

REVIEW ARTICLE

Update on rupatadine in the management of allergic disorders

J. Mullol¹, J. Bousquet², C. Bachert³, G. W. Canonica⁴, A. Giménez-Arnau⁵, M. L. Kowalski⁶, F. E. R. Simons⁷, M. Maurer⁸, D. Ryan⁹ & G. Scadding¹⁰

¹Unitat de Rinologia i Clínica de l'Olfacte, Servei d'ORL, Hospital Clínic, Clinical & Experimental Respiratory Immunoallergy, IDIBAPS, Barcelona, Spain; ²University Hôpital Arnaud de Villeneuve and INSERM, Montpellier, France; ³Department of Oto-Rhino-Laryngology, Upper Airway Research Laboratory (URL), Ghent University Hospital, Ghent, Belgium; ⁴Department of Internal Medicine, Respiratory Diseases and Allergy Clinic, University of Genoa, Genoa, Italy; ⁵Department of Dermatology, Hospital del Mar, Universitat Autònoma, Barcelona, Spain; ⁶Department of Immunology, Rheumatology and Allergy, Medical University of Lodz, Lodz, Poland; ⁷Department of Pediatrics and Child Health, and Department of Immunology, University of Manitoba, Winnipeg, Canada; ⁸Department of Dermatology and Allergy, Allergie-Centrum-Charité, Charité – Universitätsmedizin Berlin, Berlin, Germany; ⁹University of Edinburgh, Edinburgh, UK; ¹⁰Department of Allergy and Rhinology, Royal National Throat, Nose and Ear Hospital, London, UK

To cite this article: Mullol J, Bousquet J, Bachert C, Canonica GW, Giménez-Arnau A, Kowalski ML, Simons FER, Maurer M, Ryan D, Scadding G. Update on rupatadine in the management of allergic disorders. *Allergy* 2015; **70**: 1–24.

Keywords

allergic rhinitis; H₁-antihistamine; PAF antagonist; rupatadine; urticaria.

Correspondence

Joaquim Mullol, Unitat de Rinologia i Clínica de l'Olfacte, Servei d'ORL, Hospital Clínic, Clinical & Experimental Respiratory Immunoallergy, IDIBAPS, Villarroel 170, 08036 Barcelona, Catalonia, Spain.
Tel.: +34-93-227-9872
Fax: +34-93-227-9813
E-mail: jmullo@clinic.ub.es

Accepted for publication 7 October 2014

DOI:10.1111/all.12531

Edited by: J. Mullol and J. Bousquet

Abstract

In a review of rupatadine published in 2008, the primary focus was on its role as an antihistamine, with a thorough evaluation of its pharmacology and interaction with histamine H₁-receptors. At the time, however, evidence was already emerging of a broader mechanism of action for rupatadine involving other mediators implicated in the inflammatory cascade. Over the past few years, the role of platelet-activating factor (PAF) as a potent mediator involved in the hypersensitivity-type allergic reaction has gained greater recognition. Rupatadine has dual affinity for histamine H₁-receptors and PAF receptors. In view of the Allergic Rhinitis and its Impact on Asthma group's call for oral antihistamines to exhibit additive anti-allergic/anti-inflammatory properties, further exploration of rupatadine's anti-PAF effects was a logical step forward. New studies have demonstrated that rupatadine inhibits PAF effects in nasal airways and produces a greater reduction in nasal symptoms than levocetirizine. A meta-analysis involving more than 2500 patients has consolidated the clinical evidence for rupatadine in allergic rhinoconjunctivitis in adults and children (level of evidence Ia, recommendation A). Other recent advances include observational studies of rupatadine in everyday clinical practice situations and approval of a new formulation (1 mg/ml oral solution) for use in children. In this reappraisal, we revisit some key properties and pivotal clinical studies of rupatadine and examine new clinical data in more detail including studies that measured health-related quality of life and studies that investigated the efficacy and safety of rupatadine in other indications such as acquired cold urticaria, mosquito bite allergy and mastocytosis.

Allergic diseases represent some of the most common chronic diseases seen by general practitioners and are frequently under-diagnosed and under-treated (1, 2). Moreover, the prevalence of these disorders continues to increase worldwide (3–6). Two of the most common allergic diseases, allergic rhinitis and urticaria, are particularly bothersome conditions as symptoms can disturb sleeping patterns and impact on daily

activities. In their more severe forms, allergic rhinitis and urticaria can have a detrimental impact on the health-related quality of life (HRQoL) of affected individuals, negatively affecting social activities (including sport and leisure) as well as school/work performance (7). The socio-economic burden of chronic allergic diseases stemming from healthcare resource consumption, lost work time and underperformance

(presenteeism) is enormous, underscoring the need for accurate diagnosis, preventive measures and effective clinical management (7).

Allergic rhinitis represents the fifth leading chronic disease overall in the US and the third leading chronic disease among children aged under 18 years (8). Allergic rhinitis often precedes the development of other highly prevalent and costly related conditions such as asthma (9–11). Chronic urticaria has been estimated to occur in 0.1–3% of populations in Europe and the US. Its worldwide lifelong prevalence is approximately 0.5% and does not vary significantly between different communities (12–14).

In view of the prominent role of histamine in the pathophysiology of allergic conditions, H₁-antihistamines have long been the mainstay of treatment. Along with histamine, numerous other inflammatory mediators are involved in the allergic response, prompting the demand for therapeutic agents with anti-allergic/anti-inflammatory activities in addition to antihistaminic effects (9, 15). In recent years, increasing focus has been given to platelet-activating factor (PAF) as a potential target to improve symptom control (1, 16, 17).

Current guidelines for the treatment of allergic rhinoconjunctivitis and urticaria recommend modern second-generation H₁-antihistamines, replacing first-generation compounds for reasons of efficacy and safety (18, 19). Nevertheless, only a few compounds such as desloratadine, levocetirizine and rupatadine have a large body of evidence supporting their efficacy and safety in allergic disorders (20, 21). In 2008, we reviewed the efficacy and safety of rupatadine in the management of allergic disorders based on an extensive literature search (22). In this update, we will revisit some relevant earlier findings and review pivotal new findings for rupatadine in relation to PAF antagonism, clinical pharmacology, efficacy and safety in adults and paediatric patients, as well as data from observational studies in everyday practice which evaluated the effects of rupatadine on patients' quality of life (QoL), daily activities and well-being.

Allergic inflammatory reaction

Knowledge of the mechanism of the allergic reaction in rhinitis and urticaria is essential to understanding how second-generation H₁-antihistamines work and identifying ways in which their efficacy and/or safety can be improved. In this regard, a short overview is provided with a focus on recent evidence of the role of PAF in allergic disorders.

The allergic cascade is a complex immune-inflammatory response that developed primarily to improve host protection from environmental dangers (22). Chemical mediators that act in concert to facilitate the allergic response can be divided into three types: preformed granule-associated mediators (e.g. mast cell-derived histamine and proteases); newly generated phospholipid-derived mediators (e.g. eicosanoids and PAF); and macromolecular chemokines and cytokines (Fig. 1) (1). Histamine is a prominent mediator in the pathophysiology of allergic rhinitis and urticaria. Although antihistamines were traditionally considered to exert their effects through antagonism of H₁-receptors, they are now understood to act on the H₁-receptor in a positive (agonist) manner and, as such, are classed as inverse agonists (19, 23–26). As histamine is not the only mediator involved in the inflammatory process, there is a strengthening view that H₁-antihistamines that inhibit a broader range of inflammatory mediators may prove to be more effective in providing symptomatic relief in both allergic rhinitis and urticaria.

Platelet-activating factor is a lipid mediator derived from phospholipase A₂-mediated metabolism of phosphatidylcholine. Expression of PAF receptors and *de novo* synthesis of PAF occurs primarily in mast cells, and also in platelets, neutrophils, monocytes, eosinophils, basophils and epithelial cells (27). Effects attributed to PAF include platelet aggregation, mast cell degranulation, activation of macrophages and neutrophils, and eosinophil chemotaxis and activation (27). In human eosinophils, PAF activates two distinct signalling and effector pathways coupled to monomeric or dimeric

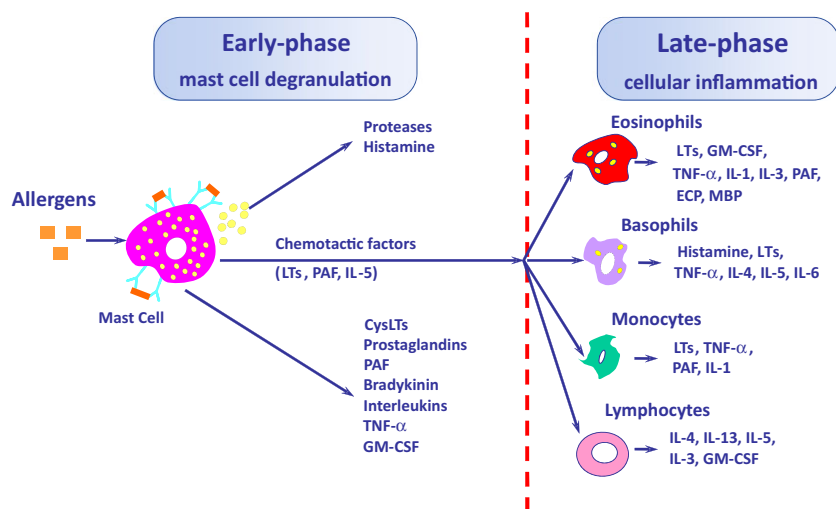


Figure 1 Schematic representation of the allergic inflammatory cascade. Adapted from (22) with permission.

PAF receptors on the cell membrane (Fig. 2). Depending on which G protein is activated, PAF can induce either eosinophil chemotaxis or eosinophil degranulation and, indeed, PAF is one of the most potent mediators of eosinophil chemotaxis in the airways (28–31). The majority of data on PAF is derived from studies in anaphylaxis (29, 32), but PAF is also known to be involved in other airway diseases including asthma (33) and allergic rhinitis (22).

Allergic rhinitis

Allergic rhinitis is an inflammatory disease of the nasal mucosa mediated by IgE. Following contact with an allergen, mast cells degranulate, releasing histamine and other mediators. In response to mast cell activation, numerous other mediators are generated within minutes or hours of the degranulation process. Certain mediators act on gland cells to produce rhinorrhoea, others on nasal blood vessels to induce oedema and nasal obstruction, and others on nasal sensory nerves to induce itching and sneezing. Histamine, for example, is instrumental in the induction of itching and sneezing, whereas leukotrienes, prostaglandins and PAF are the most relevant mediators for induction of oedema/nasal obstruction.

The G-protein-coupled PAF receptor is significantly upregulated in allergic diseases (1). It is present in a wide range of different cell types in nasal passages, particularly in inflammatory cells (34). With respect to allergic rhinitis, PAF increases vascular permeability, which contributes to increased mucous secretion and rhinorrhoea associated with the disease. PAF also attracts and activates granulocytes within the nasal endothelium, which exacerbates the inflammatory response in nasal tissues. In this regard, it was found that, in tissue samples, granulocyte accumulation occurred very rapidly (within 8 min of selectin translocation), a reaction more consistent with PAF release than with the usual cytokine response, which is slow and takes about 12 h to peak (1).

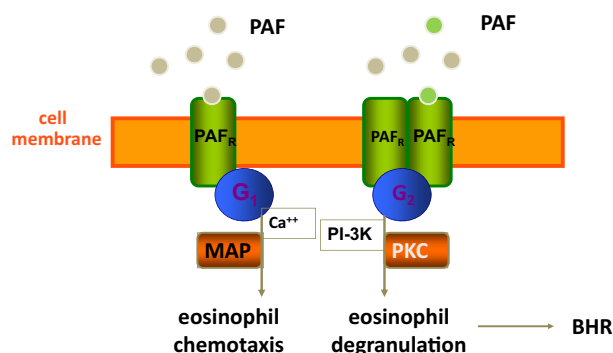


Figure 2 Interaction of platelet-activating factor (PAF) with PAF receptors on human eosinophils. BHR, bronchial hyper-responsiveness; G, G protein; MPA, mitogen-activated protein; PAF_R, PAF receptors; PI-3K, phosphoinositide 3-kinase; PKC, protein kinase C. Adapted from (28, 30).

Urticaria

Urticaria is characterized by itchy wheal and flare-type skin reactions and/or angioedema. Symptoms are caused by the release of histamine and other preformed and newly generated mediators from activated dermal mast cells (2). The pro-inflammatory mediators include, among others, prostaglandins, leukotrienes, PAF, proteases, cytokines and neuropeptides. Together, the various mast cell mediators have three main actions in the skin (Fig. 3) (2) as follows:

- 1 activation of sensory nerves (causes itch);
- 2 vasodilation (causes flare) and extravasation (causes wheals and angioedema); and
- 3 recruitment of other cells such as neutrophils and/or macrophages as well as T cells and eosinophils.

Urticaria can be spontaneous or inducible, but, irrespective of the trigger for mast cell activation, the presence of PAF is a consistent feature. Although PAF has been shown to induce histamine release from mast cells in human lung and peripheral blood, it has no degranulating effect on mast cells in human skin (31). In a study in healthy volunteers using microdialysis, 80% of the wheal response induced by intradermal injection of PAF was mediated by PAF itself with no meaningful rise in histamine levels, indicating that PAF mediates its effects on human skin by means independent of mast cell degranulation (35). Intradermal injection of PAF causes pain, extreme itch and development of a wheal and flare response similar to that observed after injection of histamine or codeine (a mast cell degranulator), although with less reflex erythema (35).

The contribution of PAF to the pathogenesis of cold contact urticaria was first recognized in the 1970s (36). Some years later, it was reported that platelet factor 4 is released into the circulation after cold challenge in individuals with cold contact urticaria, but not in normal volunteers (37), followed soon after by a report describing the association between PAF and primary acquired cold urticaria (ACU) (38). Despite such evidence, it has taken many years to fully recognize the contribution of PAF in the aetiology of skin allergy responses.

Clinical pharmacology of rupatadine

Rupatadine, an *N*-alkyl pyridine derivative (Rupatadine; J Uriach y Compañia S.A., Barcelona, Spain), is a second-generation H₁-antihistamine with dual affinity for histamine H₁- and PAF receptors (22, 39). It has a broad profile of anti-inflammatory properties through inhibition of a range of mediators involved in the early- to late-phase inflammatory response (22).

