo effect (around 30%) was also observed at 6 weeks. This finding is not unusual in paediatric trials with antiH1 compounds (12-14) in allergic rhinitis, but has not been previously reported in CSU in children.

Efficacy subanalyses showed that rupatadine is effective at the doses of 2.5 ml and 5.0 ml in children stratified by body weight (≥ 10 Kg up to < 25 Kg and ≥ 25 Kg, respectively). At the 2.5 ml dose, rupatadine and desloratadine produced significant improvement in the number of wheals (MNW variable), but in pruritus (MPS variables) these improvements were not statistically significant in comparison with placebo. With the dose of 5 ml, rupatadine and desloratadine results were more robust and provided clear statistically significant improvements of all efficacy variables (UAS7, MNW and MPS), in comparison to placebo. In our opinion, the number of wheals is a much more objective measure than pruritus, especially in children. The children treated with 2.5 ml are mainly aged 2-5 years old and therefore the assessment of efficacy is better performed by assessing the wheals by parents than the subjective pruritus reported by the child. This potential bias is more evident in children 2-5 years, and this may produce an under reporting of the UAS7 in the pruritus domain.

However, the differences versus placebo were constant and consistent in both the absolute and percentage changes in the UAS7 and MPS values in these subsets of children.

The majority of antiH1 second generation compounds are currently only licensed for the treatment of CSU in children of 2 years and older. Cetirizine has clinical evidence in children over 2 years (15) but administered twice daily. Additionally, the safety profile of cetirizine has also been evaluated in children as young as 1–2 years of age with atopic dermatitis in a placebo controlled trial lasting for 18 months and in a short-term in infants (6–12 months of age) (16,17). The same strategy was used for Loratadine and only the safety and pharmacokinetics were evaluated over 2 years (18). Levocetirizine, in atopic children aged 1-2 years, was evaluated for its safety in a well-designed placebo-controlled trial lasting 18 months and in a short-term trial in infants aged 6–12 months and children aged 1–5 years (19,20). Desloratadine can be given to children aged 1 year and older, but only safety data were obtained from placebo-controlled studies in children aged 2 years-11 years and 6 months to less 2 years (21, 22). Finally, no efficacy studies have been published for fexofenadine for urticaria in children below 12 years (23-25), and it is authorized in CSU for children over 6 years, where it should be administered before meals and where fruit juices may reduce its bioavailability (26).

Our responder analysis of children demonstrated that licenced doses, as first-line therapy for CSU, can provide acceptable control of symptoms in around of 60% of children, similar to what was reported in adults (27). Nevertheless, since more than 40% of CSU patients are refractory to licensed doses, additional pharmacological strategies are considered in children following the same criteria in adults, i.e. to increase second generation antihistamines dosing (5,28). There are, however, no formal studies that support this recommendation for children with CSU as of yet (29,30).

International guidelines recommend the use of additional tools to measure the impact of diseases on patient with CSU. The quality of life questionnaire applied in this study is the Children's Dermatology Life Quality Index (CDLQI), used in many clinical studies. This specific 10-question questionnaire is self-administered by

children aged 4 to 14 years old, with or without their parents' assistance, so children aged 2 and 3 years old did not perform any quality of life assessment. The differences were found in the change of overall CDLQI score among treatment groups in comparison with placebo, nevertheless this data are more representative of children older than 4 years. When absolute changes of the six domains comprised in the CDLQI questionnaire were individually analysed, statistical differences were only found in the domains "school/holidays activities" and "daily activities". However, a trend to superiority of active treatments over placebo was seen in all domains.

Finally, rupatadine appears to be safe and well tolerated in children aged 2-11 years, with an incidence of adverse events similar to that seen with placebo, and headache was reported as common adverse event. Second generation antiH1 are very well tolerated in children and the safety studies performed demonstrated a positive balance risk/benefits (31).

