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Efficacy and safety of the combination nasal spray olopatadine hydrochloride-mometasone furoate in the treatment of allergic rhinitis

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Abstract
Introduction Pharmacotherapy is the main pillar in the treatment of allergic rhinitis. While antihistamines (AH) and intranasal glucocorticosteroids (INCS) have long been part of the therapeutic standard, a pharmacological combination of both active substances in a nasal spray has so far only been implemented and made available in two preparations in Germany. Recently, an intranasal olopatadine hydrochloride-mometasone furoate (Olo-Mom) combination was introduced as a nasal spray for the treatment of seasonal and perennial allergic rhinitis.
Methods In a literature search, treatment options for allergic rhinitis were analyzed and the available evidence was determined by searching Medline, PubMed, and the national and international study (ClinicalTrials.gov) and guideline registers and the Cochrane Library. Human studies published on the topic in the period up to and including August 2023 were taken into account.
Results Based on the international literature and previous experience, the results are summarized and recommendations are given. The drugs used in the pharmacotherapy of AR primarily include INCS, intranasal and oral AH, leukotriene antagonists, intranasal cromoglicic acid preparations, intranasal and oral vasoconstrictors, and nasal rinses. For patients with intermittent and persistent allergic rhinitis, INCS are the first-line therapy, but in many patients they do not work sufficiently or quickly enough. The fixed combination Olo-Mom nasal spray showed significant improvements in the Reflective Total Nasal Symptom Score (rTNSS) in two phase II clinical trials with twice-daily and once-daily administration. In phase III studies, Olo-Mom nasal spray administered twice daily showed significant improvements in rTNSS compared to placebo, olopatadine monotherapy, and mometasone monotherapy.
Conclusion In summary, AH and INCS will remain the main groups of active ingredients in the treatment of allergic rhinitis in the future. In combination preparations such as the new combination nasal spray olopatadine hydrochloride-mometasone furoate, they are highly effective and safe, thus opening up new perspectives, especially for patients with moderate and severe allergic rhinitis from the age of 12 years.

Keywords INCS · AH · GSP301 · Quality of life · rTNSS · Clinical trials

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Abbreviations

ABWS	Anchored Best-Worst Scaling
ADR	Adverse drug reactions
AH	Antihistamines
AR	Allergic rhinitis
Aze-Flu	Azelastine/fluticasone nasal spray
EAACI	European Academy of Allergology and Clinical Immunology

FDA	Food and Drug Administration
INAH	Intranasal antihistamines
INCS	Intranasal glucocorticosteroids
iTOSS	Instantaneous Total Ocular Symptom Score
Olo-Mom	Olopatadine hydrochloride mometasone furoate nasal spray
OOA	Onset of action
PAR	Perennial allergic rhinitis
RCT	Randomized controlled trial
rTNSS	Reflective Total Nasal Symptom Score (reflective nasal total score)
rTOSS	Reflective Total Ocular Symptom Score (reflective total ocular symptom score)
SAR	Seasonal allergic rhinitis
TEAEs	Treatment-related adverse events

Introduction

Allergic rhinitis (AR) is very frequently caused by pollen from grasses, herbs, and trees or animal dander, house dust mites and molds, although the prevalence varies considerably in different regions of Europe and the world [1, 2]. The prevalence is clearly age-dependent. In a birth cohort study, the sensitization rate to *Phleum pratense* was 9.7% at the age of 4 years, 28.4% at the age of 8 years, and 37.1% at the age of 16 years [3]. It has long been known that the prevalence of AR peaks in the second to fourth decade of life [4]. Furthermore, AR is a known risk factor for the development of bronchial asthma, and vice versa this comorbidity is significantly increased [2, 5–7].

Typical symptoms of AR include rhinorrhea, nasal congestion, sneezing, and itching [8, 9]. Furthermore, itching and redness of the conjunctiva as well as lacrimation, itching of the throat, oral mucosa, and external auditory canals can occur, as well as nonspecific symptoms such as a general feeling of illness, weakness, tiredness and fatigue, and sleep disturbances [2, 10]. These symptoms can have a negative impact on quality of life and/or performance at work and school [11, 12].

Traditionally, AR is divided into a seasonal and perennial form depending on seasonal (mainly outdoor) allergens present in the patient's environment such as pollen or perennial (mainly indoor) allergens such as house dust mites, animal dander, and mold spores.

However, these terms can be contradictory, as the symptoms of seasonal allergies can be present for several months of the year and the concentrations of year-round allergens can change seasonally [13–15].

Seasonal and perennial AR can occur side by side, with symptoms increasing in severity during certain seasons and up to 80% of patients exhibiting a mixed form [13, 14]. Therefore, a new classification into *intermittent* and *persistent allergic rhinitis* is used today [2, 16]. The new definition does not take into account the type of triggering allergen primarily, but the duration of symptoms [16]. This classification was adapted to the German healthcare system [2]. A validation study of the ARIA classification in France found that approximately 43.7% of patients with seasonal AR actually had persistent rhinitis, while 44.6% of patients classified as having perennial AR could be classified as having intermittent rhinitis [17], which was confirmed in further studies in Germany and Western Europe [18, 19]. For therapy, it is important to note that patients with seasonal AR can also suffer from long-term symptoms over several seasons and that perennial allergic rhinitis does not necessarily mean that the patient has symptoms all year round, but that it can also be intermittent [20, 21].

Several mediators are involved in the pathophysiology of AR. In the early reaction phase (within minutes after exposure), inflammatory mediators from mast cells such as histamine, cytokines, leukotrienes, and prostaglandins are essential [22]. These mediators are responsible for clinical symptoms such as nasal congestion, sneezing, itching, and/or rhinorrhea. In the late phase (after hours), there is an influx of inflammatory cells such as eosinophils, basophils, monocytes, and neutrophils, which release interleukins and can lead to long-lasting or chronic symptoms.

Treatment options for allergic rhinitis

The treatment of AR includes avoiding contact with the triggering allergen (allergen avoidance), pharmacotherapy, allergen immunotherapy, and non-pharmacological treatment options [1, 2, 23]. As allergen avoidance is often not possible, pharmacotherapy is the mainstay of treatment in the current situation of symptomatic disease [1].

Pharmacotherapy of AR

Medications used in the pharmacotherapy of AR primarily include INCS, intranasal and oral AH, leukotriene antagonists, intranasal cromoglicic acid preparations, intranasal and oral vasoconstrictors, and nasal rinses [1, 8, 10, 15].

The ARIA guideline for the German healthcare system [2] recommends INCS as first-line therapy for patients with intermittent and persistent AR and considers them to be the treatment of first choice for any form of AR due to their superior efficacy and tolerability [2, 15]. There is no clear evidence of differences in the efficacy of individual INCS compared to others [24, 25], but there are clear differences in the systemic bioavailability of INCS [1]. The systemic bioavailability of mometasone furoate, ciclesonide, fluticasone furoate, and fluticasone propionate is the lowest among currently available INCS [23], minimizing the risk of systemic adverse events [26]. Increasing the INCS dose does not provide any additional symp-

tomatic benefit due to the flat dose–response curves. In fact, a threshold for the efficacy of INCS has now been established [27]. In patients with mild-to-moderate disease, oral or intranasal H1 antihistamines (AH) may also be effective, but these usually do not have sufficient potency in patients with severe disease [1]. Data from practice confirm that INCS are superior to oral H1-AH in all patient groups with AR [2, 28]. Rupatadine [29] and bilastine [30] can be described as the latest generation of oral AHs.