Pharmacodynamic properties and mechanism of action

In our previous review article, preclinical and early clinical pharmacology studies for rupatadine were extensively reviewed (22). The following main findings were reported:

- 1 Rupatadine possesses a high affinity for histamine H₁-receptors and demonstrated a marked selectivity for

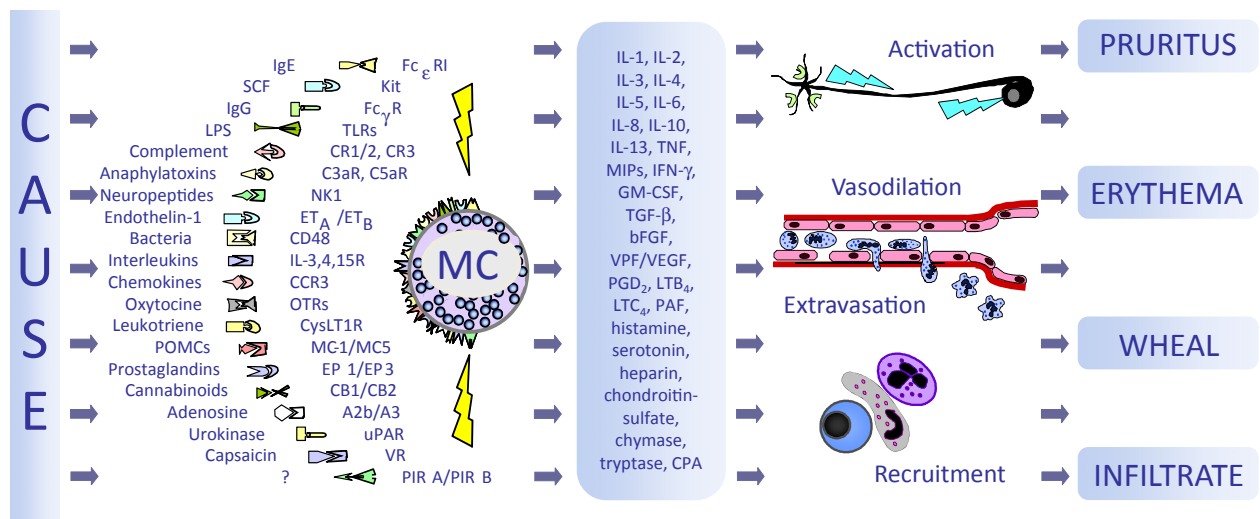


Figure 3 Actions of mast cell (MC)-derived pro-inflammatory mediators in the skin. A2b/A3, adenosine receptors; bFGF, basic fibroblast growth factor; CB, cannabinoid receptors; CCR, G-protein-coupled coreceptor (chemokine receptor); CD, cluster of differentiation; CPA, carboxypeptidase A; CR, complement receptors; CysLT1R, cysteinyl leukotriene receptor; EP, prostaglandin receptors; ET, endothelin; FcR, fragment crystallizable region; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; Ig, immunoglobulin; IL, interleukin; LPS, lipopolysaccharides; LT,

leukotriene; MC1/MC5, melanocortin receptors; MIPs, macrophage inflammatory proteins; NK, natural killer; OTRs, oxytocin receptors; PAF, platelet-activating factor; PG, prostaglandin; PIR, paired immunoglobulin-like receptor; POMC, proopiomelanocortin; SCF, stem cell factor; TGF, transforming growth factor; TNF, tumour necrosis factor; TLRs, toll-like receptors; uPAR, urokinase plasminogen activator receptor; VEGF, vascular endothelial growth factor; VPF, vascular permeability factor; VR, vanilloid receptor. Adapted from (1). Courtesy of Prof. Marcus Maurer.

binding to peripheral lung H₁-receptors compared with brain (cerebellum) H₁-receptors following oral administration of 0.16 mg/kg to guinea pigs. As assessed by *ex vivo* ³H-mepyramine binding, receptor occupancy was 70% for lung and <10% for cerebellum receptors.

- Rupatadine is a powerful and selective high-affinity inverse agonist of the histamine H₁-receptor, which, unlike other H₁-antihistamines such as desloratadine and levocetirizine, also produces specific and dose-dependent inhibition of PAF receptors (Table 1).
- Competitive inhibition of PAF receptors by rupatadine at submicromolar concentrations corresponded with dose-dependent activity in animal models such as PAF-induced wheal formation in beagle dogs as well as in humans.
- Rupatadine has been shown to inhibit other inflammatory processes/mediators such as mast cell degranulation (provoked by both immunological and nonimmunological stimuli), eosinophil and neutrophil chemotaxis, cytokine (IL-5, IL-6, IL-8, GM-CSF and TNF- α) production and neutrophil adhesion molecule (CD11b and CD18) expression.
- In patients with seasonal allergic rhinitis (SAR), rupatadine rapidly and significantly reduced nasal (including nasal congestion) and non-nasal symptoms compared with placebo following allergen exposure in the Vienna Challenge Chamber.
- Single doses of rupatadine 10, 20, 40 and 80 mg as well as multiple doses of 20 or 40 mg once daily for 7 days inhibited histamine-induced cutaneous flares in healthy

Table 1 Potency of various H₁-antihistamines/PAF antagonists as assessed by the concentration to produce 50% inhibition of platelet-activating factor (PAF)-induced antagonism of platelet aggregation. Adapted from (22)

H ₁ -antihistamine	Potency relative to rupatadine*	
	Washed rabbit platelets	Human platelet-rich plasma
WEB-2086	0.085	0.16
SCH-37370	0.125	0.49
Ginkgolide-B	0.185	Not tested
Rupatadine	1	1
Loratadine	160	>290
Ketotifen	>500	Not tested
Mepyramine	>500	Not tested
Terfenadine	>500	Not tested

*Concentration required to produce an equivalent effect to rupatadine.

male volunteers. Both the percentage and duration of flare inhibition increased with dosage. After multiple doses, inhibition of cutaneous flares occurred rapidly and remained high (70–90%).

More recently, the anti-inflammatory/anti-allergic effects of rupatadine have been demonstrated in human mast cells triggered by allergic, immune and neuropeptide stimuli. Rupatadine at concentrations of 10–50 μ M inhibited the release of

interleukin (IL)-6 from human leukaemic mast cells stimulated by IL-1; inhibited the release of IL-8, vascular endothelial growth factor and histamine from human laboratory of allergic disease 2 (LAD2) mast cells stimulated by substance P; and inhibited the release of IL-6, IL-8, IL-10, IL-13 and tumour necrosis factor (TNF) from human cord blood-derived mast cells stimulated by IgE/anti-IgE (40).

Anti-PAF properties

As reviewed previously, the anti-PAF activity of rupatadine was demonstrated *in vitro* and in animal and human models of allergic disease (22). Since then, additional evidence for a specific anti-PAF effect has come from studies of human mast cells and studies in human volunteers.

Alevizos et al. (41) demonstrated that rupatadine at concentrations of 2.5 and 25 $\mu\text{mol/l}$ inhibited the PAF-induced release of histamine, IL-8 and TNF in human cultured LAD2 mast cells; the lack of inhibition with diphenhydramine (25 $\mu\text{mol/l}$) suggested that the effect of rupatadine was PAF specific. Elsewhere, Muñoz-Cano et al. (42) showed that rupatadine 5, 10 and 25 μM inhibited PAF-induced LAD2 mast cell degranulation *in vitro* by 40%, 53% and 46%, respectively ($P < 0.01$), whereas desloratadine (1 and 10 μM) and levocetirizine (1, 10 and 100 μM) had either no or only mild inhibitory effects.

In a proof of concept study in human subjects, nasal provocation with PAF in nonatopic healthy volunteers and asymptomatic patients with SAR increased the intensity of nasal symptoms (congestion, rhinorrhoea, sneezing, itching) and reduced nasal volume. Maximum symptomatology occurred at 2 h postchallenge, and the dominant symptom was nasal congestion (16). In the second phase of this study, rupatadine 10 mg and levocetirizine 5 mg both showed a trend compared with placebo towards reducing PAF-induced total 4 symptoms scores (T4SS) in SAR patients, but not in healthy volunteers. Rupatadine, but not levocetirizine, produced a significant 54% reduction compared with placebo ($P < 0.05$) in the area under the curve for T4SS induced by PAF challenge (Fig. 4) (17).

In human volunteers, a single dose of rupatadine 40 mg (four times the recommended dose) inhibited dermal flares induced by intradermal injection of PAF and histamine. The effects of rupatadine were significant within 2 h, maximal at 6 h and remained statistically significant at 72 h. The anti-PAF activity of rupatadine was confirmed by *ex vivo* inhibition of PAF-induced platelet aggregation (43).

Pharmacokinetic studies

The pharmacokinetic profile of rupatadine is well established. After administration of a single oral dose in adults, rupatadine is rapidly absorbed with a time to maximum concentration (T_{max}) of 0.75–1 h and a maximum concentration (C_{max}) of 2.3 ng/ml. The rapid absorption of rupatadine correlates with the onset of antihistaminic and anti-PAF activity as assessed by wheal and flare inhibition (22, 44–46).

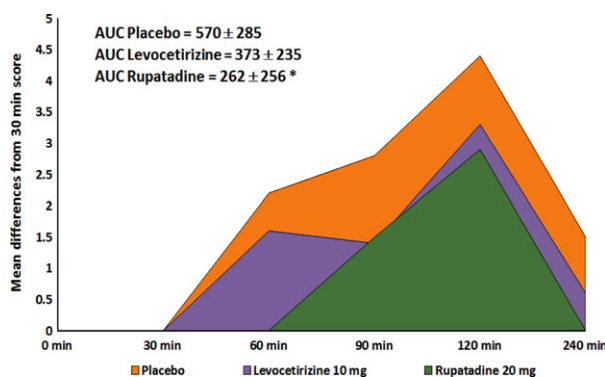


Figure 4 Area under the curve (AUC) for time course of nasal symptoms (adjusted for baseline values at 30 min) following nasal challenge with platelet-activating factor in patients with allergic rhinitis pretreated for 5 days with levocetirizine, rupatadine or placebo. * $P < 0.05$. Reproduced from (17) with permission.

A population pharmacokinetic/pharmacodynamic model has been described in which pharmacokinetic data for rupatadine and one of its active metabolites, desloratadine, were incorporated and correlated with antihistaminic effects reported in studies investigating histamine-induced wheal and flare reactions (47). The model showed good correlation between drug (concentration) and effect (inhibition of skin flare areas). Overall findings confirmed a significant and sustained antihistaminic effect over a 24-h dosing interval.

Rupatadine is extensively bound to plasma proteins, but is well distributed to other tissues and not retained in the circulating blood (44). Rupatadine undergoes extensive presystemic hepatic metabolism via oxidative processes and glucuronide conjugation (44). It is metabolized mainly by the cytochrome P450 enzyme 3A4 (CYP3A4), and some of its metabolites retain antihistaminic, but not anti-PAF, activity; the active metabolites contribute to its long duration of action (22). An elimination half-life ($t_{1/2}$) of 4.6 h after a single dose and 5.8 h after multiple once-daily administrations of rupatadine has been reported (46).

The pharmacokinetics of rupatadine after a single oral dose in children aged 2–11 years were best described by a bi-compartmental model with first-order absorption and elimination kinetics; rupatadine clearance increased with age (48, 49). In children, body weight-adjusted doses (2.5 mg if weight 10–25 kg or 5 mg if weight >25 kg) provided a similar exposure to rupatadine as that previously reported in efficacy and safety studies in adults and adolescents (aged 12 years and older) (48, 49). A population pharmacokinetic model developed using data from two paediatric pharmacokinetic studies provided similar steady state pharmacokinetic parameters in the 2- to 5-year and 6- to 11-year age groups, respectively: 1.96 and 2.54 ng/ml for C_{max} ; 10.4 and 10.7 ng·h/ml for AUC_{0-24} ; and 15.9 and 12.3 h for $t_{1/2}$ (49).

Drug–drug and other forms of interactions

Given its method of biotransformation, rupatadine has the potential to interact with drugs metabolized via oxidative

microsomal pathways, particularly those involving the CYP3A4 enzyme. In metabolic drug–drug interaction studies, systemic exposure to rupatadine 20 mg increased when it was coadministered with ketoconazole (but with no clinically relevant adverse events or changes in ECG parameters) and erythromycin (44, 50).

No interaction was observed when rupatadine was coadministered with fluoxetine (a substrate of CYP2D6) or ethanol (44). In studies performed in healthy volunteers, no clinically meaningful interaction was observed when rupatadine was coadministered with azithromycin [a gastrointestinal P-glycoprotein (Pgp) substrate] (51) and rupatadine did not potentiate the CNS depressant effects of lorazepam (52). Nevertheless, as with other antihistamines, interactions with CNS depressants cannot be excluded.

Based on the potential for drug–drug interactions, it is recommended that rupatadine be used with caution when coadministered with moderate CYP3A4 drug inhibitors and avoided with potent CYP3A4 drug inhibitors such as protease inhibitors, some macrolide antibiotics (e.g. clarithromycin) and some azole antifungals (e.g. ketoconazole). In the case of drugs metabolized mainly by CYP2D6 or substrates of the gastrointestinal Pgp transporter, no dosage adjustment should be necessary.

Other forms of interaction

Although the bioavailability of a single 20 mg dose of rupatadine was increased by about 30% under fed *vs* fasting conditions in healthy volunteers, there was no change in C_{max} (53), and rupatadine can therefore be administered either with or without food (54). Concomitant administration of grapefruit juice increased by 3.5-fold the systemic exposure of rupatadine and therefore should not be taken simultaneously (54).

After administration of alcohol, a 10 mg dose of rupatadine produced marginal effects in some psychomotor performance tests, which were not significantly different from those induced by intake of alcohol alone (44).

Clinical efficacy of rupatadine

In our previous review, we evaluated the efficacy of once-daily oral rupatadine in the management of allergic rhinitis and urticaria in adults and adolescents (22). The majority of studies reviewed were still using older classification systems to describe allergic disease. In the years since the review was published, many research groups have adopted the classification systems outlined in the Allergic Rhinitis and its Impact on Asthma (ARIA) and European Academy of Allergy and Clinical Immunology (EAACI)/Global Allergy and Asthma European Network (GA²LEN)/European Dermatology Forum (EDF)/World Allergy Organization (WAO) management guidelines (9, 15). These newer models of disease classification have been instrumental in the ongoing clinical development of rupatadine.

In this review, some previous pivotal data are revisited to provide an overall perspective of the clinical efficacy and safety of rupatadine. To maintain consistency with the

published literature, the classical terminology has been retained when discussing these studies. The overview of pivotal data is augmented by more recent studies of rupatadine in which the newer classification systems for allergic rhinitis and urticaria were used.

Rupatadine tablet formulation is indicated for symptomatic treatment of allergic rhinitis and urticaria in adults and adolescents ≥ 12 years; the recommended dose is 10 mg once daily (54). Rupatadine 1 mg/ml oral solution is approved for treatment of allergic rhinitis and urticaria in children aged 2–11 years (55).

Rupatadine in allergic rhinitis

Update and new evidence

In recognizing that the terms SAR and perennial allergic rhinitis (PAR) did not adequately reflect the presentation and clinical course of the disease, a new classification system for allergic rhinitis was developed based on symptom duration and disease severity (9, 56). The new system was designed to facilitate selection of best treatment options according to symptomatology rather than disease nomenclature (20).

Current ARIA guidelines recommend that second-generation oral or intranasal H₁-antihistamines be used for treatment of allergic rhinitis and conjunctivitis in adults and children across the entire spectrum of disease duration (intermittent to persistent) and disease severity (mild to severe) (9, 21). Other properties that should be met by oral H₁-antihistamines used in allergic rhinitis include, among others, additive anti-allergic/anti-inflammatory activities, rapid onset of action, long duration of action and no evidence of tachyphylaxis (9, 56). Rupatadine is a once-daily, long-acting, selective H₁-antihistamine with additive anti-PAF and anti-inflammatory activities, a good safety profile and no arrhythmogenic effects (22). As such, rupatadine fulfils ARIA criteria for use in the treatment of allergic rhinitis (20).

Meta-analysis

A systematic review/meta-analysis examined the efficacy of rupatadine in allergic rhinitis by pooling data on symptom reduction from ten randomized, double-blind, placebo-controlled studies involving a total of 2573 patients (57). Across studies, rupatadine performed significantly better than placebo in reducing rhinorrhoea, sneezing, nasal itching, nasal obstruction, and itchy and watery eyes (Table 2). The benefits observed with rupatadine on instantaneous and reflective evaluations were indicative of its rapid onset of action and long-lasting activity, respectively, with once-daily dosing. The meta-analytic approach provided a robust level of evidence Ia with recommendation A for use of rupatadine in allergic rhinoconjunctivitis.

