

SYSTEMATIC REVIEW

Pharmacological profile, efficacy and safety of rupatadine in allergic rhinitis

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Abstract

Allergic rhinitis (AR) is a disease with high prevalence. In AR, exposure to airborne allergens elicits an allergic response which involves epithelial accumulation of effector cells – e.g. mast cells and basophils – and subsequent inflammation. During the early response in AR, histamine has been found to be the most abundant mediator and it is associated with many symptoms of this disease mediated through the histamine H1 receptor. Therefore, anti-histamines have a role to play in the management of AR. However, the available anti-histamines have certain well-known side effects like sedation and potential pro-arrhythmic effects owing to their interactions with other drugs, as well as having poor or no effect on platelet activating factor (PAF) which also plays an important role in AR. This article is a qualitative systematic literature review on the pharmacological profile of rupatadine in order to evaluate its safety and efficacy in AR as compared to other anti-histamines. Rupatadine is a once-daily non-sedative, selective, long-acting H1 anti-histamine with antagonistic PAF effects through its interaction with specific receptors. Rupatadine significantly improves nasal symptoms in patients with AR. It has a good safety profile and is devoid of arrhythmogenic effects. These properties make rupatadine a suitable first line anti-histamine for the treatment of AR.

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Introduction

Allergic rhinitis (AR) is a common disease, with a high prevalence ranging from about 10% for seasonal allergic rhinitis (SAR) to 10–20% for perennial allergic rhinitis (PAR).¹ Besides high prevalence, AR is also associated with an impaired quality of life and co-exists with co-morbidities such as atopy and asthma.²

Most studies have classified allergic rhinitis into SAR and PAR and hence this classification is being used in this review. Seasonal allergic rhinitis (SAR) is known to be triggered mostly by various types of pollens from grasses, weeds and trees as well as outdoor moulds and spores. The disease presents usually with sneezing, rhinorrhoea, nasal obstruction, pharyngeal obstruction, ocular watering and itching.¹ Similar symptoms are found in PAR except that nasal obstruction is more pronounced. Most PAR patients exhibit sensitivity to one or more of the non-seasonal allergens – e.g. spores, moulds, animal dander and dust mites.² Depending upon the spectrum of allergen sensitivities, symptoms of AR can be

perennial and/or show seasonal exacerbation.

In allergic rhinitis, exposure to airborne allergens elicits an allergic response which involves epithelial accumulation of effector cells – for example, mast cells and basophils – with subsequent inflammation. Immunological activation of these effector cells is associated with secretion of pro-inflammatory mediators which include newly-formed mediators such as leukotrienes, prostaglandins and kinins and pre-formed mediators like histamine and tryptase.³ During the early response in AR, histamine has been found to be the most abundant mediator and has also been associated with many symptoms of this disease such as rhinorrhoea, itching, sneezing and watery eyes mediated mainly through the histamine H1 receptor.⁴

This article is a qualitative systematic literature review, undertaken to provide an insight into the pharmacological profile of rupatadine (RU) and its role in the treatment of AR. The review involves a survey of studies on RU which provide data on its side effects, safety, efficacy, and dose response

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relationships, in order to assess whether RU offers a safer and more efficacious option for the treatment of AR as compared to conventional anti-histamines which have known interactions, cardiac effects and psychomotor impairment.

Methods

Criteria for study selection

Human and animal studies and reviews on AR, its pathophysiology and its pharmacological profile; and studies on the effect of RU and other PAF antagonists alone and in comparison to other agents on AR were included. Studies involving evaluation of RU in treatment of allergic disorders other than AR were not included, except those which offered explanation regarding the mechanism of action of RU.

Data sources and data extraction

An extensive internet search was done on Medline (Ovid), EMBASE, Google, Google Scholar, OJOSE, and Trip database (allergy specialty). Key words used in different combinations were: "rupatadine," "absorption," "binding," "metabolism," "transport kinetics," "tissue distribution," "dynamics," "side effects," "clinical trial," "efficacy," "safety," "allergic rhinitis," "anti-histamines," "platelet activating factor," "cardiac effects," "cognitive effects," "psychomotor effects," "driving.". The reference section of primary studies and narrative reviews was reviewed to search for any additional primary articles that could have been overlooked by the electronic search.⁵ No date or language restriction was placed on the literature search. The table of contents of all issues and supplements (between 2000 and 2007) of the *European Journal of Allergy and Clinical Immunology* and the *Journal of Allergy and Clinical Immunology* were extensively searched manually for relevant studies, reviews and conference papers on RU and AR. Grey literature was not used unless there was no alternative study in the published literature.

Both the reviewers independently completed the search and checked all titles and abstracts of relevant studies maintained in Reference Manager 11.0.1, thereby avoiding duplication. The search results were reviewed and a final list of studies was prepared for full text review by both authors. The extracted data was discussed and any discrepancy resolved by including relevant information in appropriate sections of the review.

