Intranasal combo: fixed-dose combination of mometasone furoate and olopatadine hydrochloride in therapeutic strategies for rhinosinusitis

Bolesław Samoliński¹, Oksana Wojas¹, Agnieszka Lipiec¹, Edyta Krzych-Fała², Artur Walkiewicz¹, Jacek Borowicz¹, Krzysztof Samoliński³

¹Department of Prevention of Environmental Hazards, Allergology and Immunology, Medical University of Warsaw
²Department of Basic Nursing, Medical University of Warsaw
³Department of Emergency Medicine, Medical University of Warsaw

Article history: Received: 20.11.2023 Accepted: 20.11.2023 Published: 04.12.2023

ABSTRACT: A novel strategy for the treatment of allergic rhinitis results from the innovative combination of antihistamine and intranasal corticosteroid drugs. By combining two preparations with different mechanism of action, this novel approach facilitates quick and effective controls of all upper respiratory tract allergy symptoms. The article presents the results of a study of olopatadine hydrochloride and mometasone furoate fixed-dose combination (GSP301) administered intranasally from a spray formulation, with an attempt at positioning the treatment within the ARIA and EPOS guidelines.

KEYWORDS: allergic rhinitis, ARIA, EPOS, mometasone, olopatadine

ABBREVIATIONS

- anti-H1s – antihistamines
- AR – Allergic rhinitis
- ARIA – Allergic Rhinitis and its Impact on Asthma
- CRS – chronic rhinosinusitis
- CRSsNP – chronic sinusitis without nasal polyps
- CRSwNP – chronic sinusitis with nasal polyps
- EPOS – European Position Paper on Rhinosinusitis and Nasal Polyps
- INCS – intranasal corticosteroids
- iTNSS – instantaneous total nasal symptom score
- iTOSS – instantaneous total ocular symptom score
- MF – Mometasone furoate
- PNSS – physician-assessed nasal symptom score
- RCAT – rhinitis control assessment test
- RQLQ – rhinoconjunctivitis quality of life
- rTNSS – reflective total nasal symptom score
- rTOSS – reflective total ocular symptom score
- TIX – therapeutic index

Allergic rhinitis (AR) is the most common disease of the developmental age. It is also the most common allergic condition. According to a study concerning the period of 2006–2008, the disorder affected 23.6% of the Polish population of children aged 6–7 [1]. As a testament to the steady increase in the prevalence of the condition, 10 years later the percentage of affected children within the same age group was as high as 28.2% [2]. The disorder has a significant impact on the quality of life as well as social and economic impact through work presenteeism and absenteeism due to the fact that 3/4 of children experience sleep disturbances and 2/3 cannot fall asleep due to blocked nose [3, 4].

Standards for the diagnostics and therapy of AR are presented in the periodically updated recommendations titled „Allergic Rhinitis and its Impact on Asthma” (ARIA) [3–9]; the guidelines distinguish between intermittent and persistent forms of allergic rhinitis as characterized by mild, moderate, and severe intensity (Tab. 1).

The mechanism behind the development of the inflammatory process in AR

Allergic reaction leads to the release of inflammatory mediators, with the primary role being played by histamine. By binding the histamine H1 receptor, histamine stimulates itching, attacks of sneezing, and massive production of serous secretions released into the intranasal space. The first manifestations are observed as early as 5 minutes after contact with the allergen. In the second phase of the humoral response, i.e. after about 15–30 minutes, mucosal swelling develops through multiple mediators involved in the response of the autonomic system of nasal mucosa. The cellular response, involving the recruitment of eosinophils, neutrophils, lymphocytes, and monocytes, develops after 6–8 hours. Eosinophils secreting toxic proteins, including ECP, are of critical importance as the cause of epithelial damage. The inflammatory process is transmitted down to the bronchial tree. Numerous cytokines, most importantly IL-4, IL-13 stimulating the production of IgE, and IL-5 resulting in the formation of eosinophilic infiltrates,
production of pro-inflammatory cytokines and other inflammatory mediators as a result of the humoral response as well as the cellular response (Tab. II.) [10]. Acting within the cell nuclei, they affect nearly all stages of the inflammatory process [10].