Patients with SAR or PAR

In well-controlled comparative studies involving other H₁-antihistamines, rupatadine was shown to be at least as effective as cetirizine, desloratadine, ebastine and loratadine in relieving nasal and ocular symptoms in patients with SAR or

Table 2 Effect sizes for rupatadine vs placebo on reduction of allergic symptoms. Systematic review of 10 randomized, double-blind, placebo-controlled studies of rupatadine in allergic rhinitis involving 2573 patients. Reproduced from (57) with permission

Assessment	Standardized mean difference (95% CI)	P-value
Overall allergy symptoms score		
Reflective	−0.37 (−0.46, −0.27)	<0.00001
Instantaneous	−0.41 (−0.71, −0.11)	0.007
Nasal symptoms score		
Reflective	−0.36 (−0.48, −0.25)	<0.00001
Instantaneous	−0.39 (−0.61, −0.17)	0.0004
Individual nasal and ocular symptoms score (reflective)		
Rhinorrhoea	−0.30 (−0.41, −0.19)	<0.00001
Sneezing	−0.39 (−0.52, −0.26)	<0.00001
Nasal obstruction	−0.25 (−0.37, −0.13)	<0.0001
Nasal itching	−0.21 (−0.33, −0.10)	0.0003
Itchy eyes	−0.29 (−0.45, −0.14)	0.0001
Watery eyes	−0.25 (−0.45, −0.06)	0.01

PAR (50, 58–65). Study design details and main outcomes of these older pivotal clinical trials are summarized in Table 3 and augmented by the newer data. A more recent study comparing rupatadine and levocetirizine in patients with SAR included laboratory investigations among the main efficacy parameters (61) (Table 3). Sixty patients in total were randomized to either treatment. Compared with levocetirizine, rupatadine produced significantly greater reductions from baseline in the total nasal symptoms score (TNSS; $P < 0.001$) and serum IgE level ($P = 0.004$). Although both H_1 -antihistamines significantly reduced differential ($P = 0.01$) and absolute ($P = 0.009$) eosinophil counts from baseline, rupatadine was superior to levocetirizine in both instances.

Patients with PER

Rupatadine has been investigated in patients with persistent allergic rhinitis (PER) according to the ARIA classification system (Table 3).

An open, multicentre 2-week trial from Brazil involving 167 patients with moderate-to-severe PER provided initial evidence that rupatadine 10 mg once daily produced significant symptomatic relief of rhinorrhoea, nasal itching, sneezing, nasal congestion and total nasal symptoms on days 7 and 14 of treatment (66). Symptom severity as assessed by patients was significantly reduced by rupatadine from days 1 to 2 onwards indicating a rapid onset of effect.

Larger well-designed clinical studies of longer duration have since confirmed that rupatadine 10 mg in adults (67) and rupatadine 1 mg/ml oral solution in children (68) provides relevant symptomatic relief of PER. The multicentre, double-blind, placebo-controlled clinical trial of Fantin et al. (67) compared rupatadine 10 mg once daily with cetirizine 10 mg once daily in 543 patients with moderate-to-severe PER. After 12 weeks' treatment, the reduction from baseline in the instantaneous 6 total symptoms score (iTSS) was significantly greater with rupatadine compared with placebo (48% vs 39%; $P = 0.008$), whereas the 45% reduction

achieved with cetirizine was not statistically significant vs placebo. The mean change from baseline in the instantaneous TNSS, including nasal blockage, was significantly better with rupatadine 10 mg compared with placebo throughout the 12-week treatment period. Onset of action was within the first 24 h for both rupatadine ($P = 0.013$ vs placebo) and cetirizine ($P = 0.015$ vs placebo).

The efficacy and safety of rupatadine 1 mg/ml oral solution were evaluated in a multicentre, randomized, placebo-controlled, double-blind trial involving 360 children aged 6–11 years with PER (68). A main criterion for inclusion in the study was highly symptomatic disease defined as a total 4 symptoms score (T4SS) ≥ 24 on 4 days throughout the screening period. Rupatadine dosages were 2.5 mg/day in children weighing <25 kg and 5 mg/day in children weighing ≥ 25 kg. Despite a marked placebo effect, rupatadine produced significant improvement in T4SS reduction (including nasal congestion) after 28 days ($P = 0.018$) (primary outcome variable) and 42 days ($P < 0.05$) of treatment (Fig. 5). Rupatadine was effective as quickly as 12 h after the first dose, and efficacy was maintained throughout the 6-week treatment period.

The study of rupatadine in children with PER represents first clinical evidence in the paediatric population and demonstrated that long-term therapy provided a greater benefit, in terms of decreased disease burden and QoL (see Effect of rupatadine on patients' well-being and QoL), compared with placebo (68). In the same manner, adult patients with PER receiving 12-week continuous treatment with rupatadine attained better symptom control (67). Together, the results suggest that the PER patient population is likely to benefit from prolonged treatment.

Nasal challenge studies

Two well-controlled crossover nasal challenge studies using objective measures to assess changes in disease severity/symp-

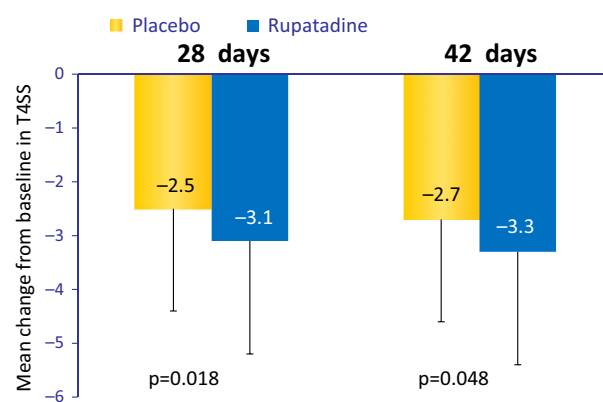


Figure 5 Change from baseline in total 4 symptoms scores (T4SS) after 28 and 42 days of treatment with rupatadine 1 mg/ml oral solution or placebo in a multicentre, randomized, double-blind study involving 360 children aged 6–11 years with highly symptomatic persistent allergic rhinitis: intention-to-treat analysis. Adapted from (68).

Table 3 Summary of clinical trials of rupatadine (RUP) in patients with allergic rhinitis

References	Study design	Treatment	No. of patients	Age (years)	Duration (weeks)	Main outcomes
Seasonal allergic rhinitis						
Izquierdo et al. (2003) (50)	m, r, db, pg	RUP 10 mg od RUP 20 mg od LOR 10 mg od	331 in total	≥12	2	RUP 10 mg, RUP 20 mg and LOR 10 mg produced similar improvement in mDTSS Individual symptom scores were similar for all three treatments although generally better for RUP 20 mg, with the difference occasionally reaching statistical significance
Martínez-Cócerca et al. (2005) (58)	m, r, db, pg	RUP 10 mg od CET 10 mg od	124 117	≥12	2	mDTSS was significantly reduced to 0.7 in both the RUP 10 mg and CET 10 mg groups at the end of treatment At 7 days, the investigator global assessment of efficacy (93% vs 84%; 0.022) and absent or mild runny nose (81% vs 69%; $P = 0.029$) both favoured RUP suggesting a faster onset of action
Guadaño et al. (2004) (59)	m, r, db, pg, pc	PLC RUP 10 mg od EBA 10 mg od	81 79 83	≥12	2	mDTSS was reduced by a greater extent with RUP 10 mg (33%) than PLC (13%; $P < 0.005$) and EBA 10 mg (22%; NS) RUP 10 mg produced a greater improvement in individual symptoms (e.g. sneezing, nasal itching and watery eyes) than EBA 10 mg
Saint-Martin et al. (2004) (60)	m, r, db, pg	RUP 10 mg od RUP 20 mg od LOR 10 mg od	112 111 116	≥12	2	mDTSS was significantly ($P = 0.03$) lower in groups treated with RUP 10 mg (0.85) and RUP 20 mg (0.80) compared with LOR 10 mg (0.92) in the per-protocol analysis; the difference did not reach statistical significance in the intention-to-treat analysis
Maiti et al. (2010) (61)	s, r, o, pg	RUP 10 mg od LEV 10 mg od	60 in total	≥12	2	RUP produced a significantly greater reduction than LEV in TNSS ($P < 0.001$) and serum IgE level ($P = 0.004$) Differential ($P = 0.01$) and absolute eosinophil ($P = 0.009$) counts were significantly lowered with both RUP and LEV, but RUP was superior to LEV in both instances
Lukat et al. (2013) (62)	m, r, db, pg, pc	PLC RUP 10 mg od DES 5 mg od	122 117 117	≥12	4	Mean change of T7SS over the 4-week treatment period was significantly reduced in the RUP (−46%, $P = 0.03$) and DES (−49%, $P = 0.01$) groups, compared with PLC. Likewise, RUP and DES were comparable and significantly superior to PLC for all secondary endpoints, including nasal and conjunctival symptoms

Table 3 (Continued)

References	Study design	Treatment	No. of patients	Age (years)	Duration (weeks)	Main outcomes
Perennial allergic rhinitis						
Marmouz et al. (2011) (63)	m, r, db, pg, pc	PLC	70	≥18	4	All active groups were significantly more effective than PLC in improving morning and evening evaluations of 5TSS ($P < 0.001$) and 4NTSS ($P < 0.001$) at 2 or 4 weeks. At morning evaluation, there was a significant reduction from baseline for 5TSS with RUP 10 mg (−37%, $P < 0.01$) and RUP 20 mg (−46%, $P < 0.01$) compared with PLC. Similarly, 4NTSS was reduced significantly more with RUP 10 mg (−34%, $P < 0.05$) and RUP 20 mg (−41%, $P < 0.01$) compared with PLC. Reductions with CET were not significant compared with PLC. RUP 10 mg, RUP 20 mg and CET 10 mg significantly increased Pd_{max1} compared with PLC; RUP 10 mg had the greatest effect. Individual symptom scores during active treatment were superior to those recorded for PLC ($P < 0.001$).
		RUP 10 mg od	65			
		RUP 20 mg od	68			
		CET 10 mg od	66			
Molina et al. (2010) (64)	m, r, db, pg, pc	PLC	73	≥12	4	Pd_{max1} was nonsignificantly lower for RUP 10 mg (49%) and EBA 10 mg (51%) than for PLC (42%) at the end of the study period. Both 5TSS ($P = 0.019$) and 4TNSS ($P = 0.025$) were significantly improved for RUP 10 mg users compared with PLC.
		RUP 10 mg od	71			
		EBA 10 mg od	79			
Kowalski et al. (2009) (65)	m, r, db, pg, pc	PLC	69	≥12	4	RUP 10 mg (49%), RUP 20 mg (50%) and LOR 10 mg (49%) increased Pd_{max1} to a greater extent than PLC (34%); only the increase with RUP 20 mg reached statistical significance. All active treatments significantly reduced the total symptoms score ($P < 0.01$) and nasal symptoms score compared with PLC.
		RUP 10 mg od	73			
		RUP 20 mg od	71			
		LOR 10 mg od	70			
Persistent allergic rhinitis according to the ARIA classification						
Mion et al. (2007) (66)	m, o	RUP 10 mg od	167	≥12	2	RUP 10 mg significantly ($P < 0.001$) reduced total nasal symptoms and individual symptoms of rhinorrhoea, nasal itching, sneezing and nasal congestion. Positive effects usually commenced on day 1 or day 2 of treatment.
Fantin et al. (2008) (67)	m, r, db, pg, pc	PLC	185	≥12	12	At 12 weeks, RUP 10 mg significantly reduced baseline i6TSS compared with PLC (48% vs 39%; $P = 0.008$). The difference between CET and PLC was not statistically significant.
		RUP 10 mg od	175			
		CET 10 mg od	183			

Table 3 (Continued)

References	Study design	Treatment	No. of patients	Age (years)	Duration (weeks)	Main outcomes
Potter et al. (2013) (68)	m, r, db, pc	PLC RUP 1 mg/ml (2.5 mg if <25 kg, 5 mg if ≥25 kg)	180 180	6–11	6	RUP and CET were both superior to PLC in improving secondary end points such as 4- and 8-week TNSS, sneezing and nasal pruritus. RUP also improved nasal blockage Onset of action for RUP and CET was within 24 h ($P = 0.013$ and $P = 0.015$, respectively, vs PLC) RUP significantly reduced T4SS from baseline at 4 weeks (–3.1 vs –2.5; $P = 0.018$) and 6 weeks (–3.3 vs –2.7; $P = 0.048$) compared with PLC

4NTSS, 4 nasal total symptoms score; 5TSS, 5 total symptoms score; ARIA, Allergic Rhinitis and its Impact on Asthma; CET, cetirizine; db, double blind; DES, desloratadine; EBA, ebastine; i6TSS, instantaneous 6 total symptoms score; LEV, levocetirizine; LOR, loratadine; m, multicenter; mDTSS, mean daily total symptoms score; NS, not significant; o, open; od, once daily; pc, placebo-controlled; Pd_{max1} , % of days in which the most severe symptom score was ≤ 1 ; pg, parallel group; PLC, placebo; r, randomized; RUP, rupatadine; s, single centre; T4SS, total 4 symptoms score; T7SS, total 7 symptoms score; TNSS, total nasal symptoms score.

tomatology in patients with SAR reported significant benefits for rupatadine compared with placebo (69, 70). In a group of 45 patients with SAR pretreated with rupatadine 10 mg once daily or placebo for 8 days before undergoing 6-h allergen exposure in a Vienna Challenge Chamber, rupatadine significantly reduced all nasal and ocular symptoms compared with placebo; the onset of action for reduction in TNSS was apparent from the first assessment 15 min postexposure (69). Valero et al. (70) used acoustic rhinometry to measure airway obstruction following nasal allergen challenge in 30 patients with SAR. At 2 h postchallenge, nasal obstruction was 47% lower following pretreatment with rupatadine 10 mg once daily for 3 days compared with placebo (9.8% vs 18.6%; $P < 0.05$).

A prospective open-label study used rhinomanometry to evaluate nasal symptoms, nasal airflow and nasal mediators in patients with PER ($n = 20$) treated with rupatadine 10 mg/day for 3 weeks (71). Compared with the pretreatment assessment, rupatadine produced significant relief of ocular ($P = 0.0004$) and nasal ($P = 0.005$) symptoms, including nasal obstruction ($P = 0.0015$), and significantly increased nasal airflow ($P = 0.0025$). A significant decrease in eosinophil cationic protein and tryptase was also measured with rupatadine.

In a proof of concept human model, nasal symptoms induced by PAF challenge were investigated in studies conducted in nonatopic healthy volunteers and asymptomatic SAR patients (outside of pollen season) (16, 17). In the first of these studies, nasal challenge with PAF significantly increased individual and total nasal symptoms scores in both sets of subjects, with no differences in response noted between the two groups. Nasal obstruction was the most relevant and long-lasting nasal symptom observed after PAF challenge (16). In the second study of this series, subjects were pretreated in crossover fashion with rupatadine 20 mg, levocetirizine 10 mg or placebo once daily for 5 days prior to PAF nasal challenge (17). In SAR patients, but not in

healthy volunteers, rupatadine demonstrated a more evident trend than levocetirizine towards decreasing PAF-induced nasal symptoms immediately following a repeated PAF challenge over 60 min. Evaluation of the overall time course of symptoms confirmed that rupatadine, but not levocetirizine, produced a significant reduction ($P < 0.05$) in total nasal symptoms compared to placebo.