In conclusion, our findings confirm that the therapeutic response to rupatadine in children with is very similar to that reported in adults. This study provides first clinical evidence using UAS7 to assess both severity and outcome following current guidelines in CSU management in children with a second generation H1 antihistamine. Furthermore, rupatadine is effective in the relief of urticaria symptoms over 6 weeks reducing UAS7 adequately adapted in children, pruritus and the mean number of wheals to a numerically greater extent than desloratadine, and it also improves the QoL significantly compared with placebo.

Finally, further well designed therapeutic studies including newest efficacy outcomes, with long-term evaluation are required in order to obtain long term information on the natural history and clinical outcomes of children with CSU and their response to treatment.

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Disclosures:

Dr Potter, has been a speaker for J Uriach y Compañia, S.A.

Marcus Maurer, is or recently was a speaker and/or adviser for FAES, Almirall Hermal, Genentech, GSK, Merckle Recordati, Novartis, Sanofi Aventis, Shering-Plough, MSD, Merck, Moxie Takeda, UCB and Uriach.

Iñaki Izquierdo and Eva Santamaria are employees of J Uriach y Compañia, S.A.

Essack Mitha and Laszlo Barkai not referred conflict interest.

Iñaki Izquierdo and Eva Santamaria are employees of J Uriach y Compañia, S.A.

Study Investigators

The study was carried out in centres from South Africa and Hungary.

The Study Coordinators were Prof. Paul Potter (Allergy Diagnostic & Clinical Research, UCT Lung Institute, Cape Town) and Prof. Marcus Maurer (Department of Dermatology and Allergy, Charité Universitätsmedizin, Berlin). The principal investigators who participated in the study were: Prof. Paul Potter (UCT Lung Institute, Cape Town), Dr. N. Siddique (Durban Medical Centre, Durban), Dr. E. Mitha (Newtown Centre, Johannesburg), Dr. A. Puterman (Kingsbury Hospital, Claremont), Dr. L. Fouché, (Centre Corner of Van der Bijl and Koedoe, Limpopo Thabazimbi), Dr. M. Kriel (Clinton Netcare Hospital, Alberton), Dr. M. F. Sacoar (Brookdal clinical research Centre, Phoenix Durban Kwa Zulu Natal), Dr. M.A. Fulat (Sunnyside Medi-Clinic, Pretoria), Dr. S. Wadvalla (Lakeview Hospital, Benoni), Dr. G. Nieuwoudt (Parow Centre, Parow), Dr. E. Bierman (Uncedo Clinical Research, Port Elizabeth), Dr. L. Barkai (Diaped KTF, Miskolc), Dr. M. Farkas (Heim Pál Gyermekkorház, Budapest), Dr. G. Mezei (Gyermekegészségügyi Klinika, Budapest), Dr. Z. Novák (Gyermekeklinika és Gyermekegészségügyi Központ, Szeged), Dr. L. Kósa (Gyermekegészségügyi Központ Ktf, Budapest), Dr. B. Noémi (Bőrgyógyászati és Allergológiai Magánrendelés, Szolnok), Dr. S. Hajnalka (Mediroyal Prevencios Központ, Kecskemét), Dr. I Kiss, (Zala Megyei Kórház, Gyermekosztály)