The role of platelet activating factor (PAF) in allergic rhinitis

The role of PAF in AR was demonstrated in the study on PAF antagonist ABT-491 in rat and guinea pig models of AR.^{6,7} PAF induces vasodilatation and an increase in vascular permeability, which may be responsible for the appearance of rhinorrhoea and nasal congestion.^{4,8,9,10} This fact is also

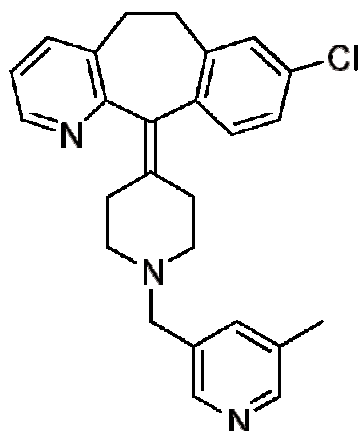
corroborated by finding that nasal fluids and plasma of patients with AR contain high levels of PAF and its metabolite lyso-PAF.^{11,12} Reverse transcriptase-PCR analysis of RNA from the nasal mucosa of AR patients demonstrated enhanced expression of PAF receptor mRNA. Immunohistochemical studies have demonstrated anti-PAF receptor antibody-labeled eosinophils, macrophages, neutrophils, mast cells, lymphocytes, vascular endothelial cells, epithelial cells, and submucosal glands in the nasal mucosa of these patients.¹³ Moreover, PAF and histamine are known to complement and promote secretion of each other.^{14,15}

Intranasal PAF has been shown to induce nasal hyperresponsiveness. Bradykinin itself does not cause hyperresponsiveness, but is shown to be involved in the hyperresponsiveness induced by PAF in the human nasal airway.¹⁶ Endogenous PAF has also been demonstrated to play an important role in eosinophil functional responses to various exogenous stimuli, such as cytokines and immunoglobulins.¹⁷ Since PAF is synthesized, it is expected to have a major role in the late phase reaction. The effect of anti-PAF agents (WEB2086, SM10661) on the changes of nasal airway resistance (NAR) and nasal symptoms after topical antigen challenge in actively sensitised guinea pigs was studied by Narita S et al.¹⁸ There was a biphasic increase in NAR after antigen challenge, with the first peak – 146.3 +/- 4.3% – at 10 min and the second greater peak – 163.3 +/- 7.8% – at 240 min after antigen challenge. Anti-PAF agents did not affect the first peak response of NAR but the late phase was significantly inhibited by anti-PAF and not by anti-histamine. The nasal symptoms, which occurred within 30 min after antigen challenge, were also significantly inhibited by anti-PAF. The results suggested that PAF activities may play an important role in the late phase. Based on these findings, it has been postulated that in the treatment of AR, simultaneous blockade of PAF & histamine receptors could exhibit higher clinical efficacy than blockade of any one of these receptors.¹⁹ Some anti-histaminics have been shown to exhibit marginal PAF antagonistic properties which can not be attributed to specific interaction with PAF receptors.^{20,21} There is an abundance of circumstantial evidence to support the role of PAF in AR. However, more studies are required to delineate its role and to provide direct evidence particularly in humans.

Rupatadine: its properties and role in allergic rhinitis

Rupatadine (RU) (see Figure 1) is a novel drug which exhibits both anti-histamine and anti-PAF effects through its interaction with specific receptors.²² Its chemical designation is 8-chloro-11-[1-[(5-methyl-3-pyridinyl)methyl]piperidin-4-ylidene]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b] pyridine fumarate. The empirical formula is C₂₆H₂₆ClN₃ and molecular weight is 415.958 g/mol.

Figure 1. Molecular structure of Rupatadine fumarate.



Pharmacokinetic properties

- Absorption:** Rapid absorption has been found in all species including mice, rats, dogs, monkeys and humans, with T_{max} in humans being 0.75 to 1 hour.²² The C_{max} after 10 mg in single and repeated doses are 2.2 and 2.0 ng/ml, respectively. The rapid absorption of RU correlates with the onset of anti-histamine and anti-PAF actions following exposure to an allergen as assessed by wheal and flare inhibition, which occurs within 1-2 hours after drug intake. Oral bio-availability has been shown to be more than 50% with its half life ($t_{1/2}$) ranging from 1 hour (mice) to 2-3 hours (rats and dogs).²³ Human studies with RU have shown the mean $t_{1/2}$ in healthy human volunteers to be ~ 6 hours (range 4.3-14.3 hours).²² The C_{max} and AUC increased in proportion to the dose with a dosage of < 40mg/day, whereas clearance and $t_{1/2}$ remained constant.
- Metabolism:** Oxidative processes, namely oxidation of pyridine methyl group to the carboxylic acid, N-dealkylation of the piperidine nitrogen and hydroxylation in the 3, 5 and 6 positions in the tricyclic ring system are the main biotransformation pathways of RU. Conjugates with glucuronic acid are also found. Some of the metabolites retain anti-histaminic activity and partially contribute to the overall efficacy of the drug and the long duration of action.²³ CYP3A4 was identified *in vitro* as the main isoenzyme responsible for the biotransformation of RU and genetic polymorphism in its biotransformation is unlikely.^{24,25}
- Distribution:** RU is 98-99% bound to the human plasma proteins. This high degree of binding does not cause the compound to be retained in the circulating blood and it is well distributed in other tissues allowing it to reach its target receptor. Its plasma concentration is far lower than would be expected to saturate plasma binding capacity – hence RU

displacement from its binding sites when co-administered with other drugs is unlikely.²⁵