As with all medications, side effects are also possible with AR therapy. The greatest risk comes from systemic glucocorticosteroids, which must be reserved for the most severe cases. A recently published consensus paper from the European Academy of Allergology and Clinical Immunology (EAACI) addresses the use of systemic glucocorticosteroids in the treatment of upper respiratory tract disease, highlights the potential harms of this therapy, and makes recommendations for their very cautious use [31]. Although less common and less severe than systemic glucocorticosteroids, oral AHs are also associated with adverse effects [32, 33].

In this situation and in view of the OTC availability of many antiallergic drugs, many patients combine different drugs such as nasal and oral AH, leukotriene receptor antagonists, mast cell stabilizers, and INCS [34–36].

However, this form of polypharmacy, such as the free combination of a nasal AH with an INCS, provides little or no symptomatic benefit compared to INCS monotherapy [37, 38].

This is due to the mismatched pharmacological or pharmacodynamic properties of these therapies [10]. For example, INCS is in a lipophilic solution and nasal AH is in a hydrophilic solution. This means that if INCS is applied, a subsequent AH application has no effect because the INCS application forms a fine lipid layer on the mucous membrane and the AH can no longer penetrate the cells to have an effect. Therefore, many patients cannot adequately treat their symptoms with the available monotherapies or their free combination [36, 39] and are not surprisingly dissatisfied with the symptomatic relief achieved [40].

Fixed combinations of INCS and intranasal H1-AHs are an innovative treatment option in this situation. They combine the advantages of H1-AHs (rapid onset of action) with those of INCS (strong, sustained efficacy, good effect also against nasal obstruction) and are also very effective in patients with severe symptoms [2, 10]. To date, only one preparation, a combination of azelastine and fluticasone [41], was available on the market in Germany. Recently, an alternative was added with an olopatadine and mometasone combination nasal spray, whose efficacy in all forms of moderate-to-severe AR was demonstrated in a meta-analysis [42].

The use of pharmacotherapies is an effective option for immediate relief of AR symptoms. However, in a survey conducted by the American Academy of Otorhinolaryngology–Allergy, 47% of AR patients taking at least one prescription medication reported using at least two or more prescription medications plus one over-the-counter medication to treat their symptoms [11]. Taking multiple medications can increase healthcare costs and result in medication dosage recommendations not being met. For effective treatment of AR symptoms, medications that provide both rapid and sustained symptom relief and have minimal side effects are important [11]. Monopreparations of AH and INCS have been the mainstay therapy for AR. Therefore, it stands to reason that a combination of a fast-acting intranasal AH and a long-lasting and potent INCS would provide more effective symptom control than monotherapy [43, 44]. The use of a single combination nasal spray for AR treatment rather than the free combination of multiple monotherapies could have the added benefit of reducing costs [45] and improving adherence [46, 47].

Fixed combinations of INCS and intranasal H1-AHs as nasal sprays

Fixed combination azelastine hydrochloride/ fluticasone propionate nasal spray (MP-AzeFlu)

MP-AzeFlu was introduced as the first fixed combination of intranasal AH (azelastine hydrochloride) and INCS (fluticasone propionate) in a novel formulation as a nasal spray for AR therapy. The results of well-designed randomized controlled trials (RCTs) showed that patients with moderate-to-severe seasonal AR (SAR) treated with MP-AzeFlu experienced a rapid onset of relief (i.e., 30 min) and 20–30% more effective treatment of nasal and ocular symptoms compared to INCS treatment alone, and twice as much relief as with an intranasal AH [27, 48, 49]. In addition, more MP-AzeFlu patients (SAR and PAR) experienced complete or near-complete relief of symptoms [50–56]. Side effects such as nosebleeds can occur very frequently (in more than one in ten patients), while headache, bitter taste, and an unpleasant odor can occur frequently (in up to one in ten patients). Side effects such as irritation/dryness of the nose, throat, and/or mouth may occur occasionally to rarely, while dizziness or drowsiness, cataract, glaucoma, damage to the skin/mucous membrane, feeling sick, faint, exhausted or weak, skin rash, bronchospasm may occur very rarely.

MP-AzeFlu has been available as a nasal spray on the European market since 2013 and can be considered an established treatment option for AR.

Fixed combination olopatadine hydrochloride/ mometasone furoate monohydrate nasal spray (Olo-Mom)

In January 2022, the US Food and Drug Administration (FDA) approved olopatadine hydrochloride and mometasone furoate monohydrate nasal spray (Olo-Mom) for the treatment of AR symptoms in patients aged 12 years and older [57, 58]. On their own, olopatadine (ophthalmic) and mometasone (nasal) are effective and well tolerated agents for the treatment of AR [59–62]. Similar to the individual components as monotherapies, the combination of Olo-Mom is also approved for AR. However, there are differences in terms of the onset and duration of action [58].

The aim of this review is to evaluate the available literature on the pharmacology, efficacy, and safety of Olo-Mom in the treatment of AR and to make recommendations for its use in the German healthcare system.

Methodology

In a literature search in Medline, PubMed, as well as the national and international study (ClinicalTrials.gov) and guideline registers and the Cochrane Library, treatment options for AR were analyzed and the available evidence was determined. Human studies published on the topic in the period up to and including August 2023 were taken into account. Particular emphasis was placed on the new fixed combination of mometasone and olopatadine and its laboratory code GSP301. Prospective clinical studies, meta-analyses, systematic reviews, and review articles in German and English were considered.

Results

The search results revealed 14 scientific articles on the new fixed combination of mometasone and olopatadine, and six clinical trials were also identified in ClinicalTrials.gov.

The analyses of these articles and study descriptions are presented here.

Clinical pharmacology of the Olo-Mom nasal spray

Olo-Mom is a fixed combination of the AH olopatadine hydrochloride and the glucocorticosteroid mometasone furoate. Olopatadine has a dual action as a selective AH with mast-cell-stabilizing properties. Olopatadine acts as an AH by binding to and stabilizing mast cells and leads to an inactive conformation of histamine 1 (H1) receptors [63]. Through a transcription factor known as nuclear factor κ B, olopatadine's effect on inflammation also decreases antigen presentation, expression of proinflammatory cytokines and cell adhesion molecules, and chemotaxis [63]. Furthermore, olopatadine can stabilize mast cells, which leads to the inhibition of mast cell activation and histamine release [63].

Mometasone is a glucocorticosteroid with a strong anti-inflammatory effect. The binding between glucocorticosteroids and glucocorticosteroid receptors in the cytoplasm creates a complex that penetrates the cell nucleus and regulates the expression of pro-inflammatory and anti-inflammatory genes [64, 65]. Mometasone inhibits the expression of genes responsible for the development and maintenance of inflammation, the production of proinflammatory cytokines, and the expression of adhesion molecules.