References

1. Grattan CE. The urticaria spectrum: recognition of clinical patterns can help management. *Clin Exp Dermatol*. 2004; **29**(3):217-21.
2. Greaves MW. Chronic idiopathic urticaria. *Curr Opin Allergy Clin Immunol*. 2003; **3**(5):363-8.
3. Gaig P, Olona M, Muñoz Lejarazu D, Caballero MT, Domínguez FJ, Echechipia S, García Abujeta JL, Gonzalo MA, Leonart R, Martínez Cócera C, Rodríguez A, Ferrer M. Epidemiology of urticaria in Spain. *J Investig Allergol Clin Immunol*. 2004; **14**(3):214-20.
4. Du Toit G, Prescott R, Lawrence P, Johar A, Brown G, Weinberg EG, Motala C, Potter PC. Autoantibodies to the high-affinity IgE receptor in children with chronic urticaria. *Ann Allergy Asthma Immunol*. 2006; **96**(2):341-4.
5. Zuberbier T, Aberer W, Asero R, Bindslev-Jensen C, Brzoza Z, Canonica GW, Church MK, Ensina LF, Giménez-Arnau A, Godse K, Gonçalo M, Grattan C, Hebert J, Hide M, Kaplan A, Kapp A, Abdul Latiff AH, Mathelier-Fusade P, Metz M, Nast A, Saini SS, Sánchez-Borges M, Schmid-Grendelmeier P, Simons FE, Staubach P, Sussman G, Toubi E, Vena GA, Wedi B, Zhu XJ, Maurer M. The EAACI/GA(2)LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy*, 2014 Jul; **69**(7):868-87.
6. Custovic A, Simons FER. Drugs used in paediatric allergy: should we conduct studies in children or extrapolate from adults? *Clin Exp Allergy Rev*, 2006; **6**: 1-5.
7. Sánchez-Borges M, Asero R, Ansotegui IJ, Baiardini I, Bernstein JA, Canonica GW, Gower R, Kahn DA, Kaplan AP, Katelaris C, Maurer M, Park HS, Potter P, Saini S, Tassinari P, Tedeschi A, Ye YM, Zuberbier T; WAO Scientific and Clinical Issues Council. Diagnosis and treatment of urticaria and angioedema: a worldwide perspective. *World Allergy Organ J*, 2012; **5**(11):125-47.
8. de Benedictis FM, de Benedictis D, Canonica GW. New oral H1 antihistamines in children: facts and unmet needs. *Allergy* 2008; **63**(10):1395-404.
9. Belloni Fortina A, Fontana E Update on Antihistamine Treatment for Chronic Urticaria in Children. *Curr Treatment Options in Allergy* 2014; **1**:287–298.
10. Merlos M, Giral M, Balsa D, Ferrando R, Queralt M, Puigdemont A, Garcia Rafanell J, Forn J Rupatadine, a new potent, orally active dual antagonist of histamine and platelet activating factor (PAF). *J Pharmacol Exp Ther* 1997; **280** (1): 114-21.
11. Lewis-Jones, M.S. and A.Y. Finlay, The Children's Dermatology Life Quality Index (CDLQI): initial validation and practical use. *Br J Dermatol*, 1995; **132**(6): p. 942-9.
12. Potter P, Maspero JF, Vermeulen J, Barkai L, Németh I, Baillieu RA, Garde JM, Giral J, Doménech A, Izquierdo I, Nieto A. Rupatadine oral solution in children with persistent allergic rhinitis: A randomized, double-blind, placebo-controlled study. *Pediatr Allergy Immunol* 2013; **24**(3): 144-50.
13. de Blic J, Wahn U, Billard E, Alt R, Pujazon MC. Levocetirizine in children: evidenced efficacy and safety in a 6-week randomized seasonal allergic rhinitis trial. *Pediatr Allergy Immunol* 2005; **16**(3): 267-75.
14. Potter PC; Paediatric Levocetirizine Study Group. Efficacy and safety of levocetirizine on symptoms and health-related quality of life of children with perennial allergic rhinitis: a double-blind, placebo-controlled randomized clinical trial. *Ann Allergy Asthma Immunol* 2005; **95**(2): 175-80.
15. La Rosa M, Leonardi S, Marchese G, Corrias A, Barberio G, Oggiano N, Grimaldi I. Double-blind multicenter study on the efficacy and tolerability of cetirizine compared with oxatamide in chronic idiopathic urticaria in preschool children. *Ann Allergy Asthma Immunol* 2001; **87** (1): 48-53.
16. Simons FE. Prospective, long-term safety evaluation of the H1-receptor antagonist cetirizine in very young children with atopic dermatitis. ETAC Study Group. Early Treatment of the Atopic Child. *J Allergy Clin Immunol*, 1999; **104**:433-40.
17. Simons FER, Silas P, Portnoy JM, Catuogno J, Chapman D, Olufade AO. Safety of cetirizine in infants 6 to 11 months of age: a randomized, double blind, placebo-controlled study. *J Allergy Clin Immunol* 2003; **111**:1244–8.
18. Salmun LM, Herron JM, Banfield C, Padhi D, Lorber R, Affrime MB. The pharmacokinetics, electrocardiographic effects, and tolerability of loratadine syrup in children aged 2 to 5 years. *Clin Ther*. 2000; **22**(5):613-21.