Conclusions

A meta-analysis of randomized, double-blind, placebo-controlled studies of rupatadine confirmed that rupatadine was significantly superior to placebo at relieving rhinoconjunctivitis symptoms in adults/adolescents/children >6 years. Rupatadine had a rapid onset of action and long-lasting efficacy with once-daily dosing. The meta-analysis provided level of evidence Ia with recommendation A for use of rupatadine in allergic rhinoconjunctivitis.

In comparative clinical trials, rupatadine 10 mg was at least as effective as desloratadine, cetirizine, loratadine and ebastine at reducing allergic symptoms in adult/adolescent patients with SAR or PAR. Rupatadine was superior to levocetirizine in reducing nasal symptoms.

Rupatadine, and not cetirizine, was significantly more effective than placebo after 12 weeks of treatment in adults with PER. In children (6–11 years), rupatadine produced significantly better symptomatic relief of PER than placebo; this was the first study to provide clinical evidence for the efficacy of an H_1 -antihistamine in children with PER (ARIA classification).

In nasal provocation studies in patients with SAR or PER, rupatadine 10 mg once daily was significantly more effective than placebo in reducing ocular and nasal symptoms, including nasal obstruction.

Rupatadine significantly reduced overall nasal symptoms (including nasal congestion) induced by nasal PAF challenge

in SAR patients, suggesting that it provides additional anti-inflammatory effects relative to levocetirizine by means of its dual ability to interact with histamine H₁- and PAF receptors.

Rupatadine in urticaria

Update and new evidence

As per the established 4-year cycle, an updated version of the EAACI/GA²LEN/EDF/WAO urticaria guidelines was published in 2014 (15). Among the features of the updated guidelines relevant to this review is a new classification system that distinguishes between chronic spontaneous urticaria and inducible urticaria (i.e. urticaria subtypes with specific triggers) (72). Modern second-generation H₁-antihistamines continue to be recommended for pharmacological treatment of urticaria, and for the first time, avoidance of first-generation antihistamines and long-term corticosteroid treatment is specifically advised (15, 72). Established second-line treatment involves increasing the dosage of second-generation H₁-antihistamine up to fourfold (15, 72), underpinning the need for clinical evidence of the efficacy and safety of second-generation H₁-antihistamines at higher doses.

The main goal of therapy intended for symptomatic relief of urticaria is to reduce the effect of mast cell mediators such as histamine, PAF and others on target organs (15). In some cases, however, especially of chronic spontaneous urticaria and inducible urticarias, the involvement of other mast cell mediators such as PAF, leukotrienes and cytokines can lead to pronounced cellular infiltrate including basophils, lymphocytes and eosinophils (15, 73).

Chronic spontaneous urticaria

The efficacy of rupatadine in patients with moderate-to-severe urticaria was demonstrated initially in two well-designed, randomized, double-blind, placebo-controlled multicentre studies (74, 75) (Table 4). Although patients included in these studies were stated as having chronic idiopathic urticaria (CIU), the new term would be chronic spontaneous urticaria (15, 72).

In both studies, rupatadine at doses of 10 or 20 mg produced significant reductions from baseline in mean pruritus severity (MPS) scores at 4 weeks (primary outcome measure) compared with placebo. The beneficial effects of rupatadine were evident from week 1 and were maintained throughout the 4-week (74) and 6-week (75) trial periods. Rupatadine also produced improvements in secondary outcomes such as mean number of wheals and mean total symptoms scores compared with placebo. Other outcome measures such as overall clinical response and global CIU assessments (investigator and patient), interference with sleep and performance of daily activities, all improved with rupatadine 10 and 20 mg (74). Importantly, MPS scores were significantly improved within 24 h of taking a first dose of rupatadine 10 mg ($P = 0.013$ vs placebo) or 20 mg ($P < 0.0001$ vs placebo), indicating a fast onset of action (75).

A pooled analysis of these studies examined responder rates, defined as the percentage of patients with a reduction

of at least 50% or 75% in the mean urticaria activity score (UAS; mean pruritus score + number of wheals) from baseline to end of treatment (76). The analysis included 538 patients. After 4 weeks' treatment, improvement rates of $\geq 50\%$ and $\geq 75\%$ for mean UAS were significantly higher with both doses of rupatadine than with placebo ($P < 0.0001$) (Fig. 6). In contrast, only a few patients (13.9%) in the placebo group achieved $\geq 75\%$ reduction in symptoms. Moreover, responder rates for patients achieving $\geq 75\%$ reduction in symptoms were significantly higher with rupatadine 20 mg compared with rupatadine 10 mg (48.0% vs 34.8%; $P < 0.01$).

Some additional single-centre comparative studies of rupatadine in the treatment of urticaria have since been published (Table 4) (77–79). Although sample sizes were smaller than those in the placebo-controlled studies discussed above, the use of active comparators (cetirizine, desloratadine, levocetirizine) has broadened the evidence base for the efficacy of rupatadine in the treatment of chronic spontaneous urticaria in adults.

Rupatadine oral solution has been investigated in children aged 2–11 years with chronic spontaneous urticaria (80). In this multicentre, double-blind study, patients were randomly allocated to receive rupatadine 1 mg/ml, desloratadine 0.5 mg/ml (approved dose) or placebo at weight-based dosages (2.5 mg/day if >10 –25 kg; 5 mg/day if >25 kg). Treatment duration was 6 weeks, and 199 patients were included in the intention-to-treat analysis. The 7-day cumulative children-adapted UAS was significantly reduced from baseline with rupatadine and desloratadine compared with placebo (Fig. 7). This was accompanied by significantly greater reductions from baseline to 6 weeks in the mean wheals score (57% vs 49% vs 23%; $P < 0.001$ and $P = 0.003$ for rupatadine and desloratadine, respectively, vs placebo) and MPS score (57% vs 47% vs 33%; $P = 0.005$ and NS for rupatadine and desloratadine, respectively, vs placebo).

Acquired cold urticaria

Acquired cold urticaria is triggered by exposure to cold, although the critical temperature threshold for symptom development can vary widely among patients. While the exact pathogenesis of ACU is not yet clear, both histamine and PAF are known to contribute to symptom development (38).

Metz et al. (81) compared rupatadine with placebo in a randomized, double-blind, crossover study in patients with ACU. Under treatment with rupatadine 20 mg/day for 7 days, 11 of the 21 patients (52%) showed a complete response (no wheal development after 5-min ice cube exposure) compared with only three patients (14%) while under treatment with placebo. Initial critical temperature thresholds ranged from 4 to 27°C among patients and were significantly improved with rupatadine ($P = 0.0006$), but not placebo (Fig. 8). Significant reductions from baseline following cold challenge were observed with rupatadine, but not placebo, for symptoms such as wheal size ($P < 0.05$), pruritus ($P < 0.01$), burning ($P < 0.05$) and subjective complaints ($P < 0.05$). Improvements in critical temperature and critical

Table 4 Summary of clinical trials of rupatadine (RUP) in patients with chronic spontaneous urticaria

References	Study design	Treatment	No. of patients	Age (years)	Duration (week)	Main outcomes
Dubertret et al. (2007) (74)	m, r, db, pg, pc	PLC RUP 5 mg od RUP 10 mg od RUP 20 mg od	69 68 73 67	≥12	4	RUP 10 mg and RUP 20 mg significantly ($P < 0.05$) reduced pruritus severity from baseline to a greater extent than PLC (63% vs 72% vs 46%) There was a linear reduction in the mean number of wheals: 30%, 34%, 45% and 58% for PLC, RUP 5 mg, RUP 10 mg and RUP 20 mg, respectively RUP 10 mg and RUP 20 mg significantly ($P < 0.05$) improved mean TSS compared with PLC (55% vs 66% vs 39%) Patient and investigator global assessments of efficacy significantly favoured RUP 10 mg and RUP 20 mg
Giménez-Arnau et al. (2007) (75)	m, r, db, pg, pc	PLC RUP 10 mg od RUP 20 mg od	111 110 108	≥12	6	RUP 10 mg ($P < 0.05$) and RUP 20 mg ($P < 0.001$) significantly reduced pruritus severity (from baseline) to a greater extent than PLC (59% vs 66% vs 49%) RUP 10 mg and RUP 20 mg produced significant improvements in secondary outcomes such as mean TSS and mean number of wheals
Giménez-Arnau et al. (2009) (76)	m, r, db, pg, pc, pooled analysis	PLC RUP 10 mg od RUP 20 mg od	182 186 179	≥12	4	In the responder analysis, RUP 10 mg and RUP 20 mg were significantly superior to PLC (both $P < 0.0001$) for the percentage of patients achieving ≥50% or ≥75% improvement in the mean urticaria activity score (mean pruritus score + number of wheals) The percentage of patients with ≥75% symptom reduction was significantly higher with RUP 20 mg than RUP 10 mg (48.0% vs 34.8%; $P < 0.01$)
Dakhale et al. (2014) (77)	r, db, pg	RUP CET	70 in total	≥12	6	RUP significantly reduced mean number of wheals, size of wheals, and intensity of erythema from baseline to week 6 (all $P < 0.001$), and effects were significantly greater than with CET ($P < 0.05$)
Kolasani et al. (2013) (78)	s, r, o, pg	RUP 10 mg od DES 5 mg od	28 28	≥12	4	RUP 10 mg decreased TSS from baseline to a significantly greater extent than DES 5 mg (22.5% vs 10.8%; $P < 0.001$) Significant changes in favour of RUP 10 mg over DES 5 mg were observed for differential eosinophil count (1.48% vs 0.55%; $P = 0.019$); absolute eosinophil count (36.2% vs 15.0%; $P < 0.001$); and serum IgE level (13.3% vs 5.9%; $P = 0.004$)
Maiti et al. (2011) (79)	s, r, sb, pg	RUP LEV	35 35	≥12	4	RUP decreased TSS from baseline by 28% to day 28 ($P = 0.02$) This was accompanied by decreases of 28% in differential eosinophil count ($P = 0.027$), 36% in absolute eosinophil count ($P = 0.036$) and 15% in serum IgE ($P = 0.024$) with RUP
Potter et al. (2014) (80)	m, r, db, pg	PLC RUP 1 mg/ml DES 0.5 mg/ml (2.5 mg if <25 kg, 5 mg if ≥25 kg)	67 63 69	≥12	6	The 7-day cumulative children-adapted urticaria activity score (UAS7) was significantly reduced in the RUP group and DES group compared to PLC (see Fig. 7) The percentage change in pruritus intensity was reduced significantly only in the RUP group

CET, cetirizine; db, double blind; DES, desloratadine; LEV, levocetirizine; m, multicenter; od, once daily; o, open; pc, placebo-controlled; pg, parallel group; PLC, placebo; r, randomized; RUP, rupatadine; sb, single blind; s, single centre; TSS, total symptoms score.

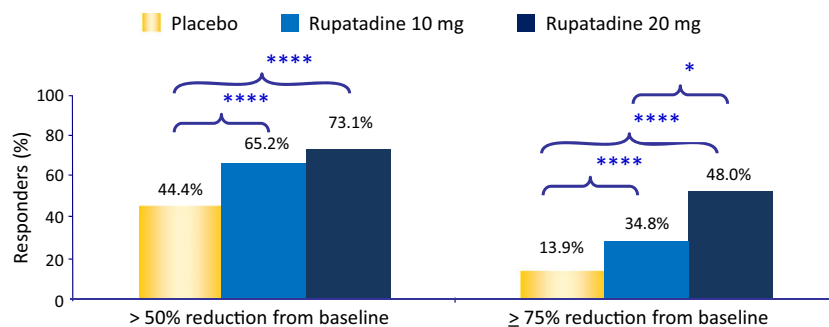


Figure 6 Responder rates (≥50% and ≥75% reduction from baseline in mean urticaria activity score) in patients with chronic urticaria ($n = 538$) treated with placebo, rupatadine 10 mg/day or rupatadine

20 mg/day for 4 weeks in a pooled analysis of multicentre, randomized, double-blind studies. $*P < 0.05$; $****P < 0.0001$. Adapted from (76).

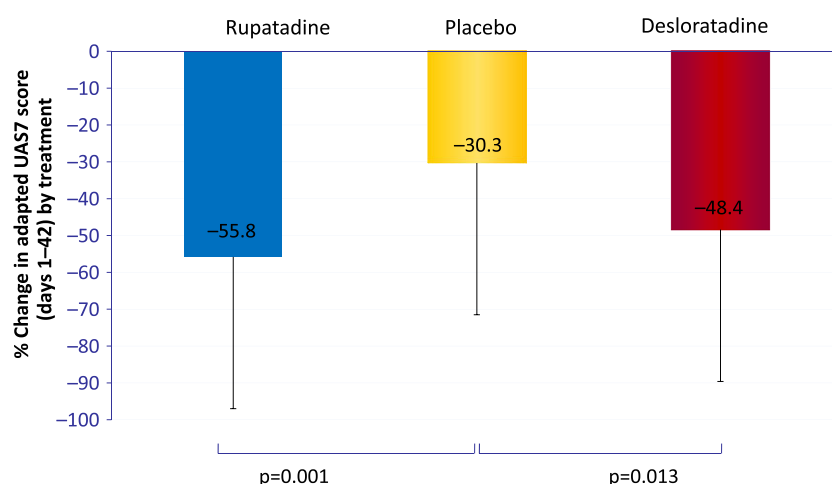


Figure 7 Percentage change from baseline in the 7-day cumulative children-adapted urticaria activity score (UAS7) after 6 weeks' treatment with rupatadine 1 mg/ml ($n = 63$), placebo ($n = 67$) or desloratadine 0.5 mg/ml ($n = 69$) in a multicentre, randomized, double-blind, parallel-group clinical trial in children aged 2–11 years with chronic spontaneous urticaria: intention-to-treat analysis (80).

time thresholds were also noted in a prospective observational study in which 19 adult patients with confirmed ACU were treated continuously with rupatadine 20 mg/day for 1 year (82). In most cases, improvements in threshold parameters were associated with clinical improvement.

Mosquito bite allergy

Based on observations that the itch and local wheal and flare reactions, which occur following intradermal injection of histamine and PAF, are identical to symptoms after a mosquito bite (1), a double-blind, placebo-controlled, crossover study was conducted comparing rupatadine 10 mg and placebo in mosquito-bite-sensitive adults (83). On the third day of each 4-day treatment period, 30 participants received two bites each from an *Aedes aegypti* mosquito on the forearm. At the time of assessment 15 min later, lesion size was 48% smaller under treatment with rupatadine than placebo (55 vs 106 mm²; $P = 0.0003$) and there was a 21% greater reduction in pruritus intensity on a visual analogue scale with rupatadine compared with placebo ($P = 0.019$), indicating a significant prophylactic effect.

Other skin diseases: cutaneous mastocytosis

Mastocytosis is a group of rare and heterogeneous disorders in children and adults characterized by pathological accumulation of mast cells in various organs, especially the skin (84). Clinical features include whealing, flushing, pruritus, abdominal pain, diarrhoea, hypotension, syncope and musculoskeletal pain; some patients may develop severe life-threatening allergic shock (84). Mastocytosis can substantially impair patients' QoL (85). Although a second-generation H₁-antihistamine is treatment of choice for cutaneous mastocytosis, no H₁-antihistamines are currently approved for this indication.