Pharmacokinetics

Given the combination of two active ingredients in the Olo-Mom product, two open-label, single-dose crossover studies were conducted to determine the pharmacokinetics for optimal Olo-Mom dosing [66, 67]. The results of both studies showed that the combination of olopatadine and mometasone in Olo-Mom had no significant effect on the pharmacokinetics of either drug compared to their monotherapies [57, 66, 67].

The protein binding of olopatadine is 55%, and interactions due to displacement from plasma proteins are not expected [57, 68].

Studies have shown that mometasone is primarily and extensively metabolized in the liver of all species studied and undergoes extensive metabolism to several metabolites [57].

In vitro studies have confirmed the primary role of cytochrome CYP3A4 in the metabolism of mometasone [69]. In one study, an increase in mometasone plasma concentrations was demonstrated after concomitant administration of ketoconazole, a strong CYP3A4 inhibitor [69]. These clinically relevant effects are highly unlikely in view of the intranasal administration of mometasone with low systemic absorption.

Dosage and administration

Different doses of Olo-Mom were investigated in two phase II studies. Once-daily (olopatadine 665 µg + mometasone 50 µg) Olo-Mom treatment and twice-daily administration (olopatadine 665 µg + mometasone 50 µg) were compared with either placebo or a comparator [70, 71], with either one spray [71] or two sprays [70] administered per nostril. The twice-daily administration of Ole-Mom with two sprays per nostril showed a significant and clinically meaningful improvement in the rTNSS (Reflected Total Nasal Symptom Score) compared to the two monotherapies [70]. This regimen was used for the phase III studies as this dosage met the regulatory threshold for fixed-dose combinations. The results are shown in Table 1.

Clinical studies

The efficacy of Olo-Mom in the treatment of AR was tested in two double-blind, randomized, placebo-controlled phase II studies (NCT03444506 [71] and NCT02318303 [70]) and three phase III studies (NCT02870205 [72], NCT02631551 [73], and NCT02709538 [74]).

The primary endpoints assessed in each clinical trial were either the iTNSS (Instantaneous Total Nasal Symptom Score) and/or the rTNSS (Reflective Total Nasal Symptom Score). The secondary endpoints measured in each clinical trial consisted of the Reflective Total Ocular Symptom Score (rTOSS), the Instantaneous Total Ocular Symptom Score (iTOSS), the RQLQ(S) Score of the Rhinoconjunctivitis Quality of Life Questionnaire, treatment-emergent adverse events (TEAEs) and/or the onset of action (OOA). OOA was determined if there was a sustained significant difference in the change in iTNSS score from baseline over the measured time interval.

Phase II studies

The first phase II study, NCT03444506, by Patel et al. [71] used a ragweed pollen exposure chamber (EEC) model to evaluate the efficacy and safety of a once- or twice-daily administration of one spray per nostril for

Table 1 Summary of clinical studies evaluating the efficacy of olopatadine hydrochloride mometasone furoate (Olo-Mom; from [70–73], modified after [58])

Study	Patient population	Methods	Regimen	Results
Patel et al. [71]	$n = 180$ 18–65 years Moderate to severe SAR ≥ 2 years	*14 days phase II R, DB, DD, PG, PC, AC, SC* Primary: mean change in iTNSS for twice-daily and once-daily Olo-Mom compared to placebo Secondary: iTOSS, OOA	Twice-daily Olo-Mom (olopatadine 665 µg + mometasone 25 µg) vs. once-daily. Olo-Mom (olopatadine 665 µg + mometasone 50 µg) vs. AzeFlu vs. twice-daily olopatadine vs. twice-daily placebo	*Twice-daily Olo-Mom vs. placebo* iTNSS: –3.60 ($p < 0.0001$) iTOSS: –1.64 ($p < 0.0001$) OOA: Occurrence 10 min after dosing: –1.26 ($p = 0.02$) Retention at 11 out of 12 timepoints ($p < 0.05$ for all) *Once-daily Olo-Mom vs. placebo* iTNSS: –3.05 ($p < 0.0001$) iTOSS: –1.20 ($p = 0.01$)
Andrews, et al. [70]	$N = 1111$ ≥ 12 years Moderate to severe SAR ≥ 2 years	*14 days phase II R, DB, PG, PC, AC, MC* Primary: mean change compared to the initial value AM and PM rTNSS Secondary: average AM&PM iTNSS, rTOSS, iTOSS, OOA rTNSS, iTNSS, rTOSS and iTOSS are reported as LSMD	Twice-daily Olo-Mom (olopatadine 665 µg mometasone 25 µg) vs. once-daily Olo-Mom (olopatadine 665 µg + mometasone 50 µg) vs. twice-daily or once-daily olopatadine 665 µg vs. twice-daily (25 µg) or once-daily (50 µg) mometasone	*Twice-daily Olo-Mom vs. placebo* rTNSS: –1.17 ($p < 0.001$) iTNSS: –1.11 ($p < 0.001$) rTOSS: –0.42 ($p = 0.033$) iTOSS: –0.39 ($p = 0.039$) RQLQ(S): –0.60 ($p < 0.001$) *Twice-daily Olo-Mom vs. olopatadine* rTNSS: –0.49 ($p = 0.049$) iTNSS: –0.45 ($p = 0.058$) *Twice-daily Olo-Mom vs. mometasone* rTNSS: –0.71 ($p = 0.004$) iTNSS: –0.65 ($p = 0.007$) *Once-daily Olo-Mom vs. placebo* rTNSS: –1.11 ($p < 0.001$) iTNSS: –1.11 ($p < 0.001$) rTOSS: –0.55 ($p = 0.005$) iTOSS: –0.55 ($p = 0.003$) RQLQ(S): –0.53 ($p = 0.002$) *Once-daily Olo-Mom vs. olopatadine* rTNSS: –0.77 ($p = 0.002$) iTNSS: –0.86 ($p < 0.001$) iTOSS: –0.44 ($p = 0.020$) *Once-daily Olo-Mom vs. mometasone* rTNSS: –0.36 ($p = 0.152$) iTNSS: –0.35 ($p = 0.145$) iTOSS: –0.40 ($p = 0.032$)
Hampel et al. [73]	$N = 1180$ ≥ 12 years Moderate to severe SAR ≥ 2 years	*14 days phase III R, DB, PG, PC, AC, MC* Primary: average change in the average AM&PM rTNSS vs. initial value Secondary: iTNSS, rTOSS, iTOSS, RQLQ(S), OOA	Twice-daily Olo-Mom (olopatadine 665 µg + mometasone 25 µg) vs. olopatadine 665 µg vs. mometasone 25 µg vs. placebo	*Twice Olo-Mom vs. placebo* rTNSS: –0.98 ($p < 0.001$) iTNSS: –0.93 ($p < 0.001$) rTOSS: –0.49 ($p = 0.001$) iTOSS: –0.50 ($p < 0.001$) RQLQ(S): –0.43 ($p < 0.001$) OOA: Occurrence 15 min after dosing; Retention at all timepoints –0.35 ($p = 0.014$) *Twice-daily Olo-Mom vs. olopatadine* rTNSS: –0.61 ($p = 0.003$) iTNSS: –0.50 ($p = 0.005$) *Twice-daily Olo-Mom vs. mometasone* rTNSS: –0.39 ($p = 0.059$) iTNSS: –0.36 ($p = 0.041$)