- Accepted Article
19. Simons FER, on behalf of the Early Prevention of Asthma in Atopic children (EPAAC) Study Group. Safety of levocetirizine treatment in young atopic children: an 18-month study. *Pediatr Allergy Immunol*. 2007; **18**: 535–42.
 20. Hampel F, Ratner P, Haeusler JMC. Safety and tolerability of levocetirizine dihydrochloride in infants and children with allergic rhinitis or chronic urticaria. *Allergy Asthma Proc*. 2010; **31**:290–5.
 21. Bloom M, Staudinger H, Herron J. Safety of desloratadine syrup in children. *Curr Med Res Opin*. 2004; **20**: 1959–65.
 22. Lutsky B, Lorber R, Bloom M. Safety of desloratadine syrup in children 6 months to less than 24 months of age: a randomized, placebo controlled study. *Ann Allergy Asthma Immunol* 2004; **92** (No. 1): 102.
 23. Nelson HS, Reynolds R, Mason J. Fexofenadine HCl is safe and effective for treatment of chronic idiopathic urticaria. *Ann Allergy Asthma Immunol*. 2000; **84**(5):517-22.
 24. Finn AF Jr, Kaplan AP, Fretwell R, Qu R, Long J. A double-blind, placebo-controlled trial of fexofenadine HCl in the treatment of chronic idiopathic urticaria. *J Allergy Clin Immunol* 1999; **104**(5):1071-8.
 25. Kaplan AP, Spector SL, Meeves S, Liao Y, Varghese ST, Georges G. Once-daily fexofenadine treatment for chronic idiopathic urticaria: a multicenter, randomized, double-blind, placebo-controlled study. *Ann Allergy Asthma Immunol* 2005; **94**(6):662-9.
 26. Mansfield LE .Fexofenadine in pediatrics: oral tablet and suspension formulations. *Expert Opin Pharmacother* 2008; **9**(2):329-37.
 27. Sanchez-Borges M, Ansotegui I, Monterol Jimenez J, Rojo MI, Serrano C, Yañez A. *World Allergy Organization Journal* 2014; **7**: 33: 1-5
 28. Maurer M, Weller K, Bindslev-Jensen C, Gimenez-Arnau A, Bousquet PJ, Bousquet J et al. Unmet clinical needs in chronic spontaneous urticaria. A GALEN task force report, *Allergy* 2011; **66**(3): 317-30.
 29. Oranje AP. Management of urticaria and angioedema in children: new trends. *G Ital Dermatol Venereol*, 2010; **145**(6):771-4.
 30. Khan DA. Alternative agents in refractory chronic urticaria: evidence and considerations on their selection and use. *J Allergy Clin Immunol Pract* 2013; **1**(5):433-440.
 31. Church MK, Weller K, Stock P, Maurer M. Chronic spontaneous urticaria in children: itching for insight. *Pediatr Allergy Immunol* 2011; **22**(1 Pt 1):1-8.