In the first randomized controlled trial of its kind to investigate a second-generation H₁-antihistamine in this indication, rupatadine 20 mg/day was compared with placebo in a 4-week crossover study involving 30 adult patients with either indolent systemic mastocytosis or cutaneous mastocytosis (85). Pruritus severity improved significantly under treatment with rupatadine vs placebo (30% reduction in visual analogue scale score; $P = 0.041$). Statistically significant reductions in favour of rupatadine were also observed for

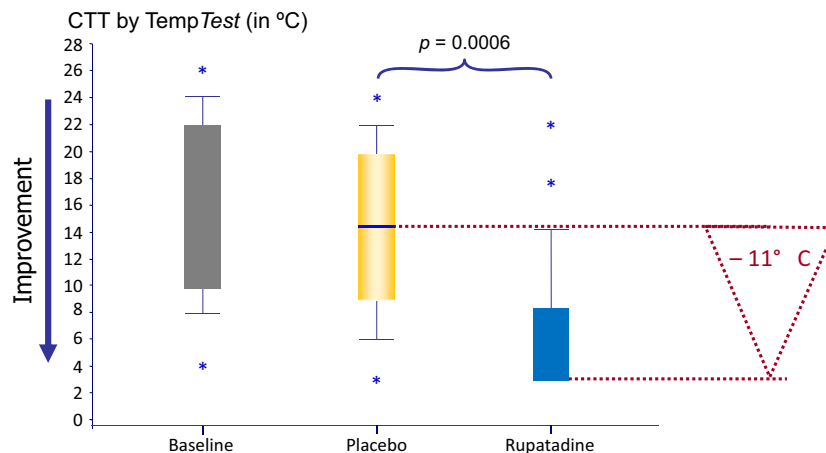


Figure 8 Critical temperature thresholds (CCTs) in °C by the TempTest 3.0 (Emosystems, Berlin, Germany) cold provocation device at baseline and after treatment with placebo or rupatadine 20 mg/day for 7 days in a crossover study of patients with acquired

cold urticaria ($n = 21$). Data points outside the 90th (upper whisker) and 10th (lower whisker) percentile ranges are represented with asterisks. Adapted from (81).

severity of itch, wheal and flare, flushing, tachycardia and headache (all $P < 0.05$ vs placebo), but not for gastrointestinal symptoms.

Conclusions

Clinical studies have demonstrated the efficacy of rupatadine in chronic spontaneous urticaria and other urticarial conditions and confirmed its rapid and sustained effect.

Significantly more patients with chronic spontaneous urticaria achieved $\geq 50\%$ or $\geq 75\%$ improvement in symptoms with rupatadine 10 or 20 mg compared with placebo. The 20 mg dose was significantly superior to the 10 mg dose at the $\geq 75\%$ improvement level, supporting guideline recommendations to use higher-than-standard doses of second-generation H_1 -antihistamines in the treatment of chronic spontaneous urticaria.

Active comparator studies showed greater improvements in urticarial symptoms with rupatadine compared with cetirizine, desloratadine and levocetirizine.

A multicentre, randomized, placebo-controlled, double-blind study demonstrated the efficacy of rupatadine oral solution for symptomatic relief of chronic spontaneous urticaria in children aged 2–11 years. In accordance with current guideline recommendations, rupatadine oral solution is an effective treatment for young children with chronic spontaneous urticaria.

Randomized, double-blind, placebo-controlled, crossover studies provided new evidence of the ability of rupatadine at dosages of 10 or 20 mg to provide relevant symptomatic relief of induced ACU and the whealing and pruritus associated with mosquito bite allergy.

First clinical evidence with rupatadine 20 mg has been reported in adult patients affected by cutaneous mastocytosis, possibly paving the way for further exploration of its use in this indication.

Effect of rupatadine on patients' well-being and QoL

In their severest forms, allergic disorders such as allergic rhinitis and urticaria can have a profoundly detrimental impact on many aspects of everyday life. Patients may be affected by poor sleep quality, emotional problems, impairment of physical and mental functioning, and disturbances in activities of daily living (86–88). A primary goal of treating patients with allergic rhinitis and urticaria is to improve their well-being and HRQoL (89).

Allergic rhinitis

In the past few years, several studies have assessed the effect of rupatadine on HRQoL in patients with allergic rhinitis. Specific and validated QoL instruments used in these studies include the following: the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) (61, 67, 90); ESPRINT-15 Questionnaire (EsQ-15) (91, 92); Mini-RQLQ (93); and Pediatric RQLQ (PRQLQ) (68).

As indicated by the study outcomes summarized in Table 5, rupatadine improved HRQoL in patients with allergic rhinitis. The positive impact of rupatadine on HRQoL was initially demonstrated in a double-blind study in patients with PER (67). Throughout the 12-week study period, rupatadine significantly improved the RQLQ dimensions of sleep, activities and nasal symptoms compared with placebo. Consistent with the significant reduction observed in PER symptoms (see Rupatadine in allergic rhinitis), improvement in all domains exceeded the predefined minimum clinically meaningful difference for reductions from baseline. In a 1-year follow-up to this pivotal study, significant ($P < 0.0001$) improvement from baseline in RQLQ total scores was maintained at 6 and 12 months, while moderate improvements were observed in the specific domains of nasal symptoms, practical problems and activities (90).

Table 5 Summary of rupatadine (RUP) studies evaluating quality of life

Reference	Study design	Treatment	No. and type of patients	Age	Duration (weeks)	Main outcomes
Allergic rhinitis						
Fantin et al. (2008) (67)	m, r, db, pg	PLC RUP 10 mg od CET 10 mg od	185, PER 175, PER 183, PER	≥12	12	RUP 10 mg and CET 10 mg significantly improved total RQLQ scores compared with PLC (both $P < 0.05$) RUP significantly improved domains of 'sleep' ($P < 0.05$), 'activities' ($P < 0.01$) and 'nasal symptoms' ($P < 0.01$) compared with PLC CET significantly improved domains of 'activities', and 'nasal' and 'eye' symptoms compared with PLC
Roger et al. (2006) (90)	o, p	RUP 10 mg od	324 adults with PER (120 for >6 months)	≥18	1 year	Significant improvement from baseline with RUP in overall RQLQ scores at 6 and 12 months ($P < 0.0001$) Moderate QoL improvements for patients in the domains of 'nasal symptoms', 'practical problems' and 'activities'
Valero et al. (2011) (92)	p, obs	RUP 10 mg od	360 adults (IAR and PER)	≥18	4	Significant decrease from baseline with RUP in EsQ-15 global score (3.0 vs 1.0; $P < 0.001$) (see Fig. 9A)
Eloy et al. (2012) (93)	p, obs	RUP 10 mg od	2838 adults (IAR and PER)	≥18	6	Significant decrease from baseline with RUP in Mini-RQLQ global score (2.77 vs 0.89; $P < 0.001$)
Potter et al. (2013) (68)	m, r, db	PLC RUP 1 mg/ml od	360 children with PER (6–11 years)	6–11	6	PRQLQ scores significantly in favour of RUP over PLC for all domains except 'other symptoms' (see Fig. 9B)
Maiti et al. (2010) (61)	r, o, pg	RUP 10 mg od LEV 10 mg od	60 patients with SAR	≥12	2	Significantly greater decrease from baseline in RQLQ scores with RUP vs LEV (18.1% vs 9.9%; $P = 0.02$)
Chronic spontaneous urticaria						
Giménez-Arnau et al. (2007) (75)	m, r, db, pg	PLC RUP 10 mg od RUP 20 mg od	111 110 108	12–65	6	RUP 20 mg significantly ($P < 0.005$) decreased DLQI from baseline by 26.6% after 4 weeks and 29.2% after 6 weeks, compared with reductions of 18.4% and 20.5% with PLC (see Fig. 10A)
Potter et al. (2014) (80)	r, db, m, pg	PLC RUP 1 mg/ml od DES 0.5 mg/ml od	67 63 69	2–11	6	Significant improvement in overall CDLQI scores for RUP ($P < 0.01$) and DES ($P < 0.05$) vs PLC (see Fig. 10B) Significant improvement for 'daily activities' with RUP vs PLC ($P < 0.05$)
Kolasani et al. (2013) (78)	r, o, pg	RUP 10 mg od DES 5 mg od	70 (aged ≥ 12 years)	12–60	4	Significantly greater decrease in total AEQLQ score with RUP vs DES (31.0% vs 17.7%; $P = 0.007$)
Maiti et al. (2011) (79)	r, sb, pg	RUP 10 mg od LEV 10 mg od	70 (aged ≥ 12 years)	12–60	4	Significantly greater decrease in total AEQLQ score with RUP vs LEV (27.3% vs 12.4%; $P = 0.006$)
Mastocytosis						
Siebenhaar et al. (2013) (85)	r, db, co	PLC RUP 20 mg od	30 adults	20–70	4	Significant improvement in ItchyQoL score under treatment with RUP vs PLC ($P = 0.004$)

AEQLQ, Aeriis Quality of Life Questionnaire; CDLQI, Children Dermatology Life Quality Index; CET, cetirizine; co, crossover; db, double blind; DES, desloratadine; DLQI, Dermatology Life Quality Index; EsQ-15, ESPRINT-15 Questionnaire; IAR, intermittent allergic rhinitis; ItchyQoL, pruritus-specific quality of life (QoL) instrument; LEV, levocetirizine; m, multicentre; Mini-RQLQ, Mini Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ); o, open; obs, observational; p, prospective; PER, persistent allergic rhinitis; PLC, placebo; pg, parallel group; PRQLQ, paediatric RQLQ; r, randomized; RUP, rupatadine; SAR, seasonal allergic rhinitis; sb, single blind.

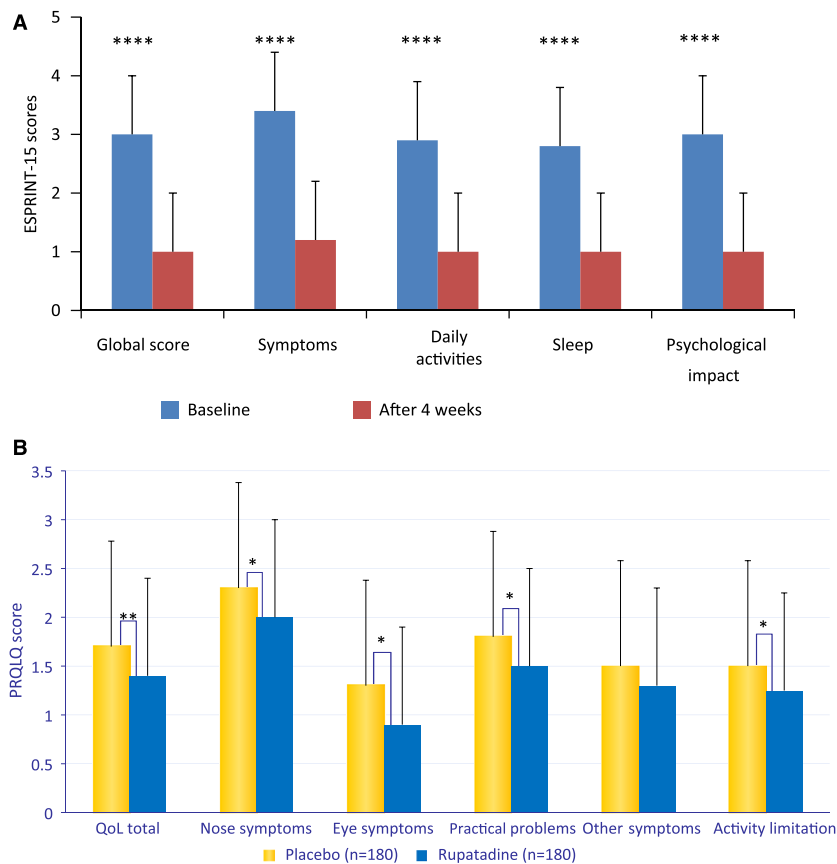


Figure 9 Effect of 4 weeks' treatment with rupatadine on ESPRINT-15 domain scores in adults with persistent allergic rhinitis ($n = 360$) (A); **** $P < 0.0001$ vs baseline. Adapted from (92). Effect of 4 weeks' treatment with rupatadine 1 mg/ml oral solution

or placebo on Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) scores in children with persistent allergic rhinitis: intention-to-treat analysis (B); * $P < 0.05$, ** $P < 0.01$ for rupatadine vs placebo. Adapted from (68).

In prospective observational studies conducted under actual clinical practice conditions involving adults with intermittent allergic rhinitis (IAR) or PER, global scores on the EsQ-15 and Mini-RQLQ, respectively, were significantly reduced from baseline as early as 4 weeks (92) and 6 weeks (93) after the start of treatment. Health-related QoL was one of the main outcome variables in the study of Valero et al. (92); after 4 weeks' treatment with rupatadine, scores for all EsQ-15 dimensions (global, symptoms, daily activities, sleep disturbances, psychological impact) were significantly ($P < 0.0001$) reduced from baseline values (Fig. 9A).

Improvements in HRQoL have also been documented for children with PER treated with rupatadine. In a randomized, double-blind study in children aged 6–11 years with PER (68), rupatadine 1 mg/ml oral solution had a consistently superior effect to placebo on most domains of the PRQLQ. Scores after 28 days of treatment were significantly in favour of rupatadine over placebo for total score, nose symptoms, eye symptoms, practical problems and activity limitations (Fig. 9B).

A single-centre comparative study of second-generation H_1 -antihistamines involving 60 patients with SAR reported a significantly greater decrease from baseline in RQLQ scores

with rupatadine compared with levocetirizine (−18.1% vs −9.9%; $P = 0.02$) (61).

Urticaria

Health-related QoL benefits with rupatadine have also been reported in studies of patients with urticaria (Table 5). In a 6-week study involving 334 patients with moderate-to-severe CIU, rupatadine 20 mg significantly decreased Dermatology Life Quality Index (DLQI) scores from baseline by 26.6% at 4 weeks and 29.2% at 6 weeks (both $P < 0.005$), compared with reductions of 18.4% and 20.5%, respectively, in placebo-treated patients (Fig. 10A) (75). Rupatadine 20 mg improved all DLQI subdomain scores to a greater extent than placebo over the course of the study, with differences being significant ($P < 0.05$ for all scores), except for 'Work and School' and 'Treatment' subdomain scores after 4 weeks and 'Personal Relationships' subdomain scores after 6 weeks.