Table 1 (Continued)

Study	Patient population	Methods	Regimen	Results
Gross et al. [72]	*N* = 1176 ≥ 12 years Moderate to severe SAR ≥ 2 years	*14 days phase III R, DB, PG, PC, AC, MC* Primary: average change in the average AM&PM rTNSS vs. initial value Secondary: average AM&PM iTNSS, rTOSS, iTOSS, RQLQ(S), OOA	Twice-daily Olo-Mom (olopatadine 665 µg + mometasone 25 µg) vs. olopatadine 665 µg vs. mometasone 25 µg vs. placebo	*Twice-daily Olo-Mom vs. placebo* rTNSS: –1.09 ($p < 0.001$) iTNSS: –0.94 ($p < 0.001$) rTOSS: –0.52 ($p = 0.001$) iTOSS: –0.50 ($p = 0.001$) RQLQ(S): –0.45 ($p < 0.001$) OOA: Observed after 15 min: –0.34 ($p = 0.03$) All following timepoints $p < 0.05$ for all *Twice-daily Olo-Mom vs. olopatadine* rTNSS: –0.44 ($p = 0.03$) iTNSS: –0.41 ($p = 0.04$) rTOSS: –0.17 ($p = 0.297$) iTOSS: –0.19 ($p = 0.227$) RQLQ(S): –0.31 ($p = 0.009$) *Twice-daily Olo-Mom vs. mometasone* rTNSS: –0.47 ($p = 0.02$) iTNSS: –0.51 ($p = 0.008$) rTOSS: –0.35 ($p = 0.030$) iTOSS: –0.36 ($p = 0.021$) RQLQ(S): –0.09 ($p = 0.424$)
Segall et al. [74]	*N* = 601 ≥ 12 years Moderate to severe PAR ≥ 2 years	*52 weeks phase III R, DB, PG, PC, AC, MC* Primary: Safety assessments in weeks 30 and 52 (TEAE) Secondary: average AM rTNSS and iTNSS and total RQLQ(S) from baseline to weeks 6, 30 and 52 (twice-daily Olo-Mom (olopatadine 665 µg and mometasone 25 µg) vs. placebo pH 3.7)	Twice-daily Olo-Mom (olopatadine 665 µg and mometasone 25 µg) vs. two placebos pH 3.7 (or 7.0) (4:1:1)	*TEAEs twice-daily Olo-Mom/placebo 3.7/placebo 7.0 (%)* 51.7/41.4/53.5 *Severity TEAEs twice-daily Olo-Mom/placebo 3.7/placebo 7.0 (%)* Mild: 30.3/24.2/28.7 Moderate: 32.6/28.3/35.6 Severe: 5.1/6.1/3.0 *Treatment-related TEAEs twice-daily Olo-Mom/placebo 3.7/placebo 7.0 (%)* 2.5/2.0/5.0 *Twice-daily Olo-Mom vs. placebo 3.7* rTNSS (6): –0.81 ($p = 0.001$) rTNSS (30): –0.96 ($p < 0.001$) rTNSS (52): –0.91 ($p < 0.001$) iTNSS (6): –0.66 ($p = 0.005$) iTNSS (30): –0.83 ($p < 0.001$) iTNSS (52): –0.75 ($p = 0.001$)

R randomized, *DB* double-blind, *DD* double-dummy, *PG* parallel group, *PC* placebo-controlled, *AC* active-controlled, *SC* single center, *MC* multi center, *SAR* seasonal allergic rhinitis, *PAR* perennial allergic rhinitis, *Olo-Mom* olopatadine hydrochloride + mometasone furoate nasal spray (GSP301), *AM&PM* morning and evening, *rTNSS* reflective total nasal symptom score, *iTNSS* instantaneous total nasal symptom score, *rTOSS* reflective total ocular symptom score, *iTOSS* instantaneous total ocular symptom score, *QoL* quality of life, *OOA* onset of action, *LSMD* least square mean difference, *RQLQ(S)* Rhinitis Quality of Life Questionnaire, Olo-Mom 665 µg olopatadine hydrochloride and 25 µg mometasone furoate, *TEAE* treatment emergent adverse event

14 days compared to placebo and two approved nasal sprays, olopatadine and a fixed combination of azelastine hydrochloride and fluticasone propionate (MP-AzeFlu). The EEC study allowed for constant exposure to the allergen throughout the study and continuous monitoring of participants' adherence to treatment compared to natural allergen exposure studies [75]. Twice-daily and once-daily administration of Olo-Mom showed statistically significant improvements in iTNSS compared to placebo ($p < 0.0001$ for twice-daily and once-daily; [71]). There was no statistically significant difference between Olo-Mom twice daily ($p = 0.12$) and once daily ($p = 0.44$) compared to azelastine and fluticasone. The study showed that Olo-Mom twice daily and once daily improved SAR symptoms compared to placebo.

Another phase II study conducted by Andrews et al. (NCT02318303; [70]) investigated the efficacy and safety of twice-daily and once-daily Olo-Mom compared to placebo and twice-daily and once-daily olopatadine and mometasone monotherapy, each with two sprays per nostril for 14 days. Twice-daily Olo-Mom resulted in a statistically significant and clinically meaningful improvement (difference of > 0.23 units) in rTNSS compared to placebo ($p < 0.001$), twice-daily olopatadine ($p = 0.049$), and mometasone ($p = 0.004$; [70]).

Phase III studies

Three phase III clinical trials were conducted. Two with SAR and one with PAR led to FDA approval of Olo-Mom (Table 1).

The phase III study (NCT02870205) conducted by Gross et al. was a 14-day randomized, double-blind, placebo-controlled study with participants older than 12 years of age who had been suffering from moderate-to-severe SAR for at least 2 years. The 1176 participants were randomized into four treatment groups: twice-daily Olo-Mom, olopatadine monotherapy, mo-

