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REVIEW

How to handle off-label prescriptions of rupatadine, a second-generation antihistamine and PAF antagonist: a review

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Abstract

The off-label use of second-generation antihistamines, used outside of the formal indications authorized by regulatory authorities, in different age groups, doses or in special populations, is very common for many allergic, autoimmune and dermatological diseases. The off-label use of rupatadine (a second-generation antihistamine with PAF antagonist activity) in these conditions is reviewed here, including in combination with immunotherapy in the treatment of food allergy or allergic rhinitis, at high doses in chronic urticaria, and with prescriptions of less common but challenging conditions such as skin pruritus or mast cell activation disorders like mastocytosis. Rupatadine use is reviewed herein to confirm if its off-label management is supported by well-designed clinical trials or by published real-world cases. This review will contribute to increasing compliance and achieving better results in clinical practice. Off-label use of rupatadine should be left to the discretion of the prescribing healthcare professional after careful clinical evaluation.

Keywords: allergic rhinitis, antihistamine, chronic spontaneous urticaria, mast cell activation disorders, off-label use, platelet-activating factor, pruritus, rupatadine.

Citation

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Introduction

This paper reviews current data regarding the day-to-day use of rupatadine, as an example of a second-generation antihistamine (sgAH), in a clinical setting, and specifically its off-label use in patients based on the extensive practical prescription of this compound over the last 20 years. Rupatadine is highly selective for histamine H1 receptors, exhibits platelet-activating factor (PAF) antagonist activity and may cause adverse effects comparable to those of other sgAHs, as described below.

In general, off-label use can be defined as prescriptions of a medication outside of the formal indications authorized by regulatory authorities, in a different age group, or at a different dose than those approved.

The objective of this review is to comment on the off-label use of rupatadine in clinically relevant situations and to highlight the available evidence and data that allow the prescriber to optimize disease management in clinical practice. In this review, we summarize the specific clinical evidence regarding the usage of rupatadine in allergic or autoimmune-related conditions. A synopsis of included case reports and clinical studies, along with their evidence level, based on the Oxford Centre for EBM (OCEBM), is presented in Table 1. In conjunction, we offer a comment on queries made by healthcare professionals and the medical departments of authorized, cross-licensing pharmaceutical companies as answered by the Medical Advice Department of BIOHORM S.L. and the Pharmacovigilance Department of NOUCOR HEALTH, S.A. It is important to point out that some of the doubts and responses are related to the use of rupatadine for indications or at dosages that are not approved in some countries. Although medical department staff handled answers to such queries based on the best evidence currently available, the answers provided herein should not be

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Table 1. Studies and case reports on the off-label use of rupatadine for several allergic and autoimmunological disorders.

Disease	Specific condition	Rupatadine dosage	Evidence type	Proposed mechanism of action	Response to the treatment	Level of evidence (OCEBM)	Refs.
Allergic rhinitis	Local allergic reactions to SLIT-T	5 mg/day × 2 weeks before SLIT-T; 10 mg OD before SLIT-T and 10 mg/day during first 2 weeks of the SLIT-T	Case series	Specific role of PAF in SLIT-T-associated side-effects; local allergic reaction pathogenesis has not been elucidated	Ameliorates local allergic reactions	4	[1]
Food allergy	Systemic and local adverse effects on OIT	Not specifically reported	Case series	Antihistamine premedication can markedly improve the safety and efficacy of OIT	Reduces the frequency and severity of reactions	–	Unpublished clinical cases
Conjunctival allergies	Ocular symptoms	10 or 20 mg/day × 2–4 weeks	Clinical trials	PAF activities are highly correlated with the signs and symptoms of allergic conjunctivitis	Fast improvement of ocular symptoms	2	[11,12]
Allergic rhinitis in paediatric patients	Patients aged 2 years old or pre-school children	2.5 or 5 mg/day × 4 weeks	Clinical trials	H1 and PAF receptor blockage improve allergic nasal and non-nasal symptoms	Improvement of nasal and ocular symptoms	2	[16,17]
CSU and inducible urticarias	High doses in adults and paediatric patients	20–40 mg/day in adults/adolescents 5, 10 mg/day in children >2 years old	Clinical trials	H1 and PAF receptor blockage improves urticaria symptoms (pruritus and wheals)	Improvement of CSU symptoms and reduction of period relapses	2	[24,25,26,27]
Atopic dermatitis; CSU and other itching skin diseases	Pruritus and prurigo	10 mg/day (first 2 weeks) or 20 mg/day × 52 weeks	Clinical trial	H1 and PAF receptor blockage improves skin itching	Significantly alleviates itch in patients with eczema, dermatitis, pruritus and CSU on a short-term and long-term basis	2	[38]

