CLINICAL INVESTIGATION

Rupatadine for the treatment of allergic rhinitis and urticaria: a look at the clinical data

The second-generation antihistamine rupatadine is a new long-acting and non-sedating drug that exerts a potent dual-antagonist activity towards the histamine H1 receptor and the PAF receptor. Rupatadine is prescribed for the relief of symptoms of seasonal and perennial allergic rhinitis and in the treatment of chronic urticaria. Clinical trials have shown that rupatadine, which shows a rapid onset of action and prolonged duration of activity, is effective and well tolerated. Safety data indicate that rupatadine does not affect the cardiovascular system, without relevant changes in the corrected QT interval, or significantly affect psychomotor activity at the doses used in clinical practice. Here, we review the efficacy and safety profile of rupatadine in patients with allergic rhinitis and urticaria.

Keywords: allergic rhinitis • chronic urticaria • histamine • platelet-activating factor • rupatadine

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The new antihistamine rupatadine is a potent, orally active, non-sedating, long-acting antagonist of both histamine H1 receptors and PAF receptors. It is one of the newest second-generation antihistamines and is currently prescribed in the treatment of chronic urticaria (CU) and seasonal or perennial allergic rhinitis (AR) in patients older than 12 years of age [1–3].

The role of histamine in allergic inflammation is unequivocal. However, other mediators are clearly involved in the allergic process and the roles of these mediators are beginning to be better defined. Similar to histamine, PAF is known to provoke increased vascular permeability and bronchoconstriction, and seems to be involved in bronchial hyper-reactivity, a common feature of asthma. Therefore, PAF is being increasingly recognized as an important mediator in the allergic response, as is demonstrated by its role in anaphylaxis [4,5].

AR and urticaria are clinical conditions that represent one of the most ordinary reasons for a patient to visit their general practitioner or allergist. Importantly, these two distinct clinical entities both respond to antihistamine treatment. This review focuses on the clinical characteristics of rupatadine and the evidence of its efficacy in the treatment of AR and urticaria.

Pharmacokinetic properties of rupatadine

Izquierdo *et al.* evaluated the pharmacokinetic properties of orally administered rupatadine in healthy volunteers of both genders, including elderly subjects [6]. Rupatadine is rapidly absorbed after oral administration (median T_{max} of 0.8 h with a single daily dose, or 0.75–1 h with multiple doses). After absorption, the drug undergoes extensive hepatic metabolism by CYP3A4, which is primarily responsible for rupatadine metabolism. The most important route of elimination for the drug is via the bile.

Test subjects were administered rupatadine in addition to known CYP3A4 inhibitors, to investigate metabolic drug–drug interactions. Ketoconazole and erythromycin, which inhibit CYP3A4 activity, were found to inhibit rupatadine metabolism, and when

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concomitantly administered, increased the exposure to rupatadine by ten-times and two- to three-times, respectively. However, despite the consequent increase in plasma concentrations of the parent compound, no clinically relevant consequences such as ECG changes or corrected QT (QTc) interval modifications were noted, and the number of adverse events reported did not increase [7]. In other studies with CYP3A4 inhibitors, the concomitant administration of azithromycin or fluoxetine did not produce clinically relevant modifications in the mean pharmacokinetic parameters of rupatadine and its active metabolites [8,9]. However, concomitant administration of rupatadine with other known CYP3A4 inhibitors should be carefully considered.

Systemic exposure to rupatadine after food intake increased by 23% compared with that under fasting conditions, while T_{max} was delayed by 1 h. These changes did not appear to have clinical consequences, and thus, the compound can be administered with or without food.