Table 1 Demographic characteristics

Variable	Rupatadine N=66	Placebo N=69	Desloratadine N=71	Test (ANOVA)
Sex (male) ^A	29 (43.9%)	40 (58.0%)	39 (54.9%)	
Age (years) ^B	5.6 (2.8)	6.1 (2.6)	6.1 (2.5)	NS
2-4 years	34	26	25	
5-11 years	32	43	46	
Race ^A				
Caucasian	11 (16.7%)	14 (20.3%)	13 (18.3%)	NS
Black	17 (25.8%)	20 (29.0%)	21 (29.6%)	
Asian (oriental)	3 (4.5%)	2 (2.9%)	4 (5.6%)	
Multiracial	35 (53.0%)	33 (47.8%)	33 (46.5%)	
Height (m) ^B	1.12 (0.20)	1.14 (0.18)	1.15 (0.17)	NS
Weight (Kg) ^B	21.5 (9.3)	22.1 (7.4)	22.9 (8.9)	NS
BMI (Kg/m ²) ^B	16.7 (2.8)	16.6 (2.6)	16.7 (2.8)	NS

A) n (%); B) mean (s.d); NS: Not statistically significant differences.

Table 2

Related Adverse Events Reported in the Study

<i>ORGAN SYSTEM</i>	<i>SIDE EFFECTS</i>	Rupatadine N=66	Placebo N=69	Desloratadine N=71
Metabolism and Nutrition Disorders	Decreased Appetite	-	1	-
Nervous System Disorders	Dizziness	-	1	-
	Headache	1	1	-
Investigations	Blood Alkaline Phosphatase Increased	0	0	1
Gastrointestinal disorder	Abdominal Pain	0	0	1
	Abdominal Pain Upper	0	0	1
	Constipation	0	1	1
	Nausea	0	1	0
TOTAL		1	5	4

Legend

Figure 1. Patients disposition.

ITT= intention to treat(modified) , PP= per protocol.

Figure 2. Overall of percentage of change from baseline in the mean adapted cumulative urticaria activity score (UAS7) over the 6-week treatment in the mITT. 2A) efficacy analysis of UAS7 in the subgroup of children of less than 6 years (with a body weight $\geq 10\text{Kg}$ up to $<25\text{Kg}$) dosed 2.5 mL. 2B) efficacy analysis of UAS7 in the subgroup of children ≥ 6 years with body weight $\geq 25\text{Kg}$ dosed 5 mL.

PCB= placebo; RUP= Rupatadine and DESL=desloratadine.

Figure 3. Mean value of the weekly UAS7 over the 6-weeks treatment in the mITT.

Figure 4. Mean absolute change from baseline of Children's Dermatology Life Quality Index (CDLQI)score (total and individual domains score) after 6 weeks of treatment.