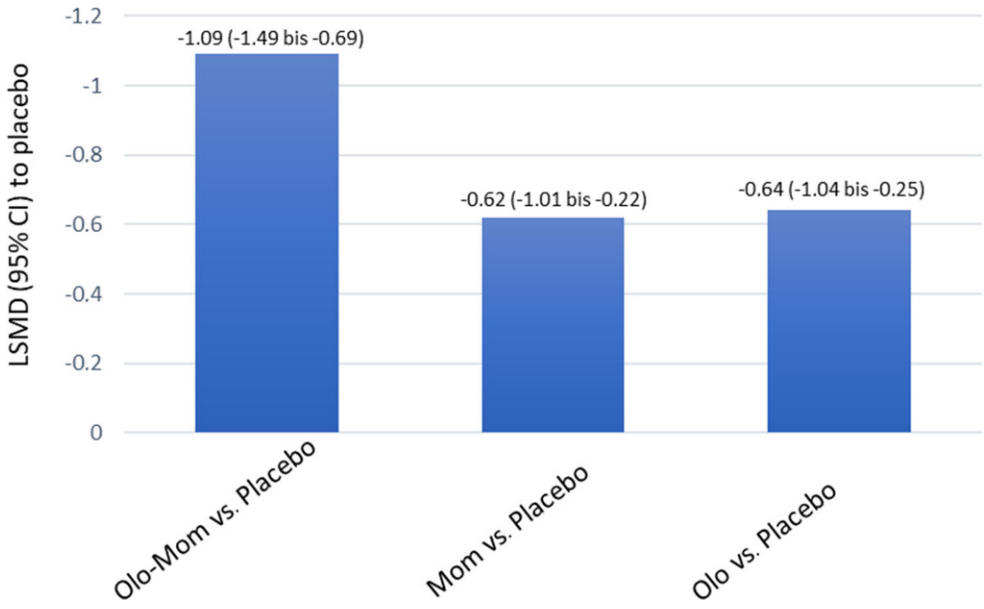

Fig. 1 Comparison of the Reflective Total Nasal Symptom Score (rTNSS) after 14 days of treatment with placebo. *Olo-Mom* olopatadine hydrochloride/mometasone furoate monohydrate, *LSMD* least mean square difference. (Modified after [72])

metasone monotherapy, or placebo. Compared to placebo, olopatadine monotherapy, and mometasone monotherapy, Olo-Mom showed statistically significant and clinically meaningful rTNSS improvements in the treatment of SAR-associated nasal symptoms in all patients aged 12 years and older ($p < 0.001$, $p < 0.03$, and $p < 0.02$, respectively; Fig. 1; [72]). The overall results showed that the improvement in nasal symptoms with Olo-Mom was rapid, with an onset of action of 15 min, and persisted throughout the 14-day treatment period, demonstrating the efficacy of the product in both acute and late allergic reactions.

The phase III study, NCT02631551, conducted by Hampel et al. was a 14-day randomized, double-blind, placebo-controlled study with participants who had been suffering from moderate-to-severe SAR for at least 2 years. A total of 1180 participants were randomized into four treatment groups: twice-daily Olo-Mom, olopatadine monotherapy, mometasone monotherapy, or placebo. The results showed that Olo-Mom had a statistically significant mean improvement in rTNSS compared to placebo and olopatadine monotherapy [73]. Olo-Mom compared to mometasone approached, but did not reach, the mean rTNSS improvements in a statistically significant manner. Olo-Mom confirmed an onset of action after 15 min that persisted over the entire 14-day treatment period.

Segall et al. conducted a study on PAR (NCT02709538). This is a 52-week phase III study with 601 patients older than 12 years and a history of PAR of at least 2 years. Patients were randomized into three treatment groups (olopatadine-mometasone twice daily [665 µg/25 µg], placebo pH 3.7 or placebo pH 7.0). The primary endpoint was the safety of the drug in long-term use and the effect of pH on nasal comfort. Twice-daily olopatadine mometasone (665 µg/25 µg) was well tolerated and led to statistically significant and clinically meaningful improvements in PAR nasal symptoms without the occurrence of tachyphylaxis compared to placebo over 52 weeks [74].

Safety aspects

Adverse drug reactions (ADRs) were described in connection with the use of Olo-Mom on the basis of pooled data ($N = 1580$) from the studies by Segall et al. [74], Gross et al. [72], and Hampel et al. [73]. The most common ADRs (incidence ≥ 1%) observed with the use of Olo-Mom were dysgeusia and epistaxis [57, 72–74]. Anaphylactic reactions were not observed in clinical studies. A decrease in efficacy was also not observed over 52 weeks [74]. The use of Olo-Mom in pregnancy has not been studied; therefore, the estimated risk of treatment with this drug is not known.

There is also insufficient experience in breastfeeding. There are no data on the presence of olopatadine or mometasone or its metabolites in breast milk that could have an effect on the breastfed child or the effects on milk production [57].

While studies with older INCS suggested a reduction in growth velocity in children, newer INCS apparently have no negative effect here [57, 76].

The use of Olo-Mom is generally contraindicated in patients with a known hypersensitivity to any of the ingredients, in particular mometasone furoate and/or olopatadine hydrochloride. Patients should be monitored regularly for local nasal side effects such as epistaxis, nasal ulceration, and nasal septal perforation. Hypercorticism and adrenal suppression may occur with inappropriate use or use of higher-than-recom-

mended doses or regular dosing in high-risk patients [57].

Relevance for patient care and clinical practice

Current guidelines recommend intranasal antihistamines (INAH) for the initial treatment of SAR, especially in mild cases [77]. However, for persistent symptoms of AR and particularly severe nasal obstruction, INCS are recommended as the preferred medication [77]. Based on these two recommendations, the guidelines recommend the combination of an INCS and an INAH for the initial treatment of moderate AR in patients aged 12 years and older with persistent symptoms who have not responded to monotherapy [77]. This could be primarily due to the differences in the onset and duration of action of INAH and INCS.

It has been shown that INAHs are effective in the treatment of nasal symptoms, but have weaknesses in their efficacy profile, particularly in nasal congestion [4]. Data from phase III studies show that the onset of action of the combination drug was around 15 min, most likely due to the fact that the onset of action of olopatadine as INAH is between 15 and 30 min [72, 73]. In addition, INAH has the advantage that the drug is delivered specifically to the nasal tissue and thus systemic effects are limited [78].

Furthermore, INCS have also demonstrated efficacy on all nasal symptoms of AR in numerous placebo-controlled clinical trials [4, 79]. In addition, INCS have had a positive effect on ocular AR symptoms [4, 80]. A significant improvement in sleep and quality of life has also been demonstrated [4, 81]. In both phase III studies on SAR, the Olo-Mom effects persisted over the entire 14-day treatment period [72, 73].

The combination of olopatadine and mometasone makes it possible to utilize the rapid onset of action of an INAH and the long duration of action of an INCS in a single product. Although the use of a combination product increases the risk of adverse effects [82], all clinical studies individually showed no statistically significant difference in the occurrence of adverse effects of the combination product compared to its individual components [72, 73]. A systematic meta-analysis of the two phase II and three phase III studies on Olo-Mom [42] showed statistically significant improvements in rTNSS and iTNSS as well as an improvement in rTOSS and iTOSS [42].

The intranasal fixed combinations of glucocorticosteroid and AH azelastine/fluticasone nasal spray (Aze-Flu) and olopatadine-mometasone nasal spray (Olo-Mom) do not appear to show any significant differences in terms of efficacy and safety [83]. However, an anchored best-worst scaling (ABWS) method was used to analyze how patients rate the treatment characteristics of the current combination nasal sprays. To do this, 426 adults in Australia with moderate-to-severe AR who used either Olo-Mom or Aze-Flu nasal sprays were asked in an online survey about 11 domains, seven of which were sensory (direct taste of medication, aftertaste of medication, smell of medication, nasal irritation, sneezing irritation, drip from nose/throat, dryness of nose/throat) and four treatment-related criteria (convenience, rapid onset of action, duration of action, and control of AR symptoms).