(Continued)

Table 1. (Continued)

Disease	Specific condition	Rupatadine dosage	Evidence type	Proposed mechanism of action	Response to the treatment	Level of evidence (OCEBM)	Refs.
Mast cell activation disorders	Cutaneous and systemic mastocytosis	20 mg × 4 weeks	Clinical trial	*In vitro*-demonstrated blockage of the effects over mast cell secretion	Improvement in symptoms (flushing, tachycardia, and reduction in itching and whealing) and quality of life	2	[41]
Mosquito bite cutaneous reaction	Hypersensitivity to mosquito bite	10 mg OD prophylactically administered	Clinical trial	H1 blockage; this mechanism is supported by reduction of wheal size and pruritus	Significant reduction of immediate bite reactions (wheal and itch) compared with placebo	2	[46]

CSU, chronic spontaneous urticaria; OCEBM, Oxford Centre for Evidence-Based Medicine (https://www.cebm.ox.ac.uk/resources/levels-of-evidence/ocebm-levels-of-evidence); OIT, oral immunotherapy; SLIT-T, sublingual immunotherapy tablets.

taken as an endorsement by the pharmaceutical company (BIOHORM SL; NOUCOR Health S.A., Spain) of the off-label use of rupatadine. However, in many cases, unauthorized use may be disseminated by an expert as a key opinion in their publications or by a researcher who bases their recommendation on recent findings obtained through specific research studies.

Data availability statement

Data derived from published articles and data file of the sponsor.

Review

Allergy-related conditions

Prevention of local allergic reactions with sublingual allergy immunotherapy

Sublingual immunotherapy tablets (SLIT-T) are a very common therapy for patients with allergies, and their safety and tolerability have been demonstrated in multiple clinical trials. However, approximately 80% of treated patients experience mild-to-moderate local allergic reactions (LAR),[1] including sore throat, itchy mouth, itchy ears, itchy tongue and oedema in the mouth. These effects usually resolve within 30–60 minutes because SLIT-T-induced LARs are generally acute allergic reactions similar to skin-prick tests or reactions caused by environmental allergens. The allergen that is introduced into the oral mucosa with this therapeutic modality leads to an acute allergic response mediated by IgE, in which histamine, PAF and other mediators participate in a relevant way.

Some cases of LAR after SLIT-T therapy have recently been treated or pre-treated with rupatadine to assess the effectiveness of this sgAH against this type of acute local reaction.[2] It is interesting to note that three of the cases were pre-treated with another sgAH to prevent LAR but the reaction continued and was upsetting enough for patients to discontinue SLIT-T. In these three cases, SLIT-T treatment was restarted in conjunction with rupatadine at the labelled dose and form (oral solution or tablets), and the LAR clearly remitted or the symptoms were reduced faster in relation to using other sgAHs'. The pathogenesis of LAR has not been elucidated, but PAF is known to have an active role in allergic inflammation and sensitivity reactions and anti-PAF agents have the ability to ameliorate these effects.[3–5] This finding shows that rupatadine possibly has advantages over conventional sgAHs in the treatment of LAR due to its dual mechanism of action. In summary, the use of rupatadine resolved LAR associated with SLIT-T treatment and rupatadine pre-treatment appeared to mitigate subsequent LAR. Thus, rupatadine may be an option to prevent and mitigate unwanted SLIT-T side-effects.

Improvement of oral immunotherapy tolerance in food allergy

Food allergy is an increasing global health problem, affecting more than 8% of children and adults in western countries and rising in other parts of Asia and South Africa, mainly in urban environments.[6] In addition to the significant impact that food restriction has on the affected individuals, food allergies influence the lives of patients, their families and the community. Oral immunotherapy (OIT) has been employed in recent years to increase the threshold of IgE-mediated responses to allergenic foods, for example, cow's milk, egg and peanuts. However, OIT is often associated with significant systemic and local adverse effects, including gastrointestinal, respiratory and cutaneous manifestations that limit compliance, hinder a good immunotherapy progression to sufficient allergen doses, and represent a major barrier to implementing an effective treatment regimen.[7] Presently, there is no consensus as to whether antihistamine premedication could improve such conditions. More recently, antihistamine premedication was shown to be able to markedly improve the safety and efficacy of OIT by reducing the frequency and severity of these reactions.[8,9]

We have been informed of clinical cases employing off-label use of rupatadine in paediatric food allergy in patients undergoing several immunotherapy regimens. The outcome was a reduced number and intensity of adverse effects and the facilitation of reintroduction of small amounts of food. Concretely, we received notifications of the usage of rupatadine oral solution or tablets to pre-treat patients undergoing OIT; unfortunately, these findings have not yet been published. Further well-controlled studies should be conducted to clarify the use of sgAHs and rupatadine in these IgE-mediated food allergy reactions.