Significant levels : * $P < 0.05$ vs placebo ; ** $p < 0.001$ vs placebo

Figure 1

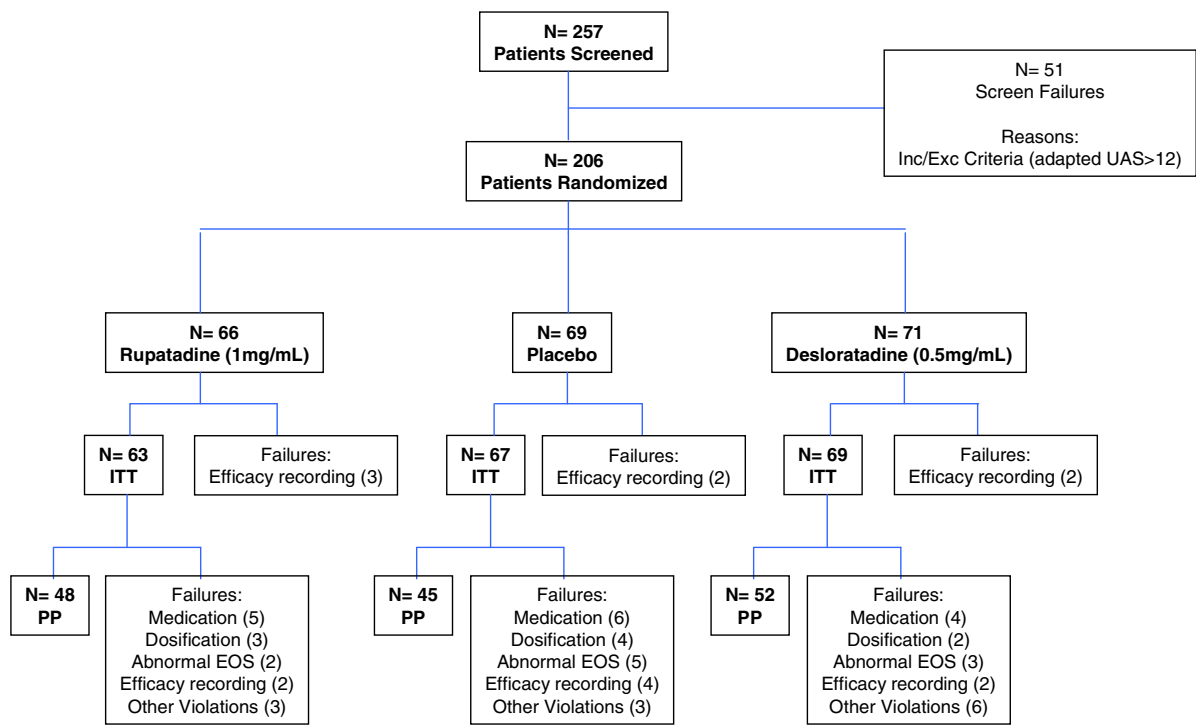


Figure 2 A

Overall efficacy UAS7: Change in Adapted UAS7 (day 1-42) by Treatment (mITT)

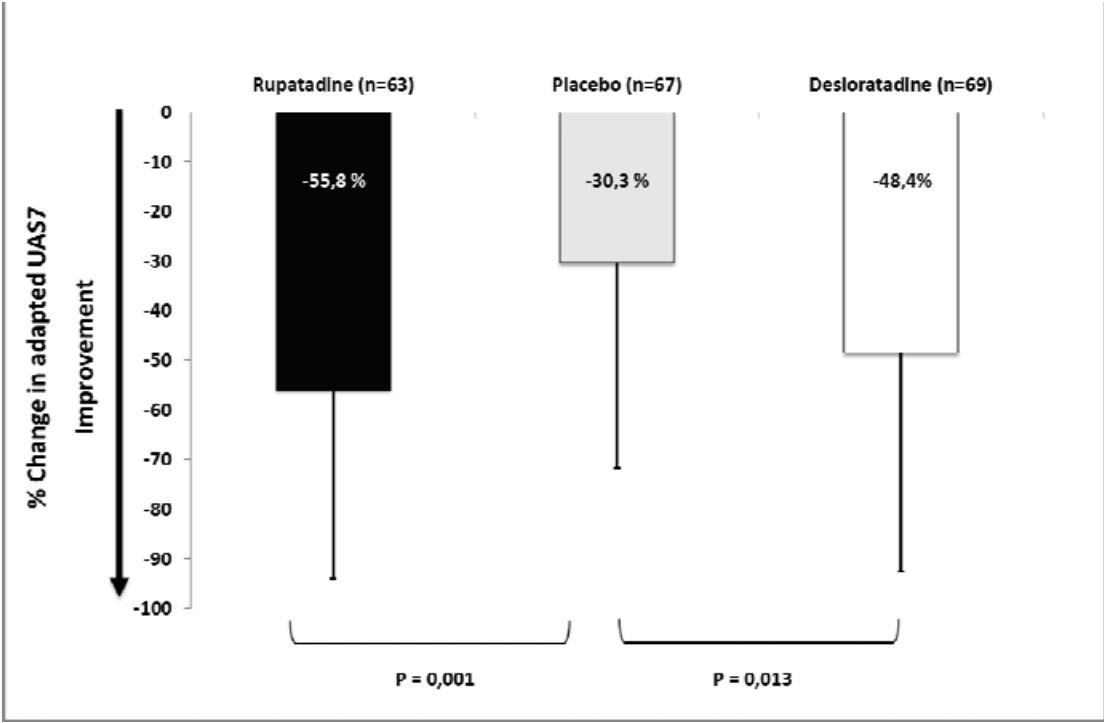


Figure 2b

Overall efficacy Mean Pruritus Score (MPS)