Participants who used Olo-Mom were significantly more satisfied than participants who used Aze-Flu in seven out of 11 areas (all $p < 0.05$). The preferred areas were predominantly the sensory properties of the products. The authors encourage prescribers of AR treatments to discuss with their patients which characteristics they value in the treatment so as to facilitate shared decision-making. The AR patients who value sensory properties in their treatment may benefit from using the Olo-Mom nasal spray as they are likely to be more satisfied with their treatment, which may increase adherence [83]. On the other hand, MP-AzeFlu would benefit patients who are somewhat more lax in its precise application, as only one spray per nostril is required twice daily [84].

Discussion

The treatment of AR comprises a variety of measures, which classically include allergen immunotherapy in addition to allergen avoidance and pharmacotherapy. Non-pharmacological measures are mainly used for allergen avoidance. Medications used in the pharmacotherapy of AR include INCS, intranasal and oral AH, leukotriene antagonists, intranasal cromoglicic acid preparations, intranasal and oral vasoconstrictors, and nasal rinses [1, 2, 10]. With sufficient penetration of the epithelial layer, topical application of the medication can achieve considerably higher concentrations in the airway mucous membranes than systemic administration, and the effect is often more rapid [1]. With significantly reduced concentrations in the blood and total body dose, topical therapies (nasal sprays) are therefore preferable to systemic application.

Fixed combinations of INCS and INAH as nasal sprays represent a significant and decisive advance in the treatment of moderate-to-severe AR [1, 2, 77]. Although treatment-related side effects may be slightly increased with the fixed combinations, fixed combinations provide significant symptom relief for patients who do not respond well or at all to the individual preparations and substantially improve their quality of life [82].

For the fixed combination Olo-Mom, data from several phase II and III clinical trials show significant improvements in AR symptoms. In patients aged 12 years and older, Olo-Mom can be considered as first-line treatment for moderate AR with persistent symptoms despite monotherapy. In terms of patient satisfaction, Olo-Mom could have advantages over the otherwise also very effective fixed combination spray

Aze-Flu and thus possibly increase patient satisfaction and thereby treatment adherence [83].

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References

1. Klimek F, Bergmann C, Hagemann J, Cuevas M, Klimek L. Therapieoptionen bei der saisonalen (intermittierenden) allergischen Rhinitis. AL. 2023;46.
2. Klimek L, Bachert C, Pfaar O, Becker S, Bieber T, Brehler R, et al. ARIA guideline 2019: treatment of allergic rhinitis in the German health system. Allergol Sel. 2019;3:22–50.
3. Westman M, Åberg K, Apostolovic D, Lupinek C, Gattinger P, Mittermann I, et al. Sensitization to grass pollen allergen molecules in a birth cohort-natural Phl p 4 as an early indicator of grass pollen allergy. J Allergy Clin Immunol. 2020;145:1174–1181.e6.
4. Seidman MD, Gurgel RK, Lin SY, Schwartz SR, Baroody FM, Bonner JR, et al. Clinical practice guideline: allergic rhinitis executive summary. Otolaryngol Head Neck Surg. 2015;152:197–206.
5. 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.
6. Guerra S, Sherrill DL, Martinez FD, Barbee RA. Rhinitis as an independent risk factor for adult-onset asthma. J Allergy Clin Immunol. 2002;109:419–25.
7. 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;372:1049–57.
8. Klimek L, Werfel T, Vogelberg C. Weißbuch Allergie in Deutschland. Allergo J Int. 2018;27.
9. Wheatley LM, Togias A. Clinical practice. Allergic rhinitis. N Engl J Med. 2015;372:456–63.
10. Klimek L, Casper I, Positionspapier BKC. Die Therapie der allergischen Rhinitis in der Routineversorgung: evidenzbasierte Nutzenbewertung der kombinierten Anwendung mehrerer Wirkstoffe. Therapy of allergic rhinitis in routine care: evidence-based benefit assessment of freely combined use of various active ingredients. AL. 2020;43:476.
11. Marple BF, Fornadley JA, Patel AA, Fineman SM, Fromer L, Krouse JH, et al. Keys to successful management of patients with allergic rhinitis: focus on patient confidence, compliance, and satisfaction. Otolaryngol Head Neck Surg. 2007;136:S107–24.
12. Meltzer EO, Rhinitis A. Burden of Illness, Quality of Life, Comorbidities, and Control. Immunol Allergy Clin North Am. 2016;36:235–48.
13. Ciprandi G, Cirillo I, Vizzaccaro A, Tosca M, Passalacqua G, Pallestrini E, et al. Seasonal and perennial allergic rhinitis: is this classification adherent to real life? Allergy. 2005;60:882–7.
14. Crown WH, Olufade A, Smith MW, Nathan R. Seasonal versus perennial allergic rhinitis: drug and medical resource use patterns. Value Health. 2003;6:448–56.
15. Wise SK, Lin SY, Toskala E. International consensus statement on allergy and rhinology: allergic rhinitis-executive summary. Int Forum Allergy Rhinol. 2018;8:85–107.
16. Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol. 2001;108:S147–334.
17. Demoly P, Allaert FA, Lecasble M, Bousquet J. Validation of the classification of ARIA (allergic rhinitis and its impact on asthma). Allergy. 2003;58:672–5.
18. Bauchau V, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. Eur Respir J. 2004;24:758–64.
19. Bauchau V, Durham SR. Epidemiological characterization of the intermittent and persistent types of allergic rhinitis. Allergy. 2005;60:350–3.
20. Meltzer EO. The role of nasal corticosteroids in the treatment of rhinitis. Immunol Allergy Clin North Am. 2011;31:545–60.
21. Schafer T, Schnoor M, Wagenmann M, Klimek L, Therapeutic Index BC. (TIX) for intranasal corticosteroids in the treatment of allergic rhinitis. Rhinology. 2011;49:272–80.
22. Tran NP, Vickery J, Blaiss MS. Management of rhinitis: allergic and non-allergic. Allergy Asthma Immunol Res. 2011;3:148–56.
23. Blaiss MS. Safety update regarding intranasal corticosteroids for the treatment of allergic rhinitis. Allergy Asthma Proc. 2011;32:413–8.