Conjunctival allergies

Many allergens reaching the ocular surface trigger allergic reactions presenting as several forms of conjunctivitis, mainly occurring as seasonal allergic conjunctivitis or, less frequently, as perennial allergic conjunctivitis. This ocular inflammatory disorder is mediated by multiple effector cells located in the conjunctiva and cornea that interact during the initiation and progression of the pathological process. Mast cell mediators, particularly histamine and PAF, trigger and maintain the acute and late phases of the allergic cascade.[10] PAF and its receptor mRNA are present in the cornea, iris, ciliary body, retinal ganglion cells, microglial cells and blood vessels of the choroid, and it is also known that PAF is released into the tear film upon conjunctival provocation.[11] Moreover, PAF causes the accumulation of eosinophils and increases the upregulation expression of PAF receptors, which in turn improves vascular permeability, oedema and ocular

itching. All these PAF-mediated effects are highly correlated with allergic conjunctivitis symptoms. It has been postulated that a combined treatment with an antihistamine and PAF-receptor antagonists would allow possible additive and/or synergistic effects for good control of ophthalmic inflammatory symptoms.[10]

Several clinical trials, in multiple geographic locations in Europe have demonstrated that rupatadine not only significantly reduces runny nose, sneezing and nasal itching but also significantly reduces ocular itch in patients with rhinitis when treated over a 4-week dosing period.[12,13] All these data support the prescription of rupatadine in patients with rhinoconjunctivitis as a first line of treatment.

Allergic rhinitis in paediatric patients

Off-label or unlicensed medicine use is very common in paediatric practice, ranging from 11% to 80%, and is a predisposing factor for adverse events (23–60%).[14] This off-label use is common for many paediatric illnesses, including allergic disease. In general, off-label prescription rates range from 11% to 37% in children treated in the community setting, and up to 62% in children in paediatric hospital wards.[15] This important prescriptive practice, outside the conditions of authorized use, is undoubtedly influenced by several factors, one of them being the paucity of clinical evidence available for children of preschool age. It is curious that very few clinical studies of sgAHs have been designed or conducted for this age group.[16] The methodological and ethical inconveniences of carrying out a clinical study in this age group are generally considered too high to be practical. Thus, efficacy studies in allergic rhinitis are very sparse for children under 6 years of age. This is true even for sgAHs that are commonly prescribed for those ages, where the only data available are open safety studies at an extrapolated dose obtained from previous studies with adults and/or adolescents.[16] Rupatadine is a valid therapeutic option for these ages due to its development and approved clinical efficacy studies in children over 2 years of age[17,18] following current recommendations in paediatric guidelines.[19]

Another factor that contributes to this excessive off-label prescription is the variety of sgAHs authorized in different countries with different approved age ranges. For example, levocetirizine was approved by the FDA in 2009 for use in children and infants from 6 months of age[20] after the publication of long-term trials that demonstrated its safety in this paediatric population. In contrast, in European countries, levocetirizine is still only approved for children over 2 years of age; therefore, off-label use in children 6 months to 2 years old is very high in countries such as Portugal, for example.[21]

Dermatology-related conditions

Off-label dosages in chronic spontaneous and inducible urticarias

The overall prevalence of chronic spontaneous urticaria (CSU) has been estimated to be between 1% and 1.5% in the general population, with a lifetime prevalence of 15–30%; acute spontaneous urticaria represents the most common clinical form.[22] Treatment with sgAHs is established with level 1 evidence and a grade A recommendation in patients with CSU.[23] At the approved dose, however, complete freedom from symptoms can only be obtained in a small number of patients, and more than 50% of individuals with CSU do not achieve complete symptom control with treatment.[23]

From real-world clinical data, patients with CSU can be categorized into one of three groups: (1) responders to the currently approved doses of sgAHs; (2) non-responders to the currently approved doses but responders to an up-dosing strategy of sgAHs; and (3) non-responders to sgAHs at any dosage.[23] These three groups do not necessarily relate only to different patients but also to different periods of the disease in the same patient. For those in the second group, the current clinical guidelines recommend a dose increase of up to four times the approved dose[24] as an off-label prescription. This strategy is supported in the case of some sgAHs because their manufacturers have performed clinical studies exploring the level of efficacy and safety up to four times the regular dose.[25]