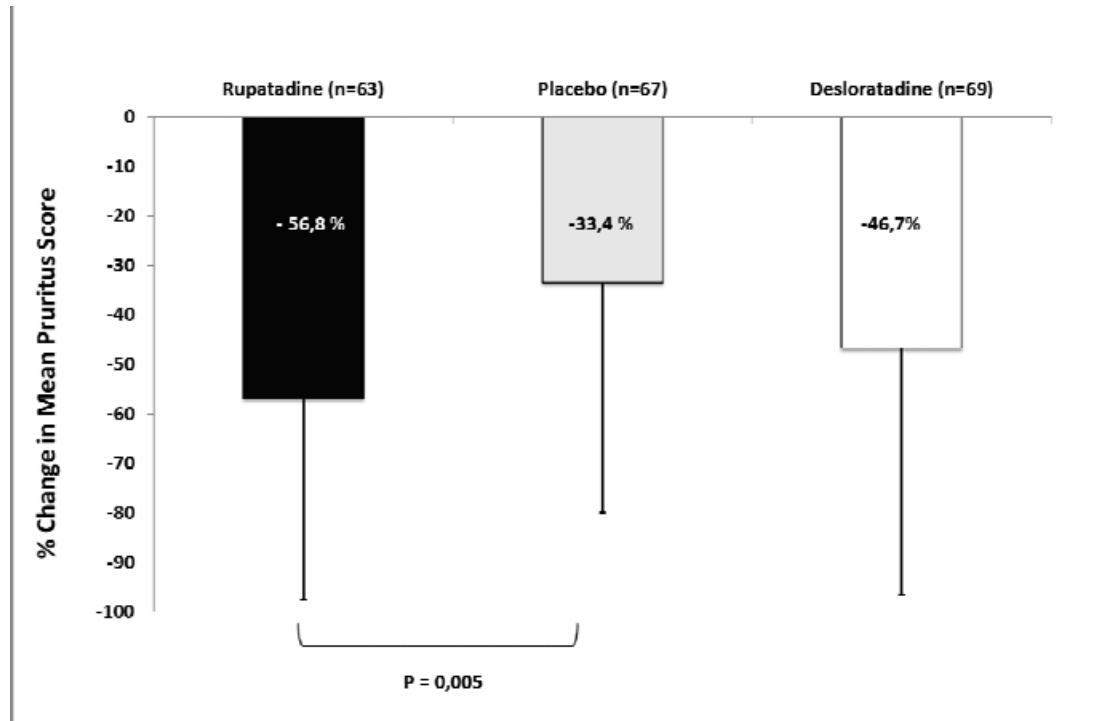


Figure 2C

Overall efficacy Mean Wheals Score (MWS)