Tolerability and safety of rupatadine

Picado [2], as well as Keam and Plosker [10] independently reviewed the results from published Phase III clinical trials of rupatadine. They claimed that this antihistamine at a dosage of 10 mg once daily was well tolerated. In addition, the percentage of adverse effects observed at this dose did not differ significantly from those associated with placebo. In clinical trials involving patients receiving rupatadine at the dose of 10 mg once daily (n = 2025) or placebo (n = 1315), somnolence, headache, and fatigue were the most common treatment-related adverse events reported (incidence: 9.5, 6.8, and 3.2% of patients, respectively, in the active group and 3.4, 5.6, and 2.0% of patients, respectively, in the placebo group). Overall, the majority of adverse effects were of mild-to-moderate severity. These data were confirmed by a clinical long-term safety study in which patients with perennial AR were exposed to the drug for 12 months [11]. Furthermore, in patients treated with rupatadine 10 mg once daily, the incidence of adverse effects decreased with time [1].

Because sedation is a common side effect of many first-generation antihistamines, compounds that do not cause sedation are clearly more advantageous in clinical practice. Sedation negatively affects patients' quality of life, and the use of sedating drugs is complicated or even avoided for patients engaged in tasks requiring mental alertness. Although one typical characteristic of second-generation H1-antihistamines is their lack of effects on the CNS, it has been proven that some second-generation compounds still produce such effects.

Barbanoj *et al.* observed that 10 or 20 mg rupatadine did not significantly affect the psychomotor activity of healthy volunteers [12]. At a higher dose of 40 or 80 mg, rupatadine caused mild deterioration or a more significant impairment of psychomotor activity, respectively. This impairment was of similar severity as that caused by 25 mg hydroxyzine.

In another study, ethanol (0.8 g/kg of body weight) in addition to 10 mg of rupatadine did not impair cognitive or psychomotor performance to a greater extent than did ethanol alone. Compared to ethanol alone, 20 mg of rupatadine was found to exacerbate cognitive and psychomotor decline [13]. This effect was similar to that observed upon co-administration of ethanol and a single dose of cetirizine (10 mg) or hydroxyzine (25 mg). Similarly, 10 mg of rupatadine was not found to potentiate lorazepam-induced mental impairment [14]. In a practical assessment of 'mental alertness' performed using a car-driving test, the effects of 10 mg rupatadine were compared with those of 50 mg hydroxyzine in 20 healthy volunteers. No difference in mental alertness was found between volunteers taking rupatadine or the placebo. Meanwhile, the mental alertness of volunteers who took hydroxyzine was impaired to an extent comparable to that associated with a blood alcohol level of 0.9% [15].

'Torsade de pointes' is a potentially fatal type of ventricular arrhythmia and a prolonged QTc interval on an ECG is typically associated with drug-induced torsade de pointes. The initial belief that cardiotoxicity was an effect of all classes of non-sedating antihistamines proved unfounded, since fexofenadine, the active metabolite of terfenadine, and other second-generation antihistamines did not produce this cardiotoxic effect [16].

The cardiac safety of rupatadine has been extensively investigated. More than 6000 ECGs were analyzed from healthy volunteers and patients given rupatadine at daily doses ranging from 2.5 to 80 mg and under various conditions. No clinically relevant changes in QT/QTc intervals were observed, despite co-administration of other CYP3A4 inhibitors [7].

A randomized, double-blind, placebo-controlled clinical trial, involving 160 healthy volunteers, called the 'Thorough QT/QTc study' was designed to determine whether rupatadine had a significant effect on QTc interval prolongation. This trial did not demonstrate a statistically or a clinically significant effect on cardiac repolarization in patients given rupatadine at doses up to 100 mg (ten-times the recommended daily dose) [17].

The US FDA has proposed classification of drugs on the basis of risks for a mother and her fetus. Drugs assigned to categories A and B are considered to be a low risk for both the mother and the fetus. Rupatadine has been included in the risk category B. Studies in animal models did not reveal harmful effects with

Table 1. Double blind randomized trials in seasonal allergic rhinitis.