The efficacy of rupatadine in the treatment of moderate-to-severe CSU was evaluated in several well-designed randomized placebo-controlled trials in white and Japanese patients.[26,27] These studies showed that rupatadine at 10 mg and 20 mg once daily significantly reduced CSU symptoms and improved the quality of life. A pooled analysis of several clinical studies was performed based on the clinical response of patients with criteria defined as the percentage of patients, after 4 weeks of treatment, who exhibited a reduction of symptoms by at least 50% or 75% compared with baseline. Responder rates (50%) as assessed by urticaria activity score over 7 days were 65%, 73% and 44% in patients treated with rupatadine at 10 mg, 20 mg and placebo, respectively. Finally, the weekly urticaria activity score reported a significant reduction of at least 75% in the 10 mg (35%) and 20 mg (48%) rupatadine groups when compared with the placebo group (14%).[26] These results are in line with the recommendation of current guidelines for the treatment of urticaria and support the use of off-label prescription of rupatadine in patients with urticaria.[24] Studies using off-label 20 mg and 40 mg doses of rupatadine have also been performed on a type of chronic inducible urticaria (CIndU) named cold urticaria. These studies

were designed as randomized, double-blind, placebo-controlled, crossover studies, and demonstrated that both 20 mg and 40 mg were effective in reducing cold-induced symptoms and in lowering the critical temperature threshold, which is the lowest temperature necessary to induce a clinical response of wheals and rashes.[28,29] Other sgAHs have no long-term use evidence in CIndU, and only evaluate outcomes up to 2–4 weeks, whereas 20 mg rupatadine was followed-up in a long-term (1 year) prospective clinical study of patients with CIndU,[30] showing good control of disease symptoms by using a continuous treatment regimen instead of on-demand therapy.

Although the widespread use of these off-label doses in patients with CSU or CIndU is observed in clinical practice, it seems that patients with the most severe disease, with a history of frequent relapses and/or poor response, do not access assessment in efficacy trials in significant proportions, which would account for the 'lower doses' usually being approved and being less effective in a non-negligible proportion of patients with more severe disease in clinical practice. We are currently investigating the management of CSU and CIndU by recording real-world patient data in a retrospective cohort with 5 years follow-up. As expected, in clinical practice, specialists prescribe off-label doses in more than half of patients treated with rupatadine and in a lower percentage of patients treated in combination with other therapeutic options (e.g. cyclosporine or omalizumab).

Finally, because urticaria is not an exclusive histamine-mediated disease and other mediators and inflammatory infiltrates are also involved in its pathogenesis, a variable percentage of patients does not respond to treatment with sgAHs, as previously mentioned.[23] PAF could be a key player in the pathogenesis of chronic urticaria. Indeed, intradermal injection of PAF has been found to induce wheal and flare reactions in human skin that are not associated with histamine release and, therefore, appear to be independent of mast cell degranulation.[31,32] A couple of recent studies showed that PAF serum levels could be a significant predictor of a poor response to off-label, high-dose sgAH. Therapeutic strategies to inhibit PAF or to stimulate PAF-acetylhydrolase may be beneficial for patients with sgAH-refractory CSU.[33,34]

Pruritus related to skin diseases

The interaction of histamine with its receptors, located on the sensory nerve endings, is responsible for the reflex erythema and pruritus associated with several diseases.[35] Various substances delivered into the dermis are pruritogenic, for example, biogenic amines, neuropeptides, proteinases, cytokines, acetylcholine, opiates, PAF-like lipids and prostaglandins.[36,37] It has been postulated that, in addition to the H1-receptor inhibitory effects of conventional antihistamines, other effects such as PAF receptor inhibition may improve the itching response. In fact, PAF receptors, like H1 receptors, are G protein-coupled receptors, the 'dual' activity of which would amplify the inhibitory effect of these receptors and could reduce itching more effectively.[38]

Although H1 antihistamines are not approved as a treatment for pruritus and prurigo, they are frequently used off-label in these diseases. Current Japanese guidelines recommend the use of a vast array of (mostly off-label) drugs with different mechanisms, including antihistamines, gabapentinoids, antidepressants, immunosuppressive drugs and μ-opioid receptor antagonists, to treat pruritus.[39] The Japanese guidelines state that the use of antihistamines can be considered as an initial treatment; although double-blind studies on antihistamines for cutaneous pruritus have not been conducted (Level C1), their use may be considered.