Drugs used in allergic rhinitis

Anti-allergic drugs can be classified into those acting on the respective receptors, i.e. symptomatic, fast-acting drugs such as antihistamines, cholinolytics, alpha-mimetics and sympathomimetics, and anti-inflammatory drugs, e.g. corticosteroids.

The mechanism for the development of an allergic reaction within the mucosa, as summarized above, gives rise to a basic premise suggesting that the treatment should be based on drugs that block the effects of histamine along with anti-inflammatory drugs that reduce eosinophilic inflammation in the mucosal lining.

Antihistamines (anti-H1s) are available in intranasal (topical) and oral formulations. Intranasal formulations exert their effect after 15–30 minutes whereas oral formulations require 60 to 120 minutes. Antihistamines have little or no effect on the inflammatory process (Tab. II.) [10].

The role of intranasal corticosteroids (INCS) in the treatment of AR

The full therapeutic effect in the treatment of AR is possible only with the use of intranasal corticosteroids, due to their ability to comprehensively block the inflammation mechanisms developing as a result of the humoral response as well as the cellular response [4, 10]. Intranasal corticosteroids exert their action by reducing the production of pro-inflammatory cytokines and other inflammatory mediators at the level of the cell nucleus. The clinical effect is achieved as late as after 12 hours, optimum results being reached on treatment day 3. INCS are at the top level of recommendations in therapeutic algorithms regarding AR as well as rhinosinusitis [11].

A new era of the use of topical corticosteroids in the treatment of respiratory tract inflammation began in 1972 [12] with the discovery that CSs are vastly eliminated by the first-pass effect within the liver, showing the treatment to be safe and effective. Corticosteroids can be found only in trace amounts, on the order of < 1% of the administered dose, within the blood serum. The unfavorable therapeutic index, i.e. the ratio of side effects vs. efficacy, has led to the virtual elimination of flunisolide, triamcinolone, and, in a large part, beclomethasone due to the high risk of systemic effects. Three corticosteroids presenting with the highest efficacy and safety, namely fluticasone propionate, furoates, and budesonide, continue to be available on the pharmaceutical market.

Of particular note are the corticosteroids of the furoate group: mometasone furoate and fluticasone furoate. The side chain of the furoate ester is responsible for the high lipophilicity of the respective molecules, facilitating their absorption into the nasal epithelium and subsequent uptake by phospholipids within the cell membranes. Thus, the drugs exert a strong local effect while being poorly available systemically. The pharmacokinetic properties improve, bringing the agents of interest closer to the ideal therapeutic index, i.e. maximum therapeutic effect with minimum side effects. The highest rate of side effects was observed for budesonide [3–25].

Schafer et al. used the therapeutic index (TIX), defined as the ratio of efficacy to safety in a comparative analysis of INCS, to demonstrate the superiority of mometasone furoate to triamcinolone, fluticasone propionate and budesonide [26]. Thus, mometasone furoate was determined to be the most effective and safest intranasal corticosteroid.

Due to the aforementioned properties, mometasone furoate is most frequently recommended and available from many pharmaceutical manufacturers, with a dozen or so generic preparations containing the molecule being currently available in the Polish market.
Therapeutic standards in AR

Based on a number of clinical trials and systematic reviews, intranasal corticosteroid therapy has been recognized as the most effective form of treatment for AR. However, as shown by real-life-based observations of the MASK-Air study, the ARIA recommendations for the treatment of AR are followed only in 50%, as both physicians and patients abandon the use of INCS in favor of anti-H1s in more than one half of the cases. Hence, in the latest revision of ARIA, experts warrant the interchangeable use of anti-H1s and INCSs in both intermittent and persistent AR of mild to moderate intensity. Only the lack of therapeutic effect of anti-H1 monotherapy or severe AR symptoms are indications for the use of INCS in monotherapy or in combination with anti-H1s instead of anti-H1 monotherapy (Fig. 2) [27, 28].