- Excretion:** The plasma concentration follows a bi-exponential drop with a mean elimination $t_{1/2}$ of 5.9 hours. Biliary excretion is the most important route of elimination. In a study on humans using radio-labeled RU (14 C-RU 40mg), 34.6% of the radio-activity administered was recovered in urine and 60.9% in faeces collected over seven days. RU undergoes considerable pre-systemic metabolism when administered orally, and hence the amounts of unaltered active substance found in faeces and urine are very low.²⁵
- Drug and food interactions:** Table 1 summarises the various drug and food interaction of RU. Though co-administration with ketoconazole or erythromycin did not result in any adverse event – including any changes in ECG parameters such as the QTc interval, changes in laboratory tests or vital signs – co-administration with ketoconazole, erythromycin (or any other potential inhibitors of CYP3A4) is not advised due to a marked increase in its concentration. As shown in the table, the combination of RU with azithromycin or fluoxetine is well tolerated and may be co-administered safely at therapeutic doses. Fluoxetine is known to inhibit some P450 cytokines such as CYP2D6, CYP3A426.
- Elderly population:** The mean $t_{1/2}$ of RU in elderly subjects is 8.7 h against 5.9 h in younger volunteers, perhaps due to a physiological decrease in pre-systemic metabolism. However, since no adverse effects of delayed clearance were noticed, and given that the 10mg dose was well tolerated by the elderly volunteers, it is not necessary to make any adjustments for elderly patients, at least at this dose.^{22,23,25}

Pharmacodynamic properties

Rupatadine is an anti-allergic drug with other benefits such as inhibition of mast cell degranulation, neutrophil and eosinophil migration and cytokine release.^{29,30} It exhibits strong antagonistic activity towards both histamine H1 and PAF receptors.¹⁹

Anti-histaminic and anti-PAF effects were studied using its ability to inhibit flare and wheals produced by intradermal injection of histamine and PAF, respectively.^{31,32} The specific inhibition of PAF was determined in blood using the *ex vivo* platelet aggregation test.¹⁹ These studies also included a nasal challenge test with a specific allergen in atopic volunteers.

Anti-histaminic activity

Rupatadine has a high affinity for the H1 receptor. Using the guinea-pig ileum functional test, the anti-histaminic activity of RU was compared with other first and second generation anti-histaminics.¹⁹ RU was more active than terfenadine, loratadine, cetirizine, hydroxyine and diphenhydramine. RU and

Table 1. Drug and food interactions of Rupatadine.

| Study ref. | Drug interaction | Effect studied | Findings |
|------------|--|-----------------------------------|--|
| 26 | Rupatadine 20mg – Ketoconazole 200mg/day | Metabolic drug - drug interaction | Ketoconazole inhibited both pre-systemic and systemic metabolism of Rupatadine, and increased the AUC of unchanged drug by about 10 fold and decreased the AUC of metabolites |
| 26 | Rupatadine 20mg – Erythromycin 500mg/day | Metabolic drug - drug interaction | Erythromycin increased the AUC of unchanged drug by 2 – 3 folds without increasing significantly elimination $t_{1/2}$ and systemic exposure of metabolites. Despite this increase in the plasma conc. of Rupatadine no adverse event was observed including any ECG parameter like QTc interval, laboratory tests, and vital signs. |
| 23 | Rupatadine 10mg – Azithromycin | Metabolic drug - drug interaction | No clinically relevant alterations in the pharmacokinetic parameters of Rupatadine and active metabolites were observed. |
| 23 | Rupatadine 20mg – Fluoxetine | Metabolic drug - drug interaction | No clinically relevant alterations in the pharmacokinetic parameters of Rupatadine and active metabolites were observed. |
| 23 | Rupatadine 10mg Rupatadine 10mg – Lorazepam | Sedation and mental ability | Does not impair mental ability and does not potentiate Lorazepam induced mental impairment |
| 27 | Rupatadine – grape fruit juice | Metabolic drug – food interaction | Grape fruit juice inhibits pre-systemic metabolism of Rupatadine, increasing the AUC of unchanged drug approximately threefold, without significant increases of systemic AUC of the two metabolites |
| 28 | Rupatadine – food | Drug – food interaction | Intake of food significantly increases the AUC of Rupatadine. The exposure to metabolites was virtually the same. The T_{max} of Rupatadine was delayed by 1 hour and C_{max} was not affected by food intake. Later differences had no clinical significance |

desloratadine show similar anti-histaminic activity *in vitro* (binding assay K_{iapp} =26 and 22 nM; RU and desloratadine, respectively). Some of the RU metabolites also exhibit anti-histaminic activity *in vitro*.

Peripheral anti-histaminic activity of RU was assessed by the percentage inhibition of flares and wheals induced by histamine pricks.³³ All RU doses (10, 20, 40, 80 mg) gave significantly different results as compared to placebo within 96 hours. The duration of wheal and flare suppression areas was dose-related. The long-lasting effect may be due to some metabolites. Low doses – i.e. 2 and 5 mg – showed percentage inhibition of approximately 50% in healthy volunteers. The percentage inhibition rose to 60% and lasted until 24 hours post 10mg dose of RU. A potent and prolonged inhibitory effect was demonstrated with the 20mg dose; a maximum inhibition of 71% was achieved and it remained above 45% until 72 hours.