Patients (n)	Duration (weeks)	Treatment	Results	Ref.
339	2	R 10 and R 20 mg L 10 mg	mTDSS significantly reduced with R20 and R10 than with L10 by protocol analysis (p = 0.03) but not by intention-to-treat analysis	[22]
250	2	R 10 mg E 10 mg Placebo	Significant reduction in mTDSS vs placebo (p = 0.005). TSS for R10 and E10 not statistically different	[23]
249	2	R 10 mg C 10 mg	mTDSS, mDSS, DSSmax, TDSSmax, Pdmax0 and Pdmax1 were no significantly different between two groups.	[24]
379	4	R 10 mg D 5 mg Placebo	Mean change of T7SS significantly reduced vs placebo with both R10 (p = 0.03) and D5 (p = 0.01). R10 and D5 were more effective in reducing nasal discharge (p = 0.03 and 0.02), sneazing (both p = 0.01), nasal itching (p = 0.05 and 0.003) and ocular itching (p = 0.002 and <0.001).	[26]

C: Cetirizine; D: Desloratadine; DSSmax: Maximum value for daily symptom score; E: Ebastine; L: Loratadine; mDSS: Mean daily symptom score; mTDSS: Mean daily total symptom score; Pdmax0: percentage of days when daily severest symptom score was 0; Pdmax1: percentage of days when daily severest symptom score was ≤1; R: Rupatadine; T7SS: Total seven symptoms (nasal discharge, nasal obstruction, sneezing, nasal pruritus, ocular pruritus, ocular redness, and tearing eyes) score; TDSSmax: Maximum value for daily total symptom score; TSS: Total symptom score.

respect to pregnancy, fetal and postnatal development, or delivery. These studies also showed that rupatadine is excreted in animal milk. In humans, only limited data are available regarding exposure to rupatadine during pregnancy. However, these studies did not show that rupatadine had adverse effects on pregnancy or on the health of the fetus and newborn. To date, it is unknown if rupatadine is excreted into breast milk. Furthermore, the available clinical data for rupatadine are insufficient to establish a safety profile during pregnancy, and thus, rupatadine should be used with caution during pregnancy and in breastfeeding mothers and only if the expected benefits clearly outweigh potential risks.

Rupatadine in allergic rhinitis

AR is a common inflammatory disease of the nasal mucosa, caused by an interaction of environmental allergens and IgE in sensitized patients. Its symptoms include sneezing, nasal itching, rhinorrhoea, and obstruction; ocular signs such as eye itching, redness, and tearing, also frequently develop in patients with AR. The current Allergic Rhinitis and its Impact on Asthma (ARIA) classification of AR is based on the duration and severity (mild or moderate to severe) of symptoms and takes into account the impact of the disease on daily activities, work/school performance, and sleep. Intermittent AR is characterized by symptoms that occur on fewer than 4 days per week or fewer than 4 consecutive weeks per year. Conversely, persistent AR occurs when symptoms are present for more than 4 days per week and for more than 4 consecutive weeks per year [18,19]. Treatment of AR is based on allergen avoidance, pharmacotherapy, and specific immunotherapy [20]. According to ARIA guidelines, second-generation non-sedating antihistamines are recommended as the first-line drugs in both mild and moderate to severe AR [21]. A number of trials compared rupatadine with placebo and other second-generation antihistamines in patients with AR (Table 1). In most studies, patients were classified as those with seasonal AR or perennial AR according to the above definitions. In patients with seasonal AR, the safety and efficacy of rupatadine was compared with those of placebo, loratadine, desloratadine, ebastine, and cetirizine in double-blind randomized trials and to levocetirizine in an open-label trial [22–26]. These trials included adult and adolescent patients (older than 12 years) with a documented history of seasonal AR for at least the previous 2 years, and who were symptomatic at the time of screening. Patients with non-allergic rhinitis or a negative skin prick test were excluded. Primary efficacy was determined using daily total symptoms score assessment. The results showed that rupatadine was superior to placebo and as effective as 10 mg cetirizine, loratadine, or ebastine over a 2-week period [22–24]. Moreover, the efficacy of rupatadine was comparable to that of 5 mg desloratadine in a 4-week trial [26]. With regard to the patients' quality of life, rupatadine was significantly superior to levocetirizine in decreasing Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) scores [25].