New therapeutic strategy for AR—combo drugs

In the middle of the last decade, a two-component drug containing intranasal antihistamine drug and intranasal corticosteroid, composed of 50 μg of fluticasone propionate and 137 μg of azelastine hydrochloride and referred to as MP29-02, was introduced to the AR treatment market. The innovation, facilitated combination of the therapeutic effects and the efficacy in the control of symptoms as offered by two therapeutic groups: fast-acting antihistaminic drugs and anti-inflammatory INCSs. Marked improvement has been experienced by the patients as the result. The phenomenon of this innovation consisted in the fact that separate administration of both preparations was able to produce a therapeutic effect only several days later than in the novel combo MP29-02 [29–34].

However, even upon the introduction of the new therapy, questions were raised regarding why azelastine and fluticasone propionate were chosen in particular over the more modern intranasal antihistamines or INCS shown to be associated with lower risk of side effects. In the following years, a novel solution was introduced consisting in the combination of olopatadine and mometasone furoate.

Olopatadine hydrochloride (olopatadine for short) is an antihistaminic agent commonly used to treat symptoms of allergic rhinitis, such as serous discharge, itching, and sneezing. It is also used to treat allergic conjunctivitis. It is available in various formulations, including eye drops and nasal sprays. Studies had also been conducted on the oral use of olopatadine in tablet formulations. The agent directly counteracts allergic symptoms. As a nasal spray, olopatadine helps in relieving the allergy symptoms by blocking histamine activity. As a selective antagonist of H1-histamine receptors, it stabilizes mast cells to reduce the release of allergic inflammatory mediators. In Japan, it has been used since 2000 for indications including AR, chronic urticaria, eczema, and other pruritic skin lesions. It is not metabolized in the liver, but excreted in the urine. Olopatadine is a very safe medicinal product [35–37].

Mometasone furoate (abbreviated as mometasone or MF) is a corticosteroid available in a spray formulation to treat the symptoms of allergic rhinitis and, in some cases, other conditions such as nasal polyps or chronic sinusitis. Mometasone exerts an anti-inflammatory effect by reducing the release of pro-inflammatory substances and modulating the immune response. The molecule belongs to the class of furoate esters, characterized by comprehensive first-pass metabolism within the liver, with less than 1% of the preparation making it into systemic circulation. As a result, the drug has no systemic effects. MF has a very low bioavailability of < 0.1%, translating to the absence of systemic action or side effects. The drug is characterized by a favorable safety profile compared to other over-the-counter medications used in the treatment of AR (both general and topical). It does not interact with other preparations used in AR treatment. No tachyphylaxis is observed. After months of MF being used for the treatment of AR (both general and topical). It does not interact with other preparations used in AR treatment. No tachyphylaxis is observed. After months of MF being

---

**Tab. II.** The effects of drugs on rhinitis symptoms. Intranasal antihistamines and corticosteroids are highlighted as representing the new form of combo therapy.

<table>
<thead>
<tr>
<th>Effect duration</th>
<th>Onset of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal congestion</td>
<td>12–48 hrs.</td>
</tr>
<tr>
<td>Itching</td>
<td>12–14 hrs.</td>
</tr>
<tr>
<td>Sneezing</td>
<td>12 hrs.</td>
</tr>
<tr>
<td>Discharge</td>
<td>6–12 hrs.</td>
</tr>
</tbody>
</table>

**Assessment of control in treated symptomatic patient**

AR—allergic rhinitis, VAS—visual analogue scale, O/IN—oral/intranasal, INCS—intranasal corticosteroids; LTRA—leukotriene receptor antagonist; AIT—allergen immunotherapy.