A study performed in children aged 2–11 years with chronic spontaneous urticaria ($n = 199$) used the Children Dermatology Life Quality Index (CDLQI) to evaluate the treatment effect of rupatadine oral solution on HRQoL (80). After 6 weeks' treatment, the absolute change from baseline

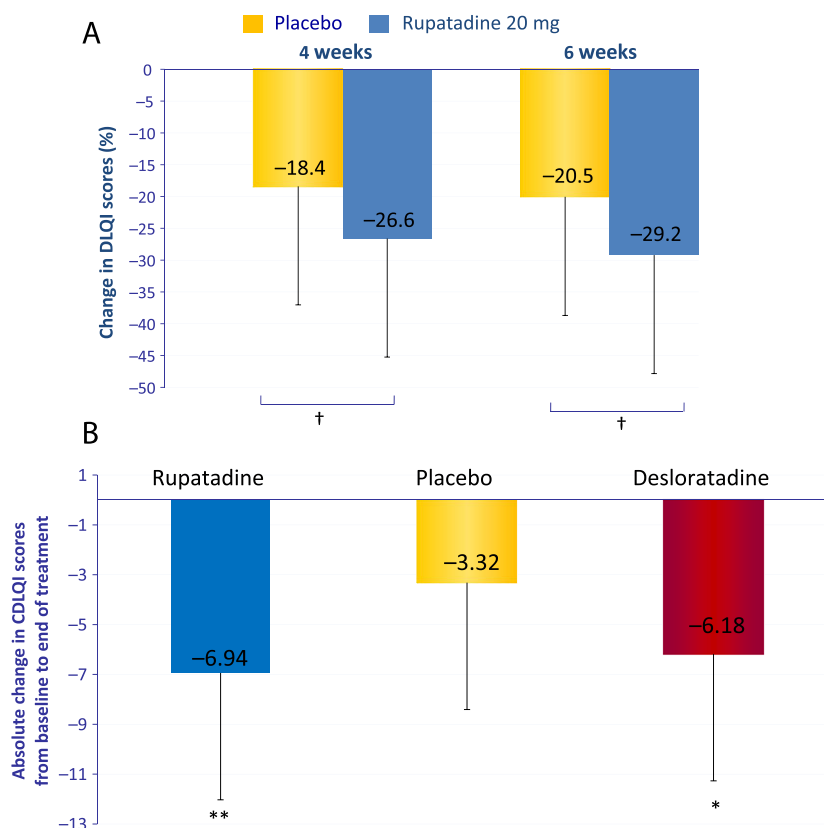


Figure 10 Effect of treatment for 4 or 6 weeks with rupatadine 20 mg/day or placebo on the change from baseline in Dermatology Life Quality Index (DLQI) scores in adults with chronic idiopathic urticaria (A); † $P < 0.005$. Adapted from (75). Effect of 6 weeks'

treatment with rupatadine 1 mg/ml oral solution or placebo on Children's Dermatology Life Quality Index (CDLQI) scores in children with chronic spontaneous urticaria (B); * $P < 0.05$ for desloratadine vs placebo, ** $P < 0.01$ for rupatadine vs placebo. Adapted from (80).

in the overall CDLQI score was significantly ($P < 0.01$) greater with rupatadine compared to placebo (Fig. 10B). Significant improvement over placebo was also noted in the individual subdomain of 'Daily Activities' ($P < 0.05$).

In smaller single-centre studies in patients with chronic urticaria, rupatadine was significantly superior to desloratadine (78) and levocetirizine (79) based on changes from baseline in Aeriis Quality of Life Questionnaire (AEQLQ) total scores after 4 weeks of treatment.

In the first controlled clinical trial to assess a second-generation H_1 -antihistamine in patients with mastocytosis, rupatadine 20 mg/day for 4 weeks was shown to have a beneficial effect on patients' QoL (85). The mean ItchyQoL total score improved by 16.1% in the rupatadine treatment phase compared with placebo phase ($P = 0.004$). Significant between-treatment differences were apparent in the individual domains of symptoms, function and emotions.

Conclusions

Rupatadine improved QoL in adults, adolescents and children with allergic rhinitis.

QoL improvements were maintained during long-term (1-year) treatment with rupatadine in patients with PER.

In the first application of the EsQ-15 instrument in a cohort of patients with IAR or PER, treatment with rupatadine improved patients' perception of their HRQoL.

Rupatadine had superior effects on HRQoL compared with other second-generation H_1 -antihistamines (desloratadine, levocetirizine) in adult patients with chronic urticaria.

Rupatadine was significantly superior to placebo in improving QoL in young children (2–11 years) with chronic spontaneous urticaria.

Rupatadine had a significant beneficial effect on QoL in adult patients with mastocytosis.

Effectiveness of rupatadine in everyday practice

Clinical trials are essential to establish the efficacy of an intervention, but the strict controls and eligibility criteria are not always reflective of routine clinical practice. The effectiveness of rupatadine under everyday conditions has been evaluated in multicentre, prospective, observational studies conducted in adult patients with IAR or PER (92, 93).

The study of Valero et al. (92) in Spain involved allergologists and ENT specialists, and that of Eloy et al. (93) in Belgium involved GPs and ENT specialists. All patients in the Belgian cohort had moderate–severe disease [total 5 symptoms score (T5SS) ≥ 6], and nearly all patients in the Spanish cohort had moderate (52.5%) or severe (45.0%) disease as per a modified ARIA classification system (m-ARIA) that differentiates between moderate and severe rhinitis (91). In both studies, treatment with rupatadine 10 mg/day produced significant relief of allergic symptoms and reduced disease severity (Table 6). Across the entire population in the Spanish study ($n = 360$), the proportion of patients with ‘severe’ allergic rhinitis (m-ARIA score) decreased significantly from baseline to the end of 4 weeks’ treatment with rupatadine (45.0% vs 3.6%; $P < 0.0001$) (92). In the Belgian study, rupatadine 10 mg/day for 6 weeks significantly reduced visual analogue scale scores for disease severity (7.0 vs 2.8, $P < 0.001$) and 83% of patients ($n = 2768$) rated their therapeutic response to rupatadine as either a ‘complete’ or a ‘strong’ relief of symptoms (93).

Conclusions

Rupatadine for 4 or 6 weeks significantly reduced the proportion of patients with moderate–severe disease and increased the proportion of patients with mild disease in patients with IAR or PER treated under everyday practice conditions.

Nasal symptoms were improved significantly during rupatadine treatment in patients with IAR and PER in real-life situations.

Observational studies in everyday practice provide a valuable insight into symptom improvement and changes in disease severity (as per the ARIA classification system) during treatment with rupatadine.

Safety and tolerability of rupatadine

To date, more than 4000 patients (adults and children aged 2–11 years) and healthy volunteers have been exposed to rupatadine in clinical studies. Subjects received rupatadine at doses ranging from 2 to 100 mg, as either single or repeated doses, with periods of exposure ranging from <1 week to more than 1 year. A total of 2141 adult subjects were exposed to the approved dose of 10 mg of rupatadine and 1104 subjects to the 20 mg dosage; the remaining 600 subjects were exposed to doses ranging from 40 to 100 mg. The paediatric studies involved a total of 306 patients treated with rupatadine oral solution at a dosage of 2.5 or 5 mg/day.

A previous review of the literature reported a good tolerability and safety profile for rupatadine (22). The incidence of treatment-related adverse events was low and as expected among patients exposed to rupatadine in clinical trials (Table 7) (44). No new safety signals have been identified in clinical trials published more recently. Indeed, evidence from a large meta-analysis of rupatadine studies in allergic rhinitis, from comparative clinical trials of rupatadine in allergic rhinitis and urticaria including studies in children and from longer term safety trials, has reaffirmed the excellent safety profile of rupatadine.

A systematic review of double-blind placebo-controlled studies of rupatadine in allergic rhinitis examined safety data for 1136 patients available from six of the 10 studies included in the analysis (57). The incidence of total adverse events did not differ substantially between rupatadine and placebo [odds ratio (OR) 1.23, 95% CI: 0.95–1.59; $P = 0.12$] (Fig. 11) nor among the rupatadine 10 mg, rupatadine 20 mg and placebo groups. The most frequently reported adverse event for all three treatment options was a low rate of somnolence, as is commonly observed in studies of other second-generation H₁-antihistamines.

Table 6 Prospective, observational studies with rupatadine in everyday clinical practice

References	Study design	Treatment	No of patients (% IAR/PER)	Age (years)	Duration (weeks)	Results (baseline vs end of treatment)
Valero et al. (2011) Spain (92)	p, obs	RUP 10 mg	360 (42.5/57.5)	≥ 18	4	Decrease in TNSS (8.2 vs 3.1; $P < 0.0001$) Increase in proportion of patients with mild disease ($P < 0.0001$): IAR 3.9% vs 62.7%; PER 1.4% vs 59.5% Decrease in proportion of patients with moderate disease ($P < 0.0001$): IAR 64.7% vs 31.4%; PER 43.5% vs 39.1% Decrease in proportion of patients with severe disease ($P < 0.0001$): IAR 31.4% vs 5.9%; PER 55.1% vs 1.9%
Eloy et al. (2012) Belgium (93)	p, obs	RUP 10 mg	2838 (44.7/55.3)	≥ 18	6	Decrease in T5SS (9.5 vs 3.3; $P < 0.001$) Increase in proportion of patients with mild disease (23.5% vs 79.5%; $P < 0.001$) Decrease in proportion of patients with moderate–severe disease (76.5% vs 20.5%; $P < 0.001$)

IAR, intermittent allergic rhinitis; obs, observational; p, prospective; PER, persistent allergic rhinitis; RUP, rupatadine; T5SS, total 5 symptoms score; TNSS, total nasal symptoms score.

Table 7 Incidence of treatment-related adverse events in clinical studies of patients treated once daily with rupatadine 10 mg or placebo. Adapted from (44)

Adverse event*	Rupatadine-treated patients <i>n</i> = 2025 (%)	Placebo-treated patients <i>n</i> = 1315 (%)
Somnolence	9.5	3.4
Headache	6.8	5.6
Fatigue	3.2	2.0
Asthenia	1.5	0
Dry mouth	1.2	0
Dizziness	1.0	0

*Possibly, probably or definitely related to study medication.

Weight-based dosages of rupatadine 1 mg/ml oral solution were not associated with any serious adverse events or clinically important adverse events in children as young as 2 years of age (68, 80). The overall incidence of adverse effects considered to be possibly, probably or definitely related to study medication was low and broadly similar to that reported with placebo (Table 8).

In a recent single-centre study in adults with CIU, Kolasani and co-workers reported an overall incidence of adverse events of 21.4% for desloratadine and 10.9% for rupatadine; both H₁-antihistamines were considered to be well tolerated with no significant changes in vital signs or laboratory parameters (78). In a similarly designed study in patients with SAR, a lower overall incidence of adverse events was observed with rupatadine compared with levocetirizine (61).

Longer term evaluations have confirmed that rupatadine is well tolerated and demonstrates no unexpected adverse events. Headache, somnolence and rhinopharyngitis were the most frequent adverse events reported in a 12-week placebo-controlled comparative study in 543 patients with moderate-to-severe PER, with no significant differences in incidence detected between treatments and placebo (67). In a 1-year, multicentre open-label study designed specifically to evaluate the safety of rupatadine, 120 of 324 eligible patients required treatment for >6 months and were followed to the end of 12 months (94). During the 1- to 6-month and 1- to 12-

Table 8 Most common adverse events reported in clinical trials of rupatadine oral solution (1 mg/ml) or placebo in children aged 2–11 years (68, 80)

Adverse event*	Placebo <i>n</i> = 249 (%)	Rupatadine 2.5 mg <i>n</i> = 147 (%)	Rupatadine 5 mg <i>n</i> = 159 (%)
Headache	4 (1.6)	2 (1.4)	4 (2.5)
Somnolence	0	0	2 (1.3)

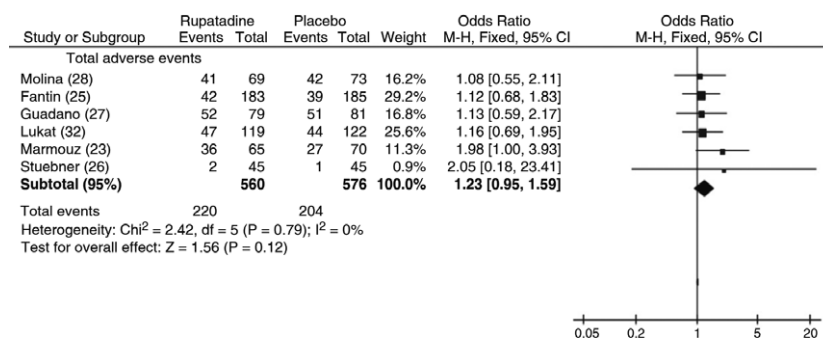
*Possibly, probably or definitely related to study medication.

month treatment periods, 20.4% and 10.8% of patients, respectively, reported at least one treatment-related adverse event. The most common treatment-related adverse events were headache, somnolence and dry mouth; for all three events, the incidence at 12 months was lower than that at 6 months (Table 9). Serious adverse events were reported in seven patients, but only one event involving increased blood enzyme levels was considered to be possibly related to rupatadine treatment. Likewise, in a large 6-week observational study of rupatadine in daily practice in Belgium (*n* = 2838), no serious adverse events occurred and reports of somnolence were rare (0.1%) (93).

Rupatadine has not been causally linked to cardiac effects. A thorough QT/QTc study involving 160 healthy volunteers, which used moxifloxacin (known to increase QTc duration) as the active control, demonstrated that rupatadine at dosages of 10 mg (the recommended dose) and 100 mg (10 times the recommended dose) for 5 days had no statistically or

Table 9 Long-term safety data for rupatadine 10 mg once daily in the treatment of patients with persistent allergic rhinitis (94)

Adverse events (AEs)	Duration of treatment	
	6 months <i>n</i> = 324 (%)	12 months <i>n</i> = 120 (%)
Patients with ≥1 AE	74	66
Patients with treatment-related AE	20.4	10.8
Somnolence	7.7	5.8
Headache	6.5	0.8
Dry mouth	2.2	0.8

**Figure 11** Systematic review of randomized, double-blind, placebo-controlled studies of rupatadine in the treatment of allergic rhino-

conjunctivitis: forest plot for risk of adverse events. Reproduced from (57) with permission.

clinically significant effect on cardiac repolarization (95). Clinical studies of rupatadine in allergic rhinitis, including a study in children with PER (68), reported no clinically relevant electrocardiograph (QTc) findings. Likewise, in a long-term open-label safety study in patients with PER, there were no clinically relevant abnormal ECG findings, nor any QTcB increases >60 ms or QTcB values >470 ms for any patient at any time during up to 12 months' treatment with rupatadine (94).

With regard to the commercial use of rupatadine, no specific warnings or pharmacovigilance alerts have been issued in the market during more than 10 years. Adverse drug reactions reported with rupatadine have been mild to moderate in severity and are in line with information provided in the Summary of Product Characteristics (54). To date, extensive postmarketing surveillance undertaken since the initial launch of rupatadine in March 2003 has not indicated any change in its positive benefit–risk ratio.

The FDA has proposed a classification of drugs on the basis of risks to mother and foetus (96). Rupatadine is risk category B meaning that it failed to demonstrate a risk to the foetus in animal reproduction studies, but there are no adequate well-controlled studies in pregnant women. Rupatadine is excreted into breast milk in animal models, but no human data are available at this time.

Conclusions

Rupatadine has a good safety and tolerability profile in adults and children with allergic rhinitis and urticaria.

Higher dosages of rupatadine (two or four times the standard dose) have not been associated with a relevant increase in adverse events.

Rupatadine oral solution was well tolerated in children with PER or chronic spontaneous urticaria, showing a safety profile not materially different to that of placebo.

No unexpected adverse events were identified during long-term use (1 year) of rupatadine, confirming its good tolerability.

Rupatadine displayed no adverse cardiovascular effects in extensive clinical trials involving adults or children. Doses of 10 and 100 mg once daily for 5 days in adult healthy volunteers had no statistically or clinically significant effects on cardiac repolarization.

An overall safety assessment based on postmarketing use of rupatadine continues to indicate a favourable benefit–risk ratio and confirms the safety profile identified during its clinical development.