24. Mandl M, Nolop K, Lutsky BN. Comparison of once daily mometasone furoate (Nasonex) and fluticasone propionate aqueous nasal sprays for the treatment of perennial rhinitis. The 194-079 Study Group. Ann Allergy Asthma Immunol. 1997;79:237–45.
25. Okubo K, Nakashima M, Miyake N, Komatsubara M, Okuda M. Comparison of fluticasone furoate and fluticasone propionate for the treatment of Japanese cedar pollinosis. Allergy Asthma Proc. 2009;30:84–94.
26. Sastre J, Mosges R. Local and systemic safety of intranasal corticosteroids. J Investig Allergol Clin Immunol. 2012;22:1–12.
27. Meltzer E, Ratner P, Bachert C, Carr W, Berger W, Canonica GW, et al. Clinically Relevant Effect of a New Intranasal Therapy (MP29-02) in Allergic Rhinitis Assessed by Responder Analysis. Int Arch Allergy Immunol. 2013;161:369–77.
28. Bédard A, Basagaña X, Anto JM, Garcia-Aymerich J, Devillier P, Arnavielhe S, et al. Mobile technology offers novel insights into the control and treatment of allergic rhinitis: The MASK study. J Allergy Clin Immunol. 2019;144:135–43:e6.
29. Compalati E, Canonica GW. Efficacy and safety of rupatadine for allergic rhino-conjunctivitis: a systematic review of randomized, double-blind, placebo-controlled studies with meta-analysis. Curr Med Res Opin. 2013;29:1539–51.
30. Lynde CW, Sussman G, Dion P-L, Guenther L, Hébert J, Rao J, et al. Multidisciplinary Real-World Experience With Bilastine, a Second Generation Antihistamine. J Drugs Dermatol. 2020;19:145–54.
31. Hox V, Lourijsen E, Jordens A, Aasbjerg K, Agache I, Alobid I, et al. Benefits and harm of systemic steroids for short- and long-term use in rhinitis and rhinosinusitis: an EAACI position paper. Clin Transl Allergy. 2020;10:1.
32. Bousquet J, Anto JM, Bachert C, Baiardini I, Bosnic-Anticevich S, Canonica WG, et al. Allergic rhinitis. Nat Rev Dis Primers. 2020;6:95.
33. Hossenbaccus L, Linton S, Garvey S, Ellis AK. Towards definitive management of allergic rhinitis: best use of new and established therapies. Allergy Asthma Clin Immunol. 2020;16:39.
34. Canonica GW, Bousquet J, Mullol J, Scadding GK, Virchow JC. A survey of the burden of allergic rhinitis in Europe. Allergy. 2007;62(Suppl 85):17–25.
35. Navarro A, Valero A, Rosales MJ, Mullol J. Clinical use of oral antihistamines and intranasal corticosteroids in patients with allergic rhinitis. J Investig Allergol Clin Immunol. 2011;21:363–9.
36. Price D, Scadding G, Ryan D, Bachert C, Canonica GW, Mullol J, et al. The hidden burden of adult allergic rhinitis: UK healthcare resource utilisation survey. Clin Transl Allergy. 2015;5:39.
37. Anolik R. Clinical benefits of combination treatment with mometasone furoate nasal spray and loratadine vs monotherapy with mometasone furoate in the treatment of seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 2008;100:264–71.
38. Esteitie R. deTineo M, Naclerio RM, Baroody FM. Effect of the addition of montelukast to fluticasone propionate for the treatment of perennial allergic rhinitis. Ann Allergy Asthma Immunol. 2010;105:155–61.
39. Bousquet PJ, Demoly P, Devillier P, Mesbah K, Bousquet J. Impact of allergic rhinitis symptoms on quality of life in primary care. Int Arch Allergy Immunol. 2013;160:393–400.
40. Ciprandi G, Incorvaia C, Scurati S, Puccinelli P, Soffia S, Frati F, et al. Patient-related factors in rhinitis and asthma: the satisfaction with allergy treatment survey. Curr Med Res Opin. 2011;27:1005–11.
41. Ridolo E, Montagni M, Melli V, Bonzano L, Incorvaia C, Canonica GW. A role for the intranasal formulation of azelastine hydrochloride/fluticasone propionate in the treatment of allergic rhinitis. Ther Deliv. 2015;6:653–9.
42. Chen R, Zheng D, Zhang Y, Sima G. Efficacy and safety of twice-daily olopatadine-mometasone combination nasal spray (GSP301) in the treatment of allergic rhinitis: a systematic review and meta-analysis. Eur Arch Otorhinolaryngol. 2022;279:1691–9.
43. Feng S, Fan Y, Liang Z, Ma R, Cao W. Concomitant corticosteroid nasal spray plus antihistamine (oral or local spray) for the symptomatic management of allergic rhinitis. Eur Arch Otorhinolaryngol. 2016;273:3477–86.
44. Prenner BM. A review of the clinical efficacy and safety of MP-AzeFlu, a novel intranasal formulation of azelastine hydrochloride and fluticasone propionate, in clinical studies conducted during different allergy seasons in the US. J Asthma Allergy. 2016;9:135–43.
45. Harrow B, Sedaghat AR, Caldwell-Tarr A, Dufour R. A Comparison of Health Care Resource Utilization and Costs for Patients with Allergic Rhinitis on Single-Product or Free-Combination Therapy of Intranasal Steroids and Intranasal Antihistamines. J Manag Care Spec Pharm. 2016;22:1426–36.
46. Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: a meta-analysis. Am J Med. 2007;120:713–9.
47. van Galen KA, Nellen JF, Nieuwkerk PT. The Effect on Treatment Adherence of Administering Drugs as Fixed-Dose Combinations versus as Separate Pills: Systematic Review and Meta-Analysis. AIDS Res Treat. 2014;2014:967073.
48. Klimek L, Berger WE, Bousquet J, Keith PK, Smith P. Sole D et al. MP-AzeFlu in Moderate-to-Severe Allergic Rhinitis: A Literature Review. Int Arch Allergy Immunol. 2021;182:1026–35.
49. Price D, Shah S, Bhatia S, Bachert C, Berger W, Bousquet J, et al. A new therapy (MP29-02) is effective for the long-term treatment of chronic rhinitis. J Investig Allergol Clin Immunol. 2013;23:495–503.
50. Canonica GW, Klimek L, Acaster S, Dollner R, Kaulsay R, Lo SH, et al. Burden of allergic rhinitis and impact of MP-AzeFlu from the patient perspective: pan European patient survey. Curr Med Res Opin. 2021;37:1259–72.
51. Klimek L, Bachert C, Mösges R, Munzel U, Price D, Virchow JC, et al. Effectiveness of MP29-02 for the treatment of allergic rhinitis in real-life: results from a noninterventional study. Allergy Asthma Proc. 2015;36:40–7.
52. Klimek L, Bachert C, Stjärne P, Dollner R, Larsen P, Haahr P, et al. MP-AzeFlu provides rapid and effective allergic rhinitis control in real life: A pan-European study. Allergy Asthma Proc. 2016;37:376–86.
53. Klimek L, Poletti SC, Sperl A, Spielhaupter M, Bardenhewer C, Mullol J, et al. Olfaction in patients with allergic rhinitis: an indicator of successful MP-AzeFlu therapy. Int Forum Allergy Rhinol. 2017;7:287–92.
54. Klimek L, Price D, Gálffy G, Emmeluth M, Koltun A, Kopietz F, et al. Effect of Specific Immunoglobulin E Response and Comorbidities on Effectiveness of MP-AzeFlu in a Real-Life Study. Int Arch Allergy Immunol. 2020;181:754–64.
55. Price D, Klimek L, Gálffy G, Emmeluth M, Koltun A, Kopietz F, et al. Allergic rhinitis and asthma symptoms in a real-life study of MP-AzeFlu to treat multimorbid allergic rhinitis and asthma. Clin Mol Allergy: Cma. 2020;18:15.
56. van Weissenbruch R, Klimek L, Gálffy G, Emmeluth M, Koltun A. Kopietz F et al. MP-AzeFlu Improves the Quality-of-Life of Patients with Allergic Rhinitis. J Asthma Allergy. 2020;13:633–45.