Consider MP-AzeFlu (combination of azelastine and fluticasone propionate) if previous treatment has failed [28–30].
administered to both the bronchial and nasal mucosa, epithelial regeneration rather than epithelial damage is observed [19–25].

Mometasone furoate exhibits the physical phenomenon of thixotropy, which involves a rearrangement of the colloidal structure of the preparation, increasing its time of dwelling on nasal mucosa. The analysis of efficacy versus side effects makes it the most effective and safe preparation, which was the basis for its inclusion in the group of OTC drugs in England, Finland, Norway, Switzerland, Sweden, Australia, Canada, New Zealand, and most recently in Poland, among others [13–25].

The new combo

A combination of olopatadine hydrochloride and mometasone furoate, known in the literature as GSP301, makes use of the characteristics of both of its components to achieve high efficacy, control of AR symptoms, and reduction of the inflammatory process in the nasal epithelial lining within the order of minutes. Both formulations are administered intranasally in an integrated liquid spray formulation. The resulting single medicinal product presents with two important features:

- olopatadine as an agent blocking the H1 receptors and having a stabilizing effect on the mast cells, uses the receptor effect, giving rapid control of symptoms;
- mometasone, leading to the resolution of the inflammatory process via a nuclear mechanism, requires a longer time to exert its action, but has a comprehensive effect on suppressing the inflammatory process and, consequently, the symptoms of AR.

Olopatadine blocks histamine receptors to prevent a cascade of allergic reactions that cause symptoms such as itching, runny nose, and sneezing. Mometasone, on the other hand, has an anti-inflammatory effect, reducing the swelling and redness of the nasal mucosa, leading to relief from nasal congestion and improved airflow.

The presented combination of two pharmaceuticals with different activities offers a chance for a comprehensive approach to the control of the symptoms of rhinitis with benefits including:

1. Faster relief of symptoms;
2. Broad spectrum of action: olopatadine acts quickly on the allergy symptoms, while mometasone exerts a more chronic effect and helps with long-term inflammation control;
3. Improved comfort: by reducing the itching and sneezing (as the effect of olopatadine) as well as nasal congestion and swelling (as the effect of mometasone), the patient can experience significant improvements in comfort;
4. Potential dose reduction: the use of two drugs with different mechanisms of action may allow for the use of lower doses of both substances, which in turn may reduce the risk of side effects;
5. A more comprehensive approach to treatment: reducing the need for several medications is more convenient for the patient and improves treatment adherence.

The combination of olopatadine and mometasone may be an effective treatment regimen for people suffering from severe cases of allergic rhinitis who do not respond sufficiently to monotherapy with either agent.

Scientific evidence to the effects of olopatadine and mometasone combo (GSP301)

The first study of the new formulation containing MF and olopatadine was published in 2018 [38]. Since then, numerous papers have been published on the use of this pharmacological innovation. In 2022, a systematic literature review was carried out by Chen [39]. Of the 86 available publications, 5 articles meeting the criteria of randomized, placebo-controlled, and double-blind studies were included for analysis by the author; 4 of these articles pertained to seasonal AR and 1 to chronic AR [40–44]. The efficacy and safety of GSP301 (665 micrograms of olopatadine and 25 micrograms of mometasone) administered twice daily was assessed against placebo control. One study involved an observation period of 52 weeks while the remaining studies were two-week observations. All cited publications cited reported on highly statistically significant differences between olopatadine therapy combined with mometasone vs. placebo at short-term follow-up (P < 0.01):

- rTNSS – reflective total nasal symptom score as averaged from the morning and evening readings collected at a 12-hour interval;
- iTNSS – instantaneous total nasal symptom score;
- rTOSS – reflective total ocular symptom score;
- iTOSS – instantaneous total ocular symptom score;
- PNSS – physician-assessed nasal symptom score;
- RQLQ – rhinoconjunctivitis quality of life;
- RCAT – rhinitis control assessment test.