Place in therapy

In 2008, the efficacy and safety of rupatadine in the management of allergic disorders was reviewed based on an extensive literature search and in line with evolving ARIA guidelines for allergic rhinitis and EAACI/GA²LEN/EDF/WAO guidelines for urticaria (22). In the current reappraisal, we have examined pivotal new findings for rupatadine, which include the following:

- 1 *In vitro* and *in vivo* studies investigating its pharmacological activity and dual mechanism of action (H₁-antihistamine and anti-PAF effects)
- 2 Evaluation of the clinical pharmacokinetics of rupatadine in children aged 2–11 years
- 3 Further assessment of its clinical efficacy and safety in allergic rhinitis and urticaria, in both adult and paediatric patient populations
- 4 Clinical findings in several types of skin allergies, including ACU, mosquito bite allergy and mastocytosis.
- 5 Real-life observational studies in everyday practice, including studies evaluating its effects on disease severity and QoL.

In allergic diseases such as rhinitis and urticaria, pharmacological treatment has traditionally centred on agents that act at the level of the histamine H₁-receptor. In recent years, the role of PAF has been explored more extensively. Recent studies in humans point clearly to its involvement in the pathogenesis of allergic rhinitis. Studies have shown that rupatadine, but not levocetirizine, produced a significant reduction relative to placebo in nasal symptoms (including nasal congestion) induced by PAF challenge.

Although the onset of allergic rhinitis generally occurs in young children, investigation of treatment options for allergic rhinitis (and many other diseases) in the paediatric population has been a neglected area of clinical research. In Europe, this prompted a mandate by the European Parliament for the pharmaceutical industry to develop clinical programmes investigating the use of medicines in children. Most first-generation H₁-antihistamines have not been formally studied in children. Consequently, dosages have been extrapolated from adult data, and the dose and/or dosing interval selected may not be optimally efficacious or safe in children. Although some earlier second-generation H₁-antihistamines such as cetirizine, desloratadine, fexofenadine, levocetirizine and loratadine have been well studied in children, to date rupatadine is the only H₁-antihistamine studied in PER in the paediatric population. Subsequent to pharmacokinetic studies to determine appropriate paediatric dosages of rupatadine, a large multicentre, randomized controlled trial in children aged 6–11 years with PER demonstrated that rupatadine oral solution 1 mg/ml was effective and well tolerated; symptomatic relief was reflected by significant improvements *vs* placebo in validated paediatric measures of HRQoL (PRQLQ).

A meta-analysis involving more than 2500 patients has consolidated the clinical evidence for rupatadine in allergic rhinoconjunctivitis in adults and children (level of evidence Ia, recommendation A), while prospective observational studies in actual clinical practice have reported marked symptomatic relief with rupatadine and a decrease in disease severity in a relevant proportion of adult patients with IAR or PER. Again, results were paralleled by improvements in QoL.

A pooled analysis of randomized, controlled studies supports the use of higher doses of rupatadine in patients with chronic spontaneous urticaria as per recommendations in the urticaria guidelines. In children aged 2–11 years with chronic

spontaneous urticaria, rupatadine 1 mg/ml oral solution provided significant symptomatic relief and improved CDLQI scores significantly compared with placebo. Small placebo-controlled crossover studies have provided early evidence of the efficacy of rupatadine in conditions such as induced ACU, mosquito bite allergy and mastocytosis. Patients with mastocytosis had significant improvement in QoL during treatment with rupatadine.

Evidence supporting the role of PAF in the inflammatory process of allergic conditions is steadily accumulating, and it is becoming increasingly clear that rupatadine is one of the most potent inhibitors of PAF amongst the second-generation H₁-antihistamines. This agrees with a key principle of the ARIA initiative stating that H₁-antihistamines with additional anti-allergic and anti-inflammatory properties are likely to play a unique role in the pharmacological management of allergic diseases. In the near future, further elucidation of the role of PAF (and other inflammatory mediators) in the pathophysiology of allergic diseases might be expected to change the 'histamine paradigm' and contribute to the development of multitargeted therapeutic options such as rupatadine for patients with allergy.

In conclusion, rupatadine is a well-studied modern second-generation H₁-antihistamine that has demonstrated a broad level of efficacy against a range of allergic disorders. In clinical studies, rupatadine was effective and well tolerated throughout the entire 24-h dosing period. Importantly, post-marketing use continues to show a favourable benefit–risk ratio and confirms the safety profile identified during clinical development. Since the previous review, rupatadine has been formally studied in children over 2 years, thus extending its use in the management of allergic rhinitis and urticaria into the paediatric population. Confirmation of the anti-PAF activity of rupatadine in humans is an important milestone in understanding allergic disorders.

Acknowledgments

Editorial assistance was kindly provided by Kerry Dechant and Steve Clissold, Content Ed Net (Madrid, Spain), with funding from Uriach (Barcelona, Spain).

Conflict of interest

Joaquim Mullol is or has been a member of national and international scientific advisory boards (consulting), received

fees for lectures, and grants for research projects from ALK-Abelló, Boehringer-Ingelheim, Crucell, Esteve, FAES, GSK, Hartington Pharmaceuticals, Johnson & Johnson, MEDA Pharma, MSD, Novartis, Pierre Fabre, Sanofi-Aventis, Schering Plough, UCB, Uriach Group and Zambon. Jean Bousquet has received honoraria for: scientific and advisory boards for Almirall, Meda, Merck, MSD, Novartis, Sanofi-Aventis, Takeda, Teva and Uriach; lectures during meetings for Almirall, AstraZeneca, Chiesi, GSK, Meda, Menarini, Merck, MSD, Novartis, Sanofi-Aventis, Takeda, Teva, Uriach; Board of Directors (Stallergènes). Claus Bachert declares that he has received fees for consultation and/or speakers bureau from Uriach, MSD, Bionorica, Allergopharma, Sanofi, GSK and Novartis. G.W. Canonica reports having received research grants as well as lecture fees from: ALK-Abelló, Allergy Therapeutics, Almirall SA, Anallergo, AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici SpA, GlaxoSmithKline, Uriach, Lallemand Inc, Lofarma SpA, Menarini, Merck & Co, Inc, Merck, Sharp & Dohme Corp, Novartis AG, Pfizer Inc, Phadia AB, Sanofi-Aventis, Schering-Plough Corp, Stallergenes and UCB Pharma. Ana Gimenez-Arnau has been a Medical Advisor for Uriach Pharma, Genentech and Novartis; received research grants supported by Intendis – Bayer, Uriach Pharma and Novartis; and taken part in educational activities sponsored by Uriach Pharma, Novartis, Genentech, Menarini, GSK, MSD and Almirall. Marek L. Kowalski is a member of the International Advisory Board of Rupatadine. Estelle Simons: Uriach Medical Advisory Board; Contributing Editor, The Medical Letter; Editor and author, UpToDate. Marcus Maurer is or recently was a Speaker and/or Advisor for FAES, Almirall Hermal, Genentech, GSK, Merckle Recordati, Novartis, Sanofi Aventis, Schering-Plough, MSD, Merck, Moxie, Takeda, UCB and Uriach. Dermot Ryan has received lecture fees from: GlaxoSmith Kline, MSD, AstraZeneca, Chiesi, Almirall and Boehringer Ingelheim. Glenis Scadding has received: research grants from GSK and ALK; honoraria for articles, lectures/chairing and advisory boards for AstraZeneca, Britannia Pharmaceuticals, Capnia, Church & Dwight, Circassia, GSK, Grupo Uriach, Meda, Merck, MSD, Ono Pharmaceuticals, Oxford Therapeutics, Sanofi-Aventis and UCB; travel funding from Bayer, GSK.

References

1. Church MK, M  spero JF, Maurer M, Ryan D. The scope of pharmacological and clinical effects of modern antihistamines, with a special focus on rupatadine: Proceedings from a Satellite Symposium held at the 21st World Allergy Congress, Buenos Aires, December 8, 2009. *World Allergy Organ J* 2010;3(Suppl 4):S1–S16.
2. Metz M, Maurer M. Rupatadine for the treatment of allergic rhinitis and urticaria. *Expert Rev Clin Immunol* 2011;7: 15–20.
3. Meltzer EO, Blaiss MS, Naclerio RM, Stoloff SW, Derebery MJ, Nelson HS et al. Burden of allergic rhinitis: allergies in America, Latin America, and Asia-Pacific adult surveys. *Allergy Asthma Proc* 2012;33(Suppl 1):S113–S141.
4. A  t-Khaled N, Pearce N, Anderson HR, Ellwood P, Montefort S, Shah J, for the ISAAC Phase Three Study Group. Global map of the prevalence of symptoms of rhinoconjunctivitis in children: The International Study of Asthma and Allergies in

- Childhood (ISAAC) Phase Three. *Allergy* 2009;**64**:123–148.
5. Katelaris CH, Lee BW, Potter PC, Maspiero JF, Cingi C, Lopatin A et al. Prevalence and diversity of allergic rhinitis in regions of the world beyond Europe and North America. *Clin Exp Allergy* 2012;**42**:186–207.
 6. Mallol J, Crane J, von Mutius E, Odhiambo J, Keil U, Stewart A, ISAAC Phase Three Study Group. The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three: a global synthesis. *Allergol Immunopathol (Madr)* 2013;**41**:73–85.
 7. Pawankar R, Canonica GW, Holgate ST, Lockey RF, editors. *The WAO White Book on Allergy*. World Health Organization, 2011: 1–216. Available at: http://www.worldallergy.org/UserFiles/file/WAO-White-Book-on-Allergy_web.pdf.
 8. AAAAI. Reducing widespread U.S. health care costs by improving quality of care for respiratory allergens. Available at: www.aaaai.org (last accessed June 2014).
 9. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A et al. Allergic rhinitis and its impact on asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 2008;**63**(Suppl 86):8–160.
 10. Shaaban R, Zureik M, Soussan D, Neukirch C, Heinrich J, Sunyer J et al. Rhinitis and onset of asthma: a longitudinal population-based study. *Lancet* 2008;**372**:1049–1057.
 11. Greiner AN, Hellings PW, Rotiroti G, Scadding GK. Allergic rhinitis. *Lancet* 2011;**378**:2112–2122.
 12. Karimkhani C, Boyers LN, Prescott L, Welch V, Delamere FM, Nasser M et al. Global burden of skin disease as reflected in Cochrane Database of Systematic Reviews. *JAMA Dermatol* 2014;**150**:945–951.
 13. Sicherer SH, Leung DY. Advances in allergic skin disease, anaphylaxis, and hypersensitivity reactions to foods, drugs, and insects in 2013. *J Allergy Clin Immunol* 2014;**133**:324–334.
 14. Stitt JM, Dreskin SC. Urticaria and autoimmunity: where are we now? *Curr Allergy Asthma Rep* 2013;**13**:555–562.
 15. Zuberbier T, Aberer W, Asero R, Bindslev-Jensen C, Brzoza Z, Canonica GW et al. The EAACI/GA(2) LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy* 2014;**69**:868–887.
 16. Muñoz-Cano R, Valero A, Roca-Ferrer J, Bartra J, Sánchez-López J, Mullol J et al. Platelet-activating factor nasal challenge induces nasal congestion and reduces nasal volume in both healthy volunteers and allergic rhinitis patients. *Am J Rhinol Allergy* 2013;**27**:e48–52.
 17. Muñoz-Cano R, Valero A, Izquierdo I, Sánchez-López J, Doménech A, Bartra J et al. Evaluation of nasal symptoms induced by platelet activating factor, after nasal challenge in both healthy and allergic rhinitis subjects pretreated with rupatadine, levocetirizine or placebo in a cross-over design. *Allergy Asthma Clin Immunol* 2013;**9**:43.
 18. Church MK, Maurer M, Simons FER, Bindslev-Jensen C, van Cauwenberge P, Bousquet J, on behalf of the Global Allergy and Asthma European Network. Risk of first-generation H(1)-antihistamines: a GA(2) LEN position paper. *Allergy* 2010;**65**:459–466.
 19. Simons FER, Simons KJ. Histamine and H₁-antihistamines: celebrating a century of progress. *J Allergy Clin Immunol* 2011;**128**:1139–1150.
 20. Mullol J. Positioning of antihistamines in the allergic rhinitis and its impact on asthma (ARIA) guidelines. *Clinical & Experimental Allergy Reviews* 2012;**12**:17–26.
 21. Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, on behalf of the Global Allergy and Asthma European Network; Grading of Recommendations Assessment, Development and Evaluation Working Group. Allergic rhinitis and its impact on asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol* 2010;**126**:466–476.
 22. Mullol J, Bousquet J, Bachert C, Canonica WG, Gimenez-Arnau A, Kowalski ML et al. Rupatadine in allergic rhinitis and chronic urticaria. *Allergy* 2008;**63**(Suppl 87):5–28.
 23. Tillement J-P. Pharmacological profile of the new antihistamines. *Clin Exp Allergy Rev* 2005;**5**:7–11.
 24. Walsh GM. Anti-inflammatory properties of antihistamines: an update. *Clin Exp Allergy Rev* 2005;**5**:21–25.
 25. Devillier P. Comparing the new antihistamines: the role of pharmacological parameters. *Clin Exp Allergy* 2006;**36**:5–7.
 26. Hoyte FC, Katial RK. Antihistamine therapy in allergic rhinitis. *Immunol Allergy Clin North Am* 2011;**31**:509–543.
 27. Spina D, Coyle AJ, Page CP. The role of platelet activating factor in allergic inflammation. *Pulm Pharmacol* 1989;**2**:13–19.
 28. Gui C, Zhu W, Chen G, Luo X, Liew OW, Puah CM et al. Understanding the regulation mechanisms of PAF receptor by agonists and antagonists: molecular modeling and molecular dynamics simulation studies. *Proteins* 2007;**67**:41–52.
 29. Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A et al. Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. *J Allergy Clin Immunol* 2006;**117**:391–397.
 30. Kato M, Kita H, Tachibana A, Hayashi Y, Tsuchida Y, Kimura H. Dual signalling and effector pathways mediate human eosinophil activation by platelet-activating factor. *Int Arch Allergy Immunol* 2004;**134**(Suppl 1):37–43.
 31. Kajiura N, Sasaki T, Bradding P, Cruse G, Sagara H, Ohmori K et al. Activation of human mast cells through the platelet-activating factor receptor. *J Allergy Clin Immunol* 2010;**125**:1137–1145.
 32. Vadas P, Gold M, Perelman B, Liss GM, Lack G, Blyth T et al. Platelet-activating factor, PAF acetylhydrolase, and severe anaphylaxis. *N Engl J Med* 2008;**358**:28–35.
 33. Kuitert LM, Angus RM, Barnes NC, Barnes PJ, Bone MF, Chung KF et al. Effect of a novel potent platelet-activating factor antagonist, modipafant, in clinical asthma. *Am J Respir Crit Care Med* 1995;**151**:1331–1335.
 34. Shirasaki H, Seki N, Kikuchi M, Kanaizumi E, Watanabe K, Konno N et al. Expression and localization of platelet-activating factor receptor in human nasal mucosa. *Ann Allergy Asthma Immunol* 2005;**95**:190–196.
 35. Krause K, Giménez-Arnau A, Martínez-Escala E, Farré-Albadalejo M, Abajian M, Church MK et al. Platelet-activating factor (PAF) induces wheal and flare skin reactions independent of mast cell degranulation. *Allergy* 2013;**68**:256–258.
 36. Soter NA, Wasserman SI, Austen KF. Cold urticaria: release into the circulation of histamine and eosinophil chemotactic factor of anaphylaxis during cold challenge. *N Engl J Med* 1976;**294**:687–690.
 37. Wasserman SI, Ginsberg MH. Release of platelet factor 4 into the blood after cold challenge of patients with cold urticaria. *J Allergy Clin Immunol* 1984;**74**:275–279.
 38. Grandel KE, Farr RS, Wanderer AA, Eisenstadt TC, Wasserman SI. Association of platelet-activating factor with primary acquired cold urticaria. *N Engl J Med* 1985;**313**:405–409.
 39. Nettis E, Delle Donne P, Di Leo E, Calogiuri GF, Ferrannini A, Vacca A. Rupatadine for the treatment of urticaria. *Expert Opin Pharmacother* 2013;**14**:1807–1813.
 40. Vasiadi M, Kalogeromitros D, Kempuraj D, Clemons A, Zhang B, Chliva C et al. Rupatadine inhibits proinflammatory mediator secretion from human mast cells triggered by different stimuli. *Int Arch Allergy Immunol* 2010;**151**:38–45.
 41. Alevizos M, Karagkouni A, Vasiadi M, Sismanopoulos N, Makris M, Kalogeromi-