57. FDA. RYALTRIS (olopatadine hydrochloride and mometasone furoate monohydrate nasal spray) https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/211746s000lbl.pdf: U.S. Food and Drug Administration;2022 [07.09.2023]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/211746s000lbl.pdf
58. Lim L, Lipari M, Kale-Pradhan P. Intranasal Olopatadine-Mometasone in the Treatment of Seasonal Allergic Rhinitis. Ann Pharmacother. 2023;57:570–8.
59. Fairchild CJ, Meltzer EO, Roland PS, Wells D, Drake M, Wall GM. Comprehensive report of the efficacy, safety, quality of life, and work impact of Olopatadine 0.6% and Olopatadine 0.4% treatment in patients with seasonal allergic rhinitis. Allergy Asthma Proc. 2007;28:716–23.
60. Hochhaus G. Pharmacokinetic/pharmacodynamic profile of mometasone furoate nasal spray: potential effects on clinical safety and efficacy. Clin Ther. 2008;30:1–13.
61. Meltzer EO, Hampel FC, Ratner PH, Bernstein DI, Larsen LV, Berger WE, et al. Safety and efficacy of olopatadine hydrochloride nasal spray for the treatment of seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 2005;95:600–6.
62. Penagos M, Eifan AO, Durham SR, Scadding GW. Duration of Allergen Immunotherapy for Long-Term Efficacy in Allergic Rhinoconjunctivitis. Curr Treat Options Allergy. 2018;5:275–90.
63. Simons FER, Simons KJ. Histamine and H1-antihistamines: celebrating a century of progress. J Allergy Clin Immunol. 2011;128:1139–1150.e4.
64. Berlucchi M, Pedruzzi B. Intranasal mometasone furoate for treatment of allergic rhinitis. Clin Med Insights Ther. 2010;2:761–9.
65. Lipiec A, Jurkiewicz D. A new therapeutic option in the management of allergic rhinitis. Otolaryngol Pol. 2021;75:1–5.
66. Patel P, Salapatek AM, Talluri RS, Tantry SK. Pharmacokinetics of intranasal mometasone in the fixed-dose combination GSP301 versus two monotherapy intranasal mometasone formulations. Allergy Asthma Proc. 2018;39:232–9.
67. Patel P, Salapatek AM, Talluri RS, Tantry SK. Pharmacokinetics of intranasal olopatadine in the fixed-dose combination GSP301 versus two monotherapy intranasal olopatadine formulations. Allergy Asthma Proc. 2018;39:224–31.
68. Alcon Laboratories I. Patanase (olopatadine hydrochloride) Nasal Spray https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021861s002lbl.pdf2009 [07.09.2023]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021861s002lbl.pdf
69. FDA. NASONEX® (mometasone furoate monohydrate) Nasal Spray https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020762s053lbl.pdf: U.S. Food and Drug Administration.;2018. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020762s053lbl.pdf
70. Andrews CP, Mohar D, Salhi Y, Tantry SK. Efficacy and safety of twice-daily and once-daily olopatadine-mometasone combination nasal spray for seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 2019;124:171–8:e2.
71. Patel P, Salapatek AM, Tantry SK. Effect of olopatadine-mometasone combination nasal spray on seasonal allergic rhinitis symptoms in an environmental exposure chamber study. Ann Allergy Asthma Immunol. 2018;122:160–6:e1.
72. Gross GN, Berman G, Amar NJ, Caracta CF, Tantry SK. Efficacy and safety of olopatadine-mometasone combination nasal spray for the treatment of seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 2019;122:630–8:e3.
73. Hampel FC, Pedinoff AJ, Jacobs RL, Caracta CF, Tantry SK. Olopatadine-mometasone combination nasal spray: Evaluation of efficacy and safety in patients with seasonal allergic rhinitis. Allergy Asthma Proc. 2019;40:261–72.
74. Segall N, Prenner B, Lumry W, Caracta CF, Tantry SK. Long-term safety and efficacy of olopatadine-mometasone combination nasal spray in patients with perennial allergic rhinitis. Allergy Asthma Proc. 2019;40:301–10.
75. Pfaar O, Calderon MA, Andrews CP, Angjeli E, Bergmann KC, Bønløkke JH, et al. Allergen exposure chambers: harmonizing current concepts and projecting the needs for the future—an EAACI Position Paper. Allergy. 2017;72:1035–42.
76. McDonnell J, Weller K, Pien LC. Safety of Intranasal Steroids: an Updated Perspective. Curr Allergy Asthma Rep. 2020;20:69.
77. Dykewicz MS, Wallace DV, Amrol DJ, Baroody FM, Bernstein JA, Craig TJ, et al. Rhinitis 2020: A practice parameter update. J Allergy Clin Immunol. 2020;146:721–67.
78. Nickels AS, Dimov V, Wolf R. Pharmacokinetic evaluation of olopatadine for the treatment of allergic rhinitis and conjunctivitis. Expert Opin Drug Metab Toxicol. 2011;7:1593–9.
79. Penagos M, Compalati E, Tarantini F, Baena-Cagnani CE, Passalacqua G, Canonica GW. Efficacy of mometasone furoate nasal spray in the treatment of allergic rhinitis. Meta-analysis of randomized, double-blind, placebo-controlled, clinical trials. Allergy. 2008;63:1280–91.
80. Bielory L, Chun Y, Bielory BP, Canonica GW. Impact of mometasone furoate nasal spray on individual ocular symptoms of allergic rhinitis: a meta-analysis. Allergy. 2011;66:686–93.
81. Herman H. Once-daily administration of intranasal corticosteroids for allergic rhinitis: a comparative review of efficacy, safety, patient preference, and cost. Am J Rhinol. 2007;21:70–9.
82. Kim M, Ryu G, Kang SY, Kim MA, Yang SI, Lee IH, et al. Intranasal antihistamine and corticosteroid to treat allergic rhinitis: A systematic review and meta-analysis. Allergy. 2022;77:3436–40.
83. Fifer S, Toh L, Barkate H, Aggarwal V, Borade D, Gordonsmith RH, et al. Patient Satisfaction and Sensory Attributes of Nasal Spray Treatments of Olopatadine Hydrochloride/Mometasone Furoate Monohydrate and Azelastine Hydrochloride/Fluticasone Propionate for Allergic Rhinitis in Australia—An Observational Real-World Clinical Study. Patient Prefer Adherence. 2023;17:141–51.
84. Gebrauchsinformation: Information für Patienten–Dymista Nasenspray 137 Mikrogramm/50 Mikrogramm pro Sprühstoß – Nasenspray, Suspension; Azelastinhydrochlorid/Fluticasonpropionat: Viatris Healthcare GmbH; 2022 [07.11.2023]. Available from: https://www.apotheken-umschau.de/medikamente/beipackzettel/dymista-nasenspray-137-g50-gspruehstoss-2834904.html?file=3ab17ceb0a8236ed2fed54f84bc6a376