Three double-blind, randomized, placebo-controlled trials compared the efficacy of rupatadine

in patients with perennial AR [27–29]. Rupatadine was as effective as loratadine, cetirizine and ebastine in improving symptoms during 4 weeks of treatment (Table 2). In particular, Marmouz and co-workers focused on morning and evening efficacy evaluations, highlighting that morning and evening relief of nasal symptoms was similar and thus confirming the 24-h effect of rupatadine, regardless of the time of administration [27]. The efficacy of rupatadine was evaluated in both adult and pediatric patients with persistent AR according to the ARIA classification. Fantin *et al.* performed a double-blind, placebo-controlled study in patients older than 12 years who had persistent moderate-to-severe AR for at least 12 months before the screening [30]. In this trial, 543 patients were randomized to receive 10 mg rupatadine, 10 mg of cetirizine, or placebo for 3 months. The primary efficacy end point, as evaluated using the instantaneous total nasal symptoms score, including nasal blockage, was significantly reduced during all 12 weeks of treatment in the rupatadine group compared with the placebo group. Rupatadine but not cetirizine treatment, compared with placebo, significantly reduced the baseline instantaneous total symptom score after 12 weeks of treatment. Moreover, rupatadine improved patients' quality of life, because RQLQ scores at week 12 were significantly lower in rupatadine-treated patients than in placebo-treated patients ($p = 0.016$). An open-label trial confirmed the efficacy of rupatadine in reducing nasal symptoms since the first day of treatment in patients with moderate-to-severe persistent AR [31]. In a 6-week randomized controlled trial in children aged between 6 and 11 years with persistent AR, the efficacy and safety of an oral solution of rupatadine (1 mg/ml) was investigated in comparison with those of placebo [32]. Children receiving rupatadine showed a higher reduction in T4SS both at week 4 ($p = 0.018$) and 6 ($p = 0.048$). Rupatadine also significantly improved the quality of life of children, as assessed using the pediatric RQLQ. The frequency and types of adverse reactions were comparable in actively treated and placebo-treated groups. No QTc or laboratory test abnormalities were reported.

A systematic review and meta-analysis of randomized, double-blind, placebo-controlled studies of the efficacy and safety of rupatadine for allergic rhino-conjunctivitis was recently published [33]. This analysis included ten trials involving 2573 patients: four studies focused on seasonal AR [22–24, 26], three focused on perennial AR [27–29], and the remaining three focused on persistent/intermittent AR [30,32,34]. A comparison between rupatadine and other antihistamines was not considered in this analysis. The reduction of total nasal symptoms, in both reflective and instantaneous evaluations, was higher in patients receiving rupatadine than in placebo-treated patients. Compared with placebo, rupatadine significantly reduced rhinorrhoea (standardized mean difference (SMD): -0.30; 95% CI: -0.41 to -0.19; $p < 0.00001$), nasal itching (SMD: -0.21; 95% CI: -0.33 to -0.10; $p < 0.0003$), and nasal obstruction (SMD: –0.25; 95% CI: -0.37 to -0.13; $p < 0.00001$), with good efficacy in managing ocular symptoms. Moreover, after 4 and 12 weeks of treatment, the authors found an improvement in the quality of life of the patients receiving rupatadine compared with that of the patients receiving placebo (mean difference in RQLQ score: -8.8% and -10%, respectively; $p = 0.016$ and $p < 0.01$, respectively). Differences were not observed in the incidence of adverse reactions between rupatadine and placebo treatments (OR: 1.23; 95% Cl: 0.95–1.59; $p = 0.12$). These data show a favorable risk–benefit ratio for rupatadine in the treatment of allergic rhino-conjunctivitis.

Table 2. Double blind randomized trials in perennial allergic rhinitis.