Platelet activating factor antagonist activity

The PAF antagonistic activity of RU was documented using inhibition of platelet aggregation in rabbit platelet-rich plasma, washed platelets and dog whole blood, with IC_{50} (inhibitory conc. of 50%) values of 2.9, 0.2, and 0.29 mM respectively. The *in vitro* inhibition shown by RU was lower than that of a

selective PAF antagonist (WEB-2086). However, the inhibition was much greater than second generation anti-histaminics, which display little or no PAF antagonist activity. Dual effect – i.e. both anti-histamine and PAF antagonistic effect – was demonstrated by RU on histamine- or PAF-induced bronchospasm in a guinea pig model. This dual effect was not seen with loratadine or WEB 2086 – which is to be expected since the latter is selective for PAF and loratadine has a negligible action on PAF.¹⁹ Loratadine and cetirizine inhibit only histamine-induced wheal, while RU has been demonstrated to inhibit PAF-induced reactions as well.³⁴ In an animal model of conjunctivitis in guinea pigs, induced by histamine and PAF, it was observed that RU applied as eye lotion was approximately 10 times more powerful than loratadine against histamine-induced conjunctivitis, and, unlike RU, loratadine had no effect on PAF-induced conjunctivitis.³⁵ The maximum effect of RU occurs after four hours, and significant effects are observed even after 24 hours following single dose, indicating a long-lasting effect. It has been demonstrated that on increasing the dose of RU the extent of maximum inhibition of wheal and flare reaction not only increases but is also achieved earlier and the effect maintained for longer. The dose response relationship of

Table 2. Dose response relationship of Rupatadine on inhibition of wheal and flare induced by PAF.

| Dose of Rupatadine | Early inhibition | | Maximum inhibition | | Remarks |
|--------------------|------------------|-----------------------------|--------------------|-----------------------------|---|
| | Extent | Time taken to achieve (hrs) | Extent | Time taken to achieve (hrs) | |
| 10 mg | -- | -- | 41% | 24 | -- |
| 20 mg | 42% | 6 | 56% | 24 | Maintained up to 48 hours |
| 40 mg | 68% | 4 | 87% | 6 | Retained above 60% until 72 hours |
| 80 mg | 91% | 4 | 93% | 48 | Effect evident even at 96 hours post dose |

RU on inhibition of wheal and flare induced by PAF is summarised in Table 2.³³ The efficacy of RU increases linearly with increasing dose up to 40mg, beyond which the dose increments are associated with far smaller increments in efficacy.

Anti-cholinergic effects

Many of the first generation anti-histaminics are known to have anti-cholinergic effects. No anti-cholinergic effects were seen with RU at single doses in the dose range 10-80 mg in humans.³³

These studies clearly demonstrate that: 1) RU exhibits dual effect (anti-platelet and anti-histaminic) *in vivo*; 2) the anti-histamine effect is equal to or greater than that of other anti-histaminics; and 3) it is the only anti-histaminic compound which has significant PAF antagonist activity.

Wide spectrum anti-inflammatory action

RU shows potent anti-allergic activity *in vitro* and *in vivo* in various type I hypersensitivity models (mast cell degranulation and eosinophil chemotaxis inhibition). Efficacy in non-histamine dependent pharmacological models such as those involving endotoxin challenge and models of type III hypersensitivity reaction can probably be due to its PAF antagonistic activity. In the early phase response of the allergic process, the effector cells are mast cells which play an important role. RU has been shown to inhibit mast cell degranulation induced by non-immunological stimuli (compound 48/80 and calcium ionophore A23187) in rat peritoneal mast cells and also immunological stimuli (*Ascaris*) in isolated skin mast cells from sensitised dogs.³⁶ RU also reduced tumour necrosis factor release from canine skin mast cells and in the human mast cell line HMC-1.^{29,37}

In the allergic late phase response, the eosinophils and lymphocytes are important effector cells. In actively-sensitised guinea pigs challenged with antigen, RU inhibited the eosinophil recruitment in the bronchoalveolar lavage fluid.³⁸ It has been shown that eosinophils from allergic volunteers exhibited a markedly increased sensitivity in their chemotactic response toward PAF compared with eosinophils from normal

donors.³⁹ PAF is a potent stimulus for human eosinophil chemotaxis which is inhibited by PAF receptor antagonists.⁴⁰ Rupatadine's potent PAF antagonistic activity represents the likely mechanism behind its inhibition of eosinophil chemotaxis. RU has also been shown to inhibit the production of inflammatory cytokines after *in vitro* activation of human T cells especially Th2 cytokine IL-5.⁴¹

It is known that most of the anti-inflammatory effect of an anti-histaminic is produced in a histamine receptor-dependent manner. On the contrary, RU has been shown to inhibit the activity of transcription factor AP-1 both dependently and independently from the H1 receptor. Owing to its high affinity for the H1 receptor (K₁ 1.6 nM), it inhibits the histamine-induced IL-6 and IL-8 production at concentrations that are below the plasma levels reached at therapeutic dose.⁴¹

RU strongly inhibits hypersensitivity reactions *in vivo*, including both active and passive anaphylaxis in several species. It displays strong inhibitory activity in models of increased vascular permeability induced by antigen in sensitised beagle dogs.¹⁹ The duration of action was prolonged (>24 hours at 1mg/kg P.O.) and parallel to those observed in studies in which histamine was injected intradermally in dogs³⁴

In conclusion, rupatadine shows anti-inflammatory and anti-allergic profiles in various allergy models, tested in various species, both *in vitro* and *in vivo*, and in healthy and atopic individuals.