- tros D et al. Rupatadine inhibits inflammatory mediator release from human laboratory of allergic diseases 2 cultured mast cells stimulated by platelet-activating factor. *Ann Allergy Asthma Immunol* 2013;**111**:542–547.
42. Muñoz Cano R, Torres Atencio I, Ainsua E, Martín Andorra M, Sánchez-López J, Bartra J et al. Effects of rupatadine on platelet activating factor (PAF) induced human mast cell degranulation compared with desloratadine and levocetirizine. *J Allergy Clin Immunol* 2012;**129**(Suppl 2):AB122.
 43. Church MK. Efficacy and tolerability of rupatadine at four times the recommended dose against histamine- and platelet-activating factor-induced flare responses and ex vivo platelet aggregation in healthy males. *Br J Dermatol* 2010;**163**:1330–1332.
 44. Picado C. Rupatadine: pharmacological profile and its use in the treatment of allergic disorders. *Expert Opin Pharmacother* 2006;**7**:1989–2001.
 45. Katiyar S, Prakash S. Pharmacological profile, efficacy and safety of rupatadine in allergic rhinitis. *Prim Care Respir J* 2009;**18**:57–68.
 46. Keam SJ, Plosker GL. Rupatadine: a review of its use in the management of allergic disorders. *Drugs* 2007;**67**:457–474.
 47. Peña J, Carbo ML, Solans A, Nadal T, Izquierdo I, Merlos M. Antihistaminic effects of rupatadine and PKPD modelling. *Eur J Drug Metab Pharmacokinet* 2008;**33**:107–116.
 48. Izquierdo I, Estévez J, Doménech A, Valle M. Population pharmacokinetics of rupatadine in children 2–11 years of age with allergic rhinitis. Abstracts of the Annual Meeting of the Population Approach Group in Europe. 5–8 June 2012, Venice, Italy [Abstract II-41].
 49. Valle M, Estevez J, Martial LC, Santamaria E, Izquierdo I. Application of population pharmacokinetic modelling and simulation in the design of the optimal dose regime of rupatadine in 2–5 year old children. *Clin Transl Allergy* 2014;**4**(Suppl 1):P39.
 50. Izquierdo I, Merlos M, García-Rafanell J. Rupatadine: a new selective histamine H₁ receptor and platelet-activating factor (PAF) antagonist. A review of pharmacological profile and clinical management of allergic rhinitis. *Drugs Today (Barc)* 2003;**39**:451–468.
 51. Solans A, Izquierdo I, Donado E, Antonijoan R, Peña J, Nadal T et al. Pharmacokinetic and safety profile of rupatadine when coadministered with azithromycin at steady-state levels: a randomized, open-label, two-way, crossover, phase I study. *Clin Ther* 2008;**30**:1639–1650.
 52. García-Gea C, Ballester MR, Martínez J, Antonijoan RM, Donado E, Izquierdo I et al. Rupatadine does not potentiate the CNS depressant effects of lorazepam: randomized, double-blind, crossover, repeated dose, placebo-controlled study. *Br J Clin Pharmacol* 2010;**69**:663–674.
 53. Solans A, Carbó ML, Peña J, Nadal T, Izquierdo I, Merlos M. Influence of food on the oral bioavailability of rupatadine tablets in healthy volunteers: a single-dose, randomized, open-label, two-way crossover study. *Clin Ther* 2007;**29**:900–908.
 54. Summary of product characteristics. Rupafin 10 mg tablets. Available at: www.medicines.org.uk/emc/medicine/21780/SPC (last accessed August 2014).
 55. Summary of product characteristics. Rupafin 1 mg/ml oral solution. Available at: www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1406266793287.pdf (last accessed August 2014).
 56. Bousquet J, Van Cauwenberge P, Khaltaev N, Aria Workshop Group, World Health Organization. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;**108**(Suppl 5):S147–S334.
 57. Compalati E, Canonica GW. Efficacy and safety of rupatadine for allergic rhinoconjunctivitis: a systematic review of randomized, double-blind, placebo-controlled studies with meta-analysis. *Curr Med Res Opin* 2013;**29**:1539–1551.
 58. Martínez-Cócerca C, De Molina M, Martí-Guadaño E, Pola J, Conde J, Borja J et al. Rupatadine 10 mg and cetirizine 10 mg in seasonal allergic rhinitis: a randomised, double-blind parallel study. *J Investig Allergol Clin Immunol* 2005;**15**:22–29.
 59. Guadaño EM, Serra-Batlles J, Meseguer J, Castillo JA, De Molina M, Valero A et al. Rupatadine 10 mg and ebastine 10 mg in seasonal allergic rhinitis: a comparison study. *Allergy* 2004;**59**:766–771.
 60. Saint-Martin F, Dumur JP, Pérez I, Izquierdo I, French Rupatadine-Rhinitis Study Group. A randomized, double-blind, parallel-group study, comparing the efficacy and safety of rupatadine (20 and 10 mg), a new PAF and H₁ receptor-specific histamine antagonist, to loratadine 10 mg in the treatment of seasonal allergic rhinitis. *J Investig Allergol Clin Immunol* 2004;**14**:34–40.
 61. Maiti R, Rahman J, Jaida J, Allala U, Palani A. Rupatadine and levocetirizine for seasonal allergic rhinitis: a comparative study of efficacy and safety. *Arch Otolaryngol Head Neck Surg* 2010;**136**:796–800.
 62. Lukat KF, Rivas P, Roger A, Kowalski ML, Botzen U, Wessel F et al. A direct comparison of efficacy between desloratadine and rupatadine in seasonal allergic rhinoconjunctivitis: a randomized, double-blind, placebo-controlled study. *J Asthma Allergy* 2013;**6**:31–39.
 63. Marmouz F, Giralt J, Izquierdo I. Morning and evening efficacy evaluation of rupatadine (10 and 20 mg), compared with cetirizine 10 mg in perennial allergic rhinitis: a randomized, double-blind, placebo-controlled trial. *J Asthma Allergy* 2011;**4**:27–35.
 64. Molina M, Pinto E, Cister A, Alamar Martínez R, Montero J, García González JJ et al. Rupatadine 10 mg in adolescent and adult symptom relief of perennial allergic rhinitis. *Therapy* 2010;**7**:429–436.
 65. Kowalski ML, Jukiewicz D, Kruszewski J, Nowak D, Zietkowski Z, Spicakova M et al. Rupatadine 10 and 20 mg are effective and safe in the treatment of perennial allergic rhinitis after 4 weeks of treatment: a randomized, double-blind, controlled trial with loratadine and placebo. *Therapy* 2009;**6**:417–425.
 66. Mion O, Mello J Jr, Castro F, Cruz A, Mocelin M, Bogart P et al. Rupatadine fumarate is effective in the treatment of persistent allergic rhinitis: a multicentre study. *Allergy* 2007;**62**(Suppl 83):137.
 67. Fantin S, Maspero J, Bisbal C, Agache I, Donado E, Borja J et al. A 12-week placebo-controlled study of rupatadine 10 mg once daily compared with cetirizine 10 mg once daily, in the treatment of persistent allergic rhinitis. *Allergy* 2008;**63**:924–931.
 68. Potter P, Maspero JF, Vermeulen J, Barkai L, Németh I, Baillieu RA et al. Rupatadine oral solution in children with persistent allergic rhinitis: a randomized, double-blind, placebo-controlled study. *Pediatr Allergy Immunol* 2013;**24**:144–150.
 69. Stuebner P, Horak F, Zieglermayr R, Arnáiz E, Leuratti C, Pérez I et al. Effects of rupatadine vs placebo on allergen-induced symptoms in patients exposed to aeroallergens in the Vienna Challenge Chamber. *Ann Allergy Asthma Immunol* 2006;**96**:37–44.
 70. Valero A, Serrano C, Bartrá J, Izquierdo I, Muñoz-Cano R, Mullol J et al. Reduction of nasal volume after allergen-induced rhinitis in patients treated with rupatadine: a randomized, cross-over, double-blind, placebo-controlled study. *J Investig Allergol Clin Immunol* 2009;**19**:488–493.
 71. Ciprandi G, Cirillo I. Rupatadine improves nasal symptoms, airflow and inflammation in patients with persistent allergic rhinitis: a pilot study. *J Biol Regul Homeost Agents* 2010;**24**:177–183.
 72. Makris M, Maurer M, Zuberbier T. Pharmacotherapy of chronic spontaneous urticaria. *Expert Opin Pharmacother* 2013;**14**:2511–2519.
 73. Kay AB, Ying S, Ardelean E, Mlynec A, Kita H, Clark P et al. Elevations in vascular markers and eosinophils in chronic spontaneous urticarial weals with low level persis-

- tence in uninvolved skin. *Br J Dermatol* 2014;**171**:505–511.
74. Dubertret L, Zalupca L, Cristodoulo T, Bena V, Medina I, Fantin S et al. Once-daily rupatadine improves the symptoms of chronic idiopathic urticaria: a randomised, double-blind, placebo-controlled study. *Eur J Dermatol* 2007;**17**:223–228.
 75. Giménez-Arnau A, Pujol RM, Ianosi S, Kaszuba A, Malbran A, Poop G et al. Rupatadine in the treatment of the treatment of chronic idiopathic urticaria: a double-blind, randomized, placebo-controlled multicenter study. *Allergy* 2007;**62**:539–546.
 76. Giménez-Arnau A, Izquierdo I, Maurer M. The use of a responder analysis to identify clinically meaningful differences in chronic urticaria patients following placebo-controlled treatment with rupatadine 10 and 20 mg. *J Eur Acad Dermatol Venereol* 2009;**23**:1088–1091.
 77. Dakhale GN, Shinde AT, Mahatme MS, Hiware SK, Mishra DB, Mukhi JI et al. Clinical effectiveness and safety of cetirizine versus rupatadine in chronic spontaneous urticaria: a randomized, double-blind, 6-week trial. *Int J Dermatol* 2014;**53**:643–649.
 78. Kolasani BP, Mudium R, Reddy N. A comparative study of efficacy and safety of rupatadine versus desloratadine in patients with chronic idiopathic urticaria. *Asian Journal of the Biomedical & Pharmaceutical Sciences* 2013;**3**:42–47.
 79. Maiti R, Jaida J, Raghavendra BN, Goud P, Ahmed I, Palani A. Rupatadine and levocetirizine in chronic idiopathic urticaria: a comparative study of efficacy and safety. *J Drugs Dermatol* 2011;**10**:1444–1450.
 80. Potter P, Mitha E, Barkai L, Domenech A, Santamaria E, Giralt J et al. Rupatadine is effective and safe in the treatment of chronic spontaneous urticaria (CSU) in paediatric patients (2–11 years old). *Clin Transl Allergy* 2014;**4**(Suppl 1):O10.
 81. Metz M, Scholz E, Ferrán M, Izquierdo I, Giménez-Arnau A, Maurer M. Rupatadine and its effects on symptom control, stimulation time, and temperature thresholds in patients with acquired cold urticaria. *Ann Allergy Asthma Immunol* 2010;**104**:86–92.
 82. Martínez-Escala ME, Curto-Barredo L, Carnero L, Pujol RM, Giménez-Arnau AM. Temperature thresholds in assessment of the clinical course of acquired cold contact urticaria: a prospective observational one-year study. *Acta Derm Venereol* 2014 Jun 30. doi: 10.2340/00015555-1918. (Epub ahead of print).
 83. Karppinen A, Brummer-Korvenkontio H, Reunala T, Izquierdo I. Rupatadine 10 mg in the treatment of immediate mosquito-bite allergy. *J Eur Acad Dermatol Venereol* 2012;**26**:919–922.
 84. Carter MC, Metcalfe DD, Komarow HD. Mastocytosis. *Immunol Allergy Clin North Am* 2014;**34**:181–196.
 85. Siebenhaar F, Förtsch A, Krause K, Weller K, Metz M, Magerl M et al. Rupatadine improves quality of life in mastocytosis: a randomized, double-blind, placebo-controlled trial. *Allergy* 2013;**68**:949–952.
 86. Bachert C. Quality of life: improvement due to treatment. *Clin Exp Allergy Rev* 2002;**2**:73–78.
 87. González-Núñez V, Valero AL, Mullol J. Impact of sleep as a specific marker of quality of life in allergic rhinitis. *Curr Allergy Asthma Rep* 2013;**13**:131–141.
 88. Maspero J, Lee BW, Katelaris CH, Potter PC, Cingi C, Lopatin A et al. Quality of life and control of allergic rhinitis in patients from regions beyond Western Europe and the United States. *Clin Exp Allergy* 2012;**42**:1684–1696.
 89. Juniper EF. Can quality of life be quantified? *Clin Exp Allergy Rev* 2002;**2**:57–60.
 90. Roger A, Arnáiz E, Valero A, De la Torre F, Castillo J, Rivas P et al. Rupatadine 10 mg improves quality of life in long-term treatment of persistent allergic rhinitis [abstract no. 761]. 25th EAACI Congress 10–14 June 2006, Vienna.
 91. Valero A, Ferrer M, Sastre J, Navarro AM, Monclús L, Martí-Guadaño E et al. A new criterion by which to discriminate between patients with moderate allergic rhinitis and patients with severe allergic rhinitis based on the allergic rhinitis and its impact on asthma severity items. *J Allergy Clin Immunol* 2007;**120**:359–365.
 92. Valero A, Izquierdo I, Giralt J, Bartra J, del Cuvillo A, Mullol J. Rupatadine improves nasal symptoms, quality of life (ESPRINT-15) and severity in a subanalysis of a cohort of Spanish allergic rhinitis patients. *J Investig Allergol Clin Immunol* 2011;**21**:229–235.
 93. Eloy P, Tobback L, Imschoot J. Rupatadine improves health related quality of life and severity of allergic rhinitis in a Belgian cohort of 2800 patients. *Allergy* 2012;**67**(Suppl s96):331.
 94. Valero A, de la Torre F, Castillo JA, Rivas P, del Cuvillo A, Antépara I et al. Safety of rupatadine administered over a period of 1 year in the treatment of persistent allergic rhinitis: a multicentre, open-label study in Spain. *Drug Saf* 2009;**32**:33–42.
 95. Donado E, Izquierdo I, Pérez I, García O, Antonijoan RM, Gich I et al. No cardiac effects of therapeutic and suprathreshold doses of rupatadine: results from a 'thorough QT/QTc study' performed according to ICH guidelines. *Br J Clin Pharmacol* 2010;**69**:401–410.
 96. Vlastarakos PV, Manolopoulos L, Ferekidis E, Antsaklis A, Nikolopoulos TP. Treating common problems of the nose and throat in pregnancy: what is safe? *Eur Arch Otorhinolaryngol* 2008;**265**:499–508.