Patients (n)	Duration (weeks)	Treatment	Results	Ref.
308	4	R 10 mg R 20 mg C 10 mg Placebo	All active group were effective vs placebo in improving 5TSS and 4TNSS ($p < 0.001$). Pdmax1 was significantly improved for all active treatment	[27]
283	4	R 20 mg R 10 mg L 10 mg Placebo	Significant reduction in total symptoms score with R10 (-4.00), R20 (-3.96) and L10 (-3.94) vs placebo ($p < 0.01$). Pdmax1 was significantly lower for R20 than for placebo	[28]
223	4	R 10 mg E10 mg Placebo	5TSS and 4TNSS were significantly improved vs placebo with both R10 ($p = 0.019$) and E10 ($p = 0.025$). Pdmax1 was non-significantly lower for R10 and E10 than for placebo	[29]

4TNSS: Total four nasal symptoms (rhinorrhea, sneezing, nasal itching, and nasal obstruction) score; 5TSS: Total five symptoms (rhinorrhea, sneezing, nasal itching, nasal obstruction, and conjunctival itching) score; C: Cetirizine; E: Ebastine; L: Loratadine; Pdmax1: percentage of days when daily severest symptom score was ≤1; R: Rupatadine;.

Rupatadine in chronic urticaria

Urticaria is characterized by the development of wheals, flare, and itch that can or cannot be associated with angio-oedema and can appear in a variety of forms. The new classification distinguishes between spontaneous and inducible urticaria [35]. Several different stimuli are involved in the pathogenesis of urticaria, including different physical factors (such as pressure, heat, sunlight and water), drugs, foods, infectious agents, cold and autoimmunity. According to the European Academy of Allergology and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization (EAACI/GA²LEN/EDF/WAO) guidelines, the term chronic urticaria (CU) is used to indicate chronic spontaneous urticaria, a debilitating disease characterized by wheal and flare reactions, redness and itching, for more than 6 weeks [35]. In European countries and in the US, CU has been reported to occur in 0.1–3% of the population, and the worldwide lifelong prevalence has been estimated at approximately 0.5% [36]. Histamine represents a key mediator in the pathophysiology of CU. For this reason, histamine H1-receptor antagonists play a primary role in the treatment of urticaria because H1-receptor activation leads to local vasodilation, the appearance of wheals, a flare response, and itching. It should also be considered that in addition to histamine, other mediators such as eicosanoids, cytokines, proteases, and PAF are involved in the inflammatory process. CU is a incapacitating, difficult-to-treat condition; it affects the daily performance and quality of life of patients, since sleep disruption, energy loss, fatigue, social isolation, sexual and emotional disturbances are common symptoms of the disease [37]. The EAACI/GA²LEN/EDF guidelines for the management of urticaria recommend second-generation, non-sedating H1-antihistamines as the first-line symptomatic treatment for CU [38]. Although rupatadine is one of the newest antihistamines, its use has been extensively investigated in the treatment of urticaria [39]. Dubertret *et al.* described a study consisting of 283 patients with CU who received rupatadine (at doses of 5, 10, or 20 mg, daily) or placebo over a period of 4 weeks. They observed a reduction from baseline in daily mean pruritus score (MPS) of -1.1819 (71.8%) in the 20-mg group ($p = 0.001$ vs placebo), -1.515 (62.0%) in the 10-mg group ($p = 0.02$ vs placebo), and -1.310 (51.2%) in the 5-mg group (not significant). The therapeutic response, global CU status, sleep, and the performance of daily activities improved with either 10 or 20 mg rupatadine. All doses were well tolerated, with safety profiles similar to that of placebo (Table 3) [40]. Gimenez *et al.* found that 10 mg rupatadine daily is a fast, long-acting, efficacious and safe treatment option for the management of patients with moderate-to-severe CU. This randomized, double blind, placebo-controlled study showed that 10 or 20 mg of rupatadine was significantly more effective than placebo over the 4-week treatment period. 10 or 20 mg rupatadine decreased the mean MPS from baseline, the primary outcome, by 57.5 and 63.3%, respectively, compared with a 44.9% reduction achieved with placebo. Moreover, the superiority of rupatadine over placebo in reducing the MPS was evident after 1 week of treatment and was maintained over an extended treatment period of 6 weeks. Similarly, 10 or 20 mg rupatadine was also significantly better than placebo in reducing the mean number of wheals score and mean total symptom score from week 1 to 6. These results support the efficacy of rupatadine in improving the quality of life in these patients (Table 3) [41]. Church *et al.* reported additional benefits of using 40 mg rupatadine for histamine- and PAF-induced dermal flares in healthy volunteers, but this issue has not yet been adequately investigated [3]. Maiti *et al.* reported that rupata-

Table 3. Double blind randomized trials in urticaria.