Safety profile

A total of 3490 patients or healthy volunteers have been exposed to rupatadine in clinical studies. The adverse effects in 2025 subjects exposed to RU 10mg in controlled clinical trials are summarised in Table 3.⁴² There is a dearth of evidence on the long-term (> 1 year) safety profile of RU in perennial allergic rhinitis. In a long-term uncontrolled study, 120 patients with persistent AR were exposed to RU for 12 months to evaluate its long-term safety according to European Medicine Agency guidelines.⁴³ The more frequent treatment-related adverse effects during this period were somnolence (6%) and headache, dry

Table 3. Summary of incidence of related adverse drug reactions in comparison with placebo in clinical controlled studies.

| Adverse events | Treatment | | | |
|----------------|-----------------------------|-----|--------------------|-----|
| | Rupatadine 10 mg (n = 2025) | | Placebo (n = 1315) | |
| | n | % | n | % |
| Somnolence | 192 | 9.5 | 45 | 3.4 |
| Headache | 139 | 6.8 | 74 | 5.6 |
| Fatigue | 64 | 3.2 | 26 | 2 |
| Dizziness | 21 | 1 | - | - |
| Asthenia | 30 | 1.5 | - | - |
| Dry mouth | 24 | 1.2 | - | - |

mouth, fatigue and rash (<1%). No relevant ECG findings or lab abnormalities were evidenced throughout the study. This study confirmed the good long-term safety profile of RU.

Cardiac safety

A prolonged QTc interval on the ECG is a feature that has been associated with drug-induced Torsades De Pointes (TDP), a potentially fatal polymorphic ventricular tachyarrhythmia identified by the continuously twisting appearance of the QRS complex in the 12-lead ECG.

In recent years, there has been a concern about the cardiotoxicity of non-sedating anti-histamines, with reports of TDP first with astemizole and later with terfenadine. The initial belief that cardiotoxicity was a class effect of non-sedating anti-histamines proved unfounded, since fexofenadine, the active metabolite that mediates the anti-histamine actions of terfenadine, does not seem to have these cardiotoxic effects. A dose of RU more than 100 times the clinically recommended dose of 10mg neither extended the QTc or QRS intervals nor did it produce arrhythmia in various species of animals such as rats, guinea pigs, and dogs.⁴⁴ RU and its main active metabolite in humans, 3-hydroxy desloratadine, does not affect cardiac action potential and isolated dog Purkinje fibres at concentrations >2000 times greater than the C_{max} reached after the administration of RU 10 mg in humans. In a study that evaluated the effect on cloned human HERG channels, RU inhibited the channel at a concentration of 1685 times greater than the C_{max} obtained after the administration of 10mg RU. A distribution study shows that it has no cardiac tropism, showing low cardiac tissue levels that are not even detectable at 24 hours after administration.⁴⁴ It has been demonstrated that the new generation of H1 receptor antagonists blocked several cardiac potassium (K^+) currents.⁴⁵ Moreover, it has been shown that they block hKv1.5 channels cloned from human heart and expressed in mammalian cell lines.⁴⁶ These channels are the counterpart of the ultra-rapid delayed rectifier current which is involved in the

control of duration of atrial action potentials in the human heart.⁴⁷ Caballero *et al.* studied the effects of RU on human cloned hKv1.5 channels expressed in Ltk⁻ cells using the whole-cell patch-clamp technique.⁴⁸ They demonstrated that RU blocked hKv1.5 channels in a concentration-, time-, and voltage-dependent manner. C_{max} achieved in healthy volunteers after oral administration of RU 20 mg per day is 5.5 nM.⁴⁹ This study indicated that these C_{max} values were almost 400-fold below the K_D for hKv1.5 block. Therefore, a pro-arrhythmic effect of RU due to blockade of this human K^+ channel is not expected. Recently a study by Hove-Madsen *et al.* revealed that the proarrhythmic anti-histaminic drug terfenadine alters intracellular calcium handling in isolated human atrial myocytes. Terfenadine also inhibits the L-type calcium current, significantly increases the spontaneous Na-Ca exchange current frequency and spontaneous calcium release from the sarcoplasmic reticulum. These effects were not seen with RU.⁵⁰

In accordance with guideline recommendation ICH E14, June 2004,⁵¹ a thorough QT/QTc study was performed in order to determine whether or not RU has a threshold pharmacological effect on cardiac repolarization, as detected by QT/QTc interval prolongation.⁵² The validity of the trial was demonstrated by the fact that moxifloxacin, the positive control group, demonstrated the expected change in QTc duration. The ECG data for RU at both 10 and 100 mg did not reveal any effect. There was no gender effect, pharmacodynamic relation of RU and its main metabolites, or imbalance in the outliers, which also confirms the lack of any effect of RU specifically on QTc duration. This study demonstrated that RU, at even 10 times the therapeutic dose, does not have any pro-arrhythmic side effects.

Central nervous system, cognitive and psychomotor effects

Even at high doses (100mg and 10 mg/kg orally in mice and cynomolgus monkey, respectively) RU has not been found to