Clinical evidence is available in Japan, where doses of 10 mg and 20 mg of rupatadine were evaluated in a prospective clinical trial and both doses are authorized for the treatment of itchy skin diseases.[40] Despite the use of sgAHs for pruritus or prurigo in Japan, in many western countries, sgAHs are not indicated for itching and must be prescribed off-label to treat the symptoms. Therefore, off-label prescription of sgAH for symptomatic treatment is common for a multitude of dermatological and/or systemic diseases, where chronic pruritus is the main symptom. These dermatological diseases include scarring and non-scarring alopecia, acne, Darier disease, eosinophilic dermatoses, paraneoplastic dermatoses, psoriasis, lichen nitidus, radiation dermatitis, skin dysesthesia and cutaneous malignancies. However, most of these pathologies have only been documented at best as case reports or cohort studies.[41] Therefore, more randomized controlled trials are needed to evaluate the true clinical efficacy.

Mast cell activation disorders

Mast cell activation disorders (MCADs) are a rare, heterogeneous group of diseases characterized by an abnormal proliferation and accumulation of mast cells in one or more organs of the body. These cells release large amounts of histamine and other chemical mediators into the bloodstream, causing symptoms such as skin rash, itchy skin and hot flushes.[42] Clinically, patients may experience skin lesions and symptoms related to the release of mast cell mediators (histamine, PAF, leukotrienes or prostaglandins), which can dramatically impact their quality of life.

The off-label use of sgAHs is routinely prescribed to accelerate the diagnosis of MCADs in many patients and

also to prevent or reduce the effects of the released mast cell mediators; for example, sgAHs and/or histamine type 2 receptor antagonists are used to mitigate the effects of histamine release. Such medications are typically given in a stepwise dosage on a regular (daily or twice-daily) basis for a 3–6-month trial period. If a patient responds appropriately to this treatment, a diagnosis of MCADs is probable. Despite this common application, no evidence-based studies showing efficacy of sgAH in the treatment of MCADs has been performed during the last two decades.[43] In general, only very sparse data from small studies (enrolling 8–15 patients) have been published, and these use agents and/or dosing regimens that are now less commonly used in clinical practice (i.e. azelastine, chlorpheniramine, hydroxyzine and ketotifen).

The pharmacological profile of rupatadine offers some benefits as a strong antagonist of both histamine H1 and PAF receptors. Rupatadine has demonstrated, in vitro, its unique capacity to block the effects of mast cell secretions.[44] Treatment with 20 mg of rupatadine was shown to cause a clear improvement in Darier's sign in a double-blind crossover study (compared with placebo) in patients with MCAD after a standardized skin challenge. Additionally, there were statistically significant reductions in the severity of skin reactions, flushing, tachycardia and headache but not gastrointestinal symptoms during the rupatadine treatment period compared with placebo.[45]

In conclusion, rupatadine has shown moderate efficacy in MCADs. It is, however, urgent to investigate the use of this and other sgAHs in the treatment of primary MCADs. Well-executed dose–response studies are also needed given that high-dose treatment with sgAHs is now recommended in much the same way as in the CSU guidelines.[24]

Cutaneous allergy after mosquito bites

Mosquitoes cause uncomfortable skin reactions after a bite such as immediate hives or wheals and delayed papules in children and adults. People exposed for the first time to the bites of certain mosquito species are first non-reactive but, after repeated bites, they can become sensitized and persist for years.[46] In heavily exposed areas, such as Nordic countries in Europe, Canada and Japan, children and most adults are more sensitized and react to the bites of the most prevalent mosquitoes such as the *Aedes* genus.

Allergic reactions, including severe local and systemic reactions to mosquito bites, are immunological in nature, and involve IgE, IgG and T lymphocyte-mediated hypersensitivities in response to allergens in mosquito saliva.[47] In agreement with this, off-label use of oral sgAHs in adults and in children has been shown to decrease whealing and accompanying pruritus in placebo-controlled trials.[48] Rupatadine 10 mg is effective in reducing itching and wheals associated with mosquito bite allergy as evaluated in a double-blind, placebo-controlled study.[49]

Conclusion

This review aimed to increase clinicians' awareness of off-label prescription of sgAHs, specifically rupatadine, to increase the available clinical information, provide a justification for its use, assess the benefits relative to the risks, increase compliance and treatment adherence, and to contribute to achieving better treatment results in clinical practice. Additional, well-designed studies are encouraged given the relatively low cost and safety of sgAHs and the likely benefits of their use on disease symptoms and costs of healthcare compared with more expensive therapies.

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