Patients (n)	Duration (weeks)	Treatment	Results	Ref.
283	4	R 5 mg R 10 mg R 20 mg Placebo	R10 and R20 significantly reduced MPS vs placebo ($p < 0.05$ and < 0.001). R20 was significantly greater compared with R5 ($p < 0.001$) and R10 ($p < 0.05$)	[40]
334	6	R 10 mg R 20 mg Placebo	R10 and R20 significantly reduced MPS vs placebo ($p < 0.005$ and $= 0.0001$) After 24 h treatment R10 and R20 was significantly different from placebo ($p = 0.013$ and < 0.0001)	[41]
21	1	R 20 mg Placebo	Significant improvement in CSTT vs placebo after ice cube and TempTest challenge ($p = 0.03$ and $= 0.004$). Significant reduction of critical temperature threshold ($p < 0.001$), pruritus ($p = 0.005$), burning sensation ($p = 0.03$) vs placebo.	[43]

CSTT: critical stimulation time threshold; MPS: mean pruritus score; MTSS: mean total symptom score; R: Rupatadine.

dine was superior in a comparative study of the efficacy and safety of rupatadine with levocetirizine in CU. This randomized single-blind, single-centre trial involved 70 patients suffering from CU who took the two drugs for 4 weeks: 35 patients were treated with rupatadine (10 mg daily) and 35 with levocetirizine (5 mg daily). In the rupatadine group, statistically significant reductions in the differential count of eosinophils, absolute eosinophil count, serum IgE, total symptoms score, and Aerius Quality of Life Questionnaire were observed [42]. In addition, Metz *et al.* demonstrated the efficacy of rupatadine in preventing acquired cold urticaria (ACU), a physical urticaria triggered by exposure of the skin to cold. This randomized, double-blind, placebo-controlled study involved 21 patients with ACU, receiving 20 mg of rupatadine daily, or placebo for 1 week. Rupatadine improved exposure time thresholds, critical temperature thresholds and symptom control compared with placebo treatment [43]. Di Leo *et al.* also described the efficacy of rupatadine in three patients suffering from ACU. In two patients, they observed a significant reduction in the reaction to the ice cube-challenge test, as well as in subjective symptoms, without observed differences between dosages (10 and 20 mg), while one subject was unresponsive at both dosages [44]. According to currently available studies, rupatadine seems to be efficacious and safe in the treatment of CU and ACU. However, controlled studies in larger cohorts of patients are required to establish its value in ACU.

The clinical role of rupatadine

AR and CU are common chronic diseases that have many consequences on the health and quality of life of patients, including sleep quality. These diseases also impact a patient's social life, school performance and work productivity, with the consequence of raising both social- and health-care costs [45–47]. The management of both disorders includes nonpharmacologic therapy (allergen avoidance, lifestyle modification) and pharmacologic treatment. The international guidelines state that second-generation antihistamines represent the mainstay of treatment for AR and CU, while first-generation antihistamines do not provide significant benefits because of their use is limited by sedative and anticholinergic side effects [19,48]. The risk associated with first-generation antihistamines was reviewed by a GA(2)LEN position paper that stressed the superior risk–benefit ratio of the newer compounds [49]. An ideal antihistamine should have the following characteristics: complete and selective H1-receptor blockade, no clinically relevant interference with the intake of foods and drugs, a rapid onset of therapeutic effects, a long duration of action, no development of tachyphylaxis and no sedative effects. Due to its rapid absorption and the presence of active metabolites, rupatadine rapidly controls symptoms and its prolonged duration of action allows a once daily administration. In addition, the interactions with other drugs taken concurrently appear clinically insignificant. All of these features are very attractive to patients, as rupatadine not only quickly relieves symptoms when taken on demand, but also is safe for continuous treatment.