cause any behavioural changes. In a study on guinea pigs, H1 receptor occupancy was studied in lungs and the central nervous system (CNS) – specifically the cerebellum.¹⁹ RU was administered at doses comparable to those used in humans and this ensured effective blockade of H1 receptors in the lungs. At these doses, in spite of effective blockade of H1 receptors in the lung, there was almost no H1 receptor blockade found in the CNS. This phenomenon was also seen with loratadine (a non-sedating anti-histamine) but not with hydroxyzine (a first generation anti-histamine).³³ Barbanoj *et al.* assessed the CNS activity of single increasing doses of RU in comparison with hydroxyzine and placebo in a crossover, randomised, double-blind, placebo-controlled study; treatments tested were RU 10, 20, 40 and 80 mg and hydroxyzine 25 mg, as a positive standard. CNS effects were obtained by objective tests of psychomotor performance and subjective mood scales. The study revealed significant impairment, of a similar magnitude, after hydroxyzine 25 mg ($p=0.01$) and RU 80 mg ($p=0.02$), while therapeutically-relevant lower doses of RU (10 and 20 mg) were similar to placebo.³³ Another study by Barbanoj *et al.* assessed the effects of alcohol 0.8 g/Kg on RU-associated CNS effects with doses of 10 and 20mg. Seven psychomotor performance tests (finger tapping, fine motor skills, nystagmus, temporal estimation, critical-flicker-fusion frequency, d2 cancellation, simple reaction) and 11 subjective self-reports (drunkenness, sleepiness, alertness, clumsiness, anger, inattentiveness, efficiency, happiness, hostility, interest and extraversion) were carried out. Results showed that single oral doses of RU 10 mg in combination with alcohol do not produce more cognitive and psychomotor impairment than alcohol alone. It was concluded that higher doses of RU, in combination with alcohol, may induce cognitive and psychomotor deterioration similar to hydroxyzine and cetirizine, even at therapeutic doses.⁵³

The effects of RU on driving were evaluated in a study performed on healthy human volunteers, and was compared with 50mg hydroxyzine or placebo.⁵⁴ Driving performance was assessed using a standard highway test, standard deviation of the lateral position, Stanford sleepiness scale, driving quality scale and rate of sedation. There was no difference between RU and placebo, whereas driving performance was impaired by hydroxyzine. The non-significant effects of RU on driving performance has also been highlighted by Jáuregui *et al.*⁵⁵

In conclusion, as regards CNS side effects, RU behaves similarly to second generation anti-histamines, and is non-sedative.

Clinical studies on rupatadine in allergic rhinitis

The efficacy of rupatadine as a treatment for allergic rhinitis has been investigated in several international, randomised, double-

blind, multi-centre trials. The target study population was patients suffering from moderate to severe AR – as documented by clinical records – for at least two years. Patients were required to score > 5 points for nasal symptoms in a standardised scale at inclusion, in order to recruit patients in the acute stage of the disease; in addition, this also ensured that only patients suffering from acute episodes of at least mild intensity would be included.

The main efficacy variables in these studies were based on daily subjective assessment of symptom severity recorded by patients in their diary. Overall efficacy impression was calculated from the score assigned by both the investigator and the patient in all studies according to the conventional scale.

The main efficacy variables were:

- 1) Mean daily total symptom score (DTSSm) – the main variable in the SAR studies. This is the mean of the daily symptom scores recorded for each of the assessed symptoms.⁵⁶
- 2) The percentage of days with a severity symptom score <1 (PDmax) for each patient – the main variable in the PAR studies.⁵⁷
- 3) Mean daily symptom score (DSSm); a secondary variable – the mean of all the scores recorded for a given symptom per patient and for all the study days.

Seasonal allergic rhinitis

All doses of RU have been shown to be more effective than placebo in alleviating the symptoms of SAR in a dose-dependent manner.⁵⁸ A summary of clinical trials covering the indications for the treatment of SAR is provided in Table 4.

Rupatadine 10 and 20 mg were superior ($p<0.05$) at improving nasal and ocular symptoms of SAR in comparison with placebo. Except for a general trend towards quicker relief of symptoms with RU 20mg after one week of treatment, no significant differences were detected between RU 10 and 20mg.⁵⁸

Rupatadine 10mg once daily was compared to ebastine 10 mg once daily and placebo.⁵⁹ Significant differences were detected in DTSSm between RU treatment and placebo (33% lower for RU group; $p=0.005$) after two weeks of treatment. Total symptom scores were 22% lower for RU than for ebastine; however, this could not reach statistical significance. In the symptom by symptom scores analysis, RU was superior to ebastine and placebo. As compared to placebo, RU reduced the severity of all symptoms with a statistically significant reduction found in sneezing, rhinorrhoea, lacrimation, and nasal itching. The greatest difference between active treatments and placebo was for rhinorrhoea (RU versus placebo, $p<0.001$; ebastine versus placebo, $p<0.005$).

The efficacy of RU and cetirizine was compared at 10mg/day for two weeks in SAR patients.⁶⁰ Both groups had similar responses in terms of mean DTSSm values. However,

Table 4. Summary of efficacy of Rupatadine in adults and adolescents (aged > 12 years) with seasonal allergic rhinitis.

| Ref | Study design | RU dose and comparative treatment | Treatment duration | Number of patients (randomized/ treated) | Efficacy results (DTSSm) |
|-----|--------------|-----------------------------------|--------------------|--|--|
| 58 | R, DB, PC | 10mg 20mg | 2 weeks | 178/174 | RU 10 vs PL* RU 20 vs PL* |
| 26 | R, DB, PC | 2.5mg 5mg 10mg 20mg | 2 weeks | 395/392 | Ru 2.5 vs pl* Ru 5 vs pl* Ru 10 vs pl* Ru 20 vs pl* |
| 59 | R, DB, PC | 10mg EBA (10mg) | 2 weeks | 250/243 | RU 10 vs PL* EBA vs PL ns |
| 60 | R, DB | 10mg 20mg CTZ | 2 weeks | 373/362 | RU 10 vs CTZ ns RU 20 vs CTZ ns |
| 61 | R, DB | 10mg 20mg LOR (10mg) | 2 weeks | 339/339 | RU10 vs LOR ns RU20 vs LOR ns* |

R: randomised, DB: double blinded, PC: placebo controlled, RU: Rupatadine, CTZ: cetirizine, PL: placebo, LOR: Loratadine
* p<0.05

evaluation of overall efficacy at day 7 revealed that 93.3% patients in the RU group and 83.7% patients in the cetirizine group showed significant improvement ($p=0.022$). The study suggested a faster effect of RU, since 81.1% of patients on RU had insignificant or absent symptoms of runny nose versus 68.6% in the cetirizine group.