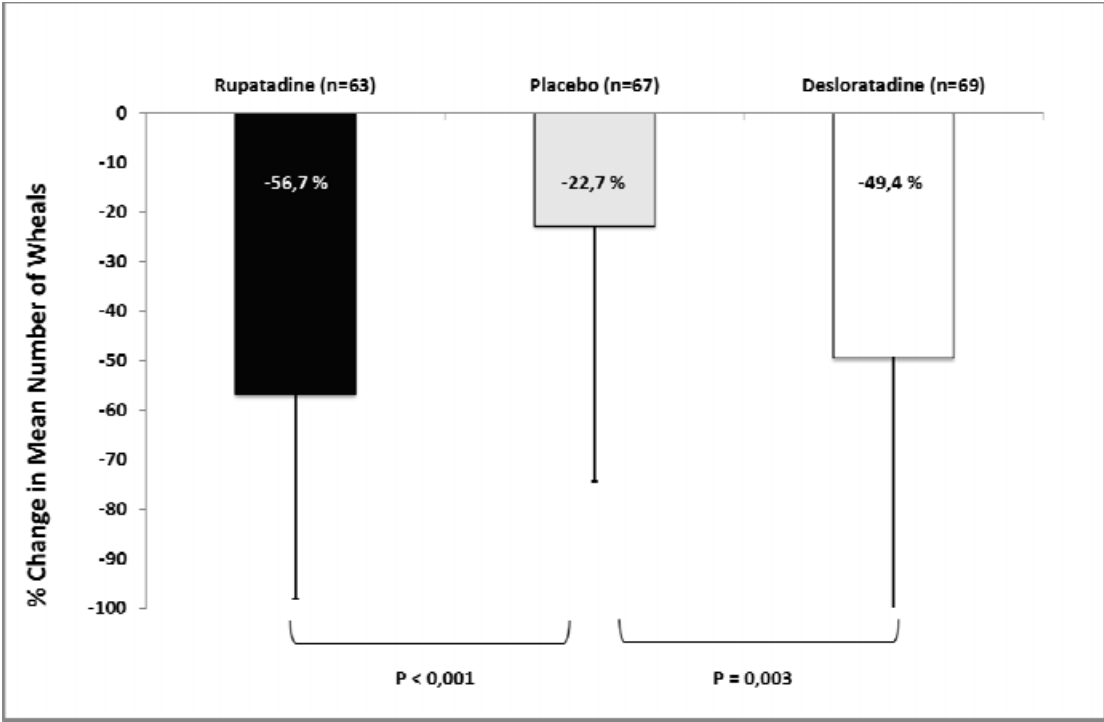
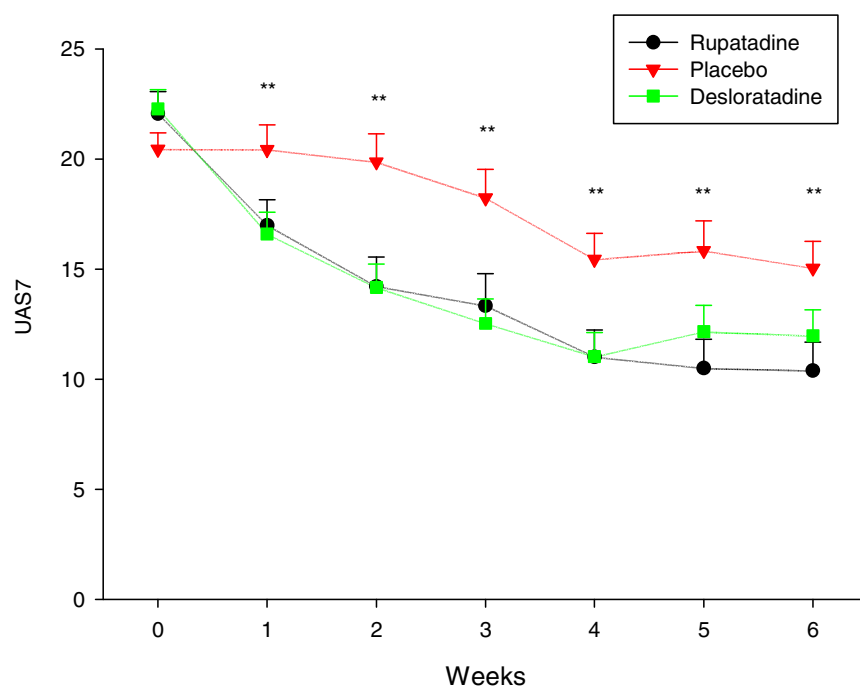


Figure 3



** Statistical significance: $p < 0.01$ among treatments

Figure 4