The distinctive feature of rupatadine is the dual PAF and H1 receptor antagonism. PAF is a lipid mediator that is produced by many types of inflammatory cells and exerts a proinflammatory activity in the allergic cascade, promoting the late phase of the allergic response and exerting a chemotactic activity [50,51]. Recent clinical and experimental evidence indicates that PAF plays a role in the pathogenesis of AR, particularly in the development of nasal obstruction and rhinorrhoea by increasing vascular permeability [52,53]. Rupatadine significantly reduced nasal congestion compared with placebo [54] in patients exposed in a controlled allergen-exposure chamber, establishing that PAF can affect nasal congestion. Moreover, rupatadine also inhibits cytokine secretion from human mast cells in response to different triggers [55]. These effects provide an additional benefit to rupatadine treatment because nasal congestion is frequently a troublesome symptom, on which the efficacy of other antihistamines is often unsatisfactory. This should define a superiority of rupatadine over antihistamines with no activity on nasal congestion. When compared with other antihistamines, rupatadine has been shown to improve greater nasal obstruction, even if the difference was not statistically significant [23,24,27,30]. However, the clinical significance of these additional effects of rupatadine needs to be investigated further.

In the treatment of CU, rupatadine plays an important role, as the safety profile allows for higher dosing than the licensed recommendations provided by World Allergy Organization, for patients who do not achieve a good control of symptoms at standard doses [49]. In fact, less than 50% of patients achieve complete remission at the recommended doses [56]. For these patients, an increase of up to fourfold of the recommended dose of a non-sedating antihistamine, such as fexofenadine, cetirizine, levocetirizine, desloratadine, or bilastine can be provided, with variable efficacy for different agents [57]. However, it should be considered that PAF induces the releases of histamine from human lung mast cells *in vitro* [58], and recent data indicate that PAF also induces wheal and flare skin reactions without histamine release and, thus, independently of mast cell degranulation [59]. These findings suggest a favorable pharmacological profile of rupatadine that may affect urticaria in many different ways. It should also be noted that the inhibitory mechanisms against mast cell-mediator release is particularly important for the treatment of other disorders

involving mast cells, such as mastocytosis. Recently, it has been shown that 20 mg of rupatadine daily improves quality of life in patients with mastocytosis with skin involvement [60]. In addition, rupatadine is an effective treatment for the mosquito-bite-induced whealing and itching in adult patients with mosquito-bite allergy [61].

In conclusion, Rupatadine is one of the newest second-generation antihistamines, with a rapid onset and a prolonged duration of action, which was demonstrated to be effective and safe for the treatment of allergic rhinitis (including persistent allergic rhinitis) and urticaria. According to Simons, "novel agents, such as rupatadine, an H1-antihistamine/anti-platelet activating factor agent, might play a unique role" [62]. Actually, for its mechanism of action, which includes the PAF receptor antagonism, rupatadine differs from the other currently available antihistamines improving the possibility to work on the inflammatory cascade and on the effector cells. The recent data reported on mastocytosis are an example of the possible future clinical applications of rupatadine.

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Executive summary

- Rupatadine is a new second-generation antagonist of the histamine H1 receptor and the PAF receptor and is indicated in the treatment of seasonal and perennial allergic rhinitis and chronic urticaria.
- Clinical trials showed that rupatadine has a rapid onset of action, a prolonged duration of activity. Rupatadine improves symptoms and quality of life in patients older than 6 years with allergic rhinitis (including the persistent form) and in patients older than 12 years with urticaria.
- Based on its anti-inflammatory effect, rupatadine improves nasal obstruction, which is the most disturbing and unresponsive to the symptoms of rhinitis.
- The safety data for rupatadine indicate that it does not affect the cardiovascular system, change the corrected QT interval, or significantly affect psychomotor activity at the doses used in clinical practice.
- Because of the importance of PAF in the pathogenesis of allergy, a role for rupatadine in the treatment of other allergic disorders warrants investigation.

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