The efficacy of RU at 10 and 20mg was evaluated against loratadine 10mg over two weeks in SAR patients.⁶¹ RU was more effective than loratadine at both doses. Patients on RU demonstrated scores for sneezing and nasal itching which were significantly lower than those observed in patients on loratadine.

A recent trial was performed to evaluate the efficacy of RU 10mg/day and placebo on allergen-induced symptoms (including nasal congestion), nasal airflow, nasal secretion and subjective tolerability in response to grass pollen in a controlled allergen exposure chamber.⁶² In a randomised double-blind placebo-controlled trial, 45 subjects with a history of SAR received RU or placebo every morning for eight days for two subsequent periods which were separated by a 14-day washout interval. On day 8 of each crossover period, subjects underwent a 6-hour allergen exposure in the exposure chamber in which a constant and homogenous concentration of aeroallergens was maintained. Subjective and objective assessments were performed online during the exposure. Subjective single and composite nasal and non-nasal symptoms were consistently less

severe with RU than placebo, starting from assessment time up to 15 min before the end of the 6-hour allergen challenge, with the most significant effects seen for nasal rhinorrhoea, nasal itching, sneezing attacks, and total nasal symptoms (all $p<0.0001$). All other symptoms including nasal congestion were also significantly reduced with the active treatment compared to placebo. The results suggest that, in patients with allergen-induced SAR, RU significantly reduced nasal and non-nasal symptoms as well as nasal secretion and subjective complaints, as compared with placebo. RU showed a rapid onset of action as indicated by statistically lower total nasal symptom score values compared with placebo, which were observed already at the first assessment time during controlled allergen exposure (15 min. $p=0.001$).

Perennial allergic rhinitis

Studies on the efficacy of rupatadine in PAR are summarised in Table 5. A dose-ranging placebo-controlled study demonstrated that RU 10 and 20mg provided better efficacy than placebo. However, the dose relationship was not established in this trial.^{26,64} The study compared RU at doses 10 and 20mg, loratadine 10mg, and placebo. Results showed that the mean PDmax over 28 days' treatment duration for RU and loratadine were consistently better than those for placebo (34.1%). Superior mean PDmax values were observed for RU 20mg (50.4%) which was slightly higher than that for RU 10mg (48.7%) and loratadine 10mg (48.6%). Statistically significant

Table 5. Summary of efficacy of Rupatadine in adults and adolescents (aged > 12 years) with perennial allergic rhinitis.

| Ref | Study design | RU dose and comparative treatment | Treatment duration | Number of patients (randomized/ treated) | Efficacy results (DTSSm) |
|-------|--------------|-----------------------------------|--------------------|--|--|
| 26,64 | R, DB, PC | 10mg 20mg | 4 weeks | 248/245 | RU 10 vs PL* RU 20 vs PL* |
| 26,64 | R, DB, PC | 10mg 20mg LOR 10mg | 4 weeks | 283/283 | RU 10 vs PL* RU 20 vs PL* LOR vs PL* |
| 26,64 | R, DB, PC | 10mg EBA 10mg | 4 weeks | 223/219 | RU 10 vs PL* EBA vs PL* |
| 26,64 | R, DB, PC | 10 mg 20 mg CTZ 10mg | 4 weeks | 282/273 | RU 10 vs PL* RU 20 vs PL* CTZ vs PL |
| 63 | R, DB, PC | 10mg CTZ 10mg | 12 weeks | 543/542 | RU 10 vs PL* CTZ vs PL ns |

R: randomised, DB: double blinded, PC: placebo controlled, RU: Rupatadine, EBA: Ebastine, CTZ: cetirizine, PL: placebo, LOR: Loratadine
* p<0.05

differences for mean PDmax were only detected between RU 20mg and placebo. According to DTSSm values the two active treatments with RU and loratadine were superior to placebo, reaching statistical significance in all three active treatment groups. RU produced a greater reduction in symptom severity compared with placebo in five symptoms, of which rhinorrhoea, sneezing and conjunctival itching were statistically significant, whilst differences between loratadine and placebo were statistically significant only for rhinorrhoea and nasal itching.

Another study compared RU 10mg, ebastine 10mg and placebo to evaluate the efficacy and safety of RU in the treatment of PAR over 28 days' duration.⁴² PDmax for both treatment groups was similar and was significantly better than placebo. RU 10mg produced a greater reduction than placebo in the severity of each of five symptoms, with statistically significant differences found for sneezing, itchy eyes and itchy nose. On the other hand the difference between ebastine and placebo was significant only for sneezing and itchy nose. The investigator's impression was that only RU showed statistically significant improvements over placebo.

A similar trial was performed comparing two doses of RU (10 and 20mg), cetirizine 10 mg and placebo in patients suffering from PAR.²⁵ PDmax scores recorded in all three treatment groups were significantly higher than in the placebo group (p<0.0001). The best value was reported with RU 20 mg in comparison with placebo (p<0.0001), RU 10mg and cetirizine 10mg (43%). Improvements were also superior to

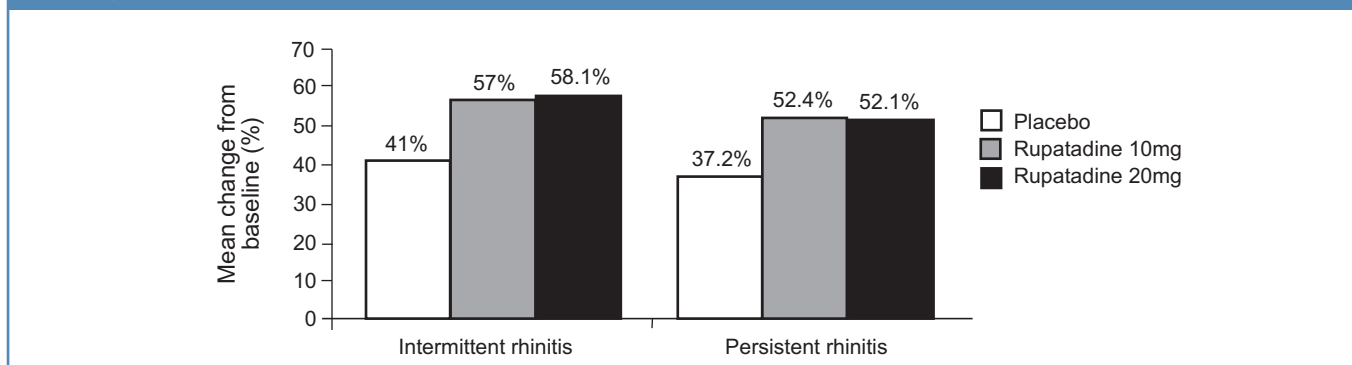
placebo (p<0.01). There was no significant difference in the pair-wise comparison between the three active treatment groups. Patients treated with RU 10 and 20 mg as well as cetirizine 10 mg had lower scores for the evaluated symptoms than patients receiving placebo. Individual symptom scores for active treatments were better than with placebo (p<0.001). Differences reached a higher level of significance in all four nasal symptoms (including nasal obstruction) and near to significance (p=0.057) in conjunctival itching. Investigator rating of overall efficacy was similar to that of patients. Both reported active treatment to be more effective than placebo at the second and last week of therapy.

Recently, a study was conducted to assess the efficacy of RU in moderate to severe AR.⁶³ Patients were randomised to treatment with either RU 10mg, cetirizine 10mg or placebo for 12 weeks. The primary efficacy endpoint was the 12-week average change from baseline of the patients' Total Symptom Score (Tss). Rupatadine, but not cetirizine, reduced the baseline Tss statistically more than placebo (p=0.008). Study treatments were well tolerated and no relevant ECG changes or symptomatic lab abnormalities were evidenced throughout the study.

Post-ARIA pooled analysis of efficacy studies in allergic rhinitis

An exploratory analysis was performed to assess the efficacy of RU, pooling data from pivotal clinical studies developed before the ARIA document.^{64,65,66} The existing ten studies, using the seasonal and perennial rhinitis classifications, were re-examined

Figure 2. Pooled analysis of efficacy of Rupatadine 10 and 20 mg in comparison to placebo. Data obtained from seven clinical trials expressed as percentage of reduction from baseline of total symptoms score during the entire double blinded period



Key Messages

Rupatadine is a once-daily non-sedative, selective, long-acting H1 anti-histamine with antagonistic PAF effects. Rupatadine significantly improves nasal symptoms in patients with allergic rhinitis. It has a good safety profile devoid of arrhythmogenic effects and several interactions. Rupatadine does not affect driving performance. These properties make rupatadine a suitable first-line anti-histamine for the treatment of allergic rhinitis.

to assess whether the AR characteristics of patients enrolled in these studies met the ARIA classification criteria.⁶⁵ Intermittent rhinitis was defined when symptoms were present for less than four weeks and persistent when symptoms lasted for more than four weeks.

A total of seven studies were included in the analysis, involving a population of 560 patients with intermittent, and 708 with persistent, allergic rhinitis. A summary is presented in Figure 2. Both doses (10 and 20mg) of RU caused high and significant reduction of Tss ($p < 0.001$) in comparison with placebo in both intermittent and persistent rhinitis. This study confirms that these doses of rupatadine – 10mg and 20mg – are effective in the control of rhinitis symptoms using the ARIA rhinitis criteria.

Conclusions

Rupatadine (RU) is a once-daily non-sedative, selective, long-acting H1 anti-histamine with antagonistic PAF effects through its interaction with specific receptors. In the treatment of allergic rhinitis (AR), RU 10mg and 20 mg per day is better than placebo and at least as effective as ebastine, cetirizine, loratadine and desloratadine, with a possible faster effect than cetirizine. RU significantly improves nasal symptoms in patients with AR. It has a good safety profile devoid of arrhythmogenic

effects, and has no interactions with azithromycin, fluoxetine and lorazepam, though co-administration with erythromycin, ketoconazole or grapefruit should be avoided. It has been safely administered for over one year. Rupatadine does not affect driving performance. Adverse events related to RU have been similar to those with comparators. These properties make RU a suitable first-line anti-histamine for the treatment of AR.

Conflicts of interest

None declared.

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