However, the therapeutic effect as observed at long-term follow-up did not reach the level of statistical significance in terms of the quality of life, with the difference in the resolution of symptoms between the active treatment versus the placebo group remaining statistically significant in favor of GSP301 [42].

Four types of adverse effects were identified, including headache, dysgeusia, nasal discomfort, and upper respiratory tract infec-
tions. A statistically significant difference was observed only for dysgeusia in the actively treated group (p < 0.01). The remaining side effects occurred with statistically insignificant differences between groups. On the basis of the analysis, the authors concluded that GSP301 was an effective and safe drug over a two-week treatment period, providing good control of both nasal and conjunctival symptoms. The drug’s safety remains high in the long-term analysis. However, after 52 weeks of systematic use, the difference in the quality of life improvement scores as compared to placebo disappeared. This effect was most likely due to the habituation to the new health situation, as at the same time patients reported on a statistically significant improvement with regard to the resolution of AR symptoms, the level of the effect being the same as in the two-week observations.

Hampel et al. demonstrated the efficacy of GSP301 as early as 15 minutes after administration, achieving a statistically significant difference against placebo which persisted on the first and the subsequent days for the entire two weeks of follow-up (Fig. 3.). All symptoms of seasonal AR were controlled, including rhinorrhea, itching, feeling of congestion, and sneezing. The formulation was more effective than olopatadine and mometasone administered separately [43]. Similar results were obtained by Gross et al. [41].

Prenner et al. demonstrated the efficacy of GSP301 as administered 2 × one dose into both nostrils in a group of children aged 6–11 years. Just as in the studies in adults [40–43], the authors reported on the resolution of seasonal AR symptoms and improved quality of life at two-week follow-up, with minor adverse effects of no statistical significance when compared to the control group [44].

In the Polish literature, the use of GSP301 was reported on by Ląpiec and Jurkiewicz, who also pointed to the high safety and good tolerability of the combined intranasal formulation of mometasone and olopatadine [45].

**GSP301 in chronic rhinosinusitis (CRS)**

As of present, no clear literature data are available to suggest the use of GSP301 in other inflammatory conditions of the upper respiratory tract. However, based on the 2020 EPOS guidelines, the aforementioned regimen can be suggested in the management of chronic sinusitis without nasal polyps (CRSsNP) and with nasal polyps (CRSwNP) [11].

CRS is often associated with AR. The percentage of patients with AR within the overall Polish population is twice lower than that in the group of patients with CRSwNP: 22% AR vs. 42% AR concomitant to CRSwNP [unpublished ECAP data], translating to the coexistence of AR with nasal polyps. The mechanism of allergic inflammation is very similar to that underlying nasal polyps, leading to both histamine release and eosinophilic cellular reaction within the nasal mucosa in both conditions. The use of a preparation integrating the antihistamine and anti-inflammatory activity, namely GSP301, is therefore fully warranted in this group of patients [11].

A somewhat worse situation is observed with regard to CRSsNP. In this case, neutrophilic inflammation predominates. Available evidence suggests that the administration of intranasal corticosteroids is beneficial in improving the condition of nasal mucosa in CRSsNP [11] while the validity of antihistamine use remains questionable and requires further research.

**Acute sinusitis and infection**

There is no data indicating that anti-H1 and INCS treatment is effective in acute bacterial sinusitis and viral infections. The treatment is not recommended by the authors of the EPOS 2020 guidelines [11].

So how do we differentiate between AR and an acute viral infection (common cold) or acute sinusitis in order to properly use GSP301? The differential diagnostic scheme is presented in monographs and in ARIA, PSLeNN, and EPOS standards and [5, 10, 11, 46–48]:

- AR presents predominantly with histamine-mediated symptoms: nasal itching, attacks of sneezing, massive serous discharge, with the absence of systemic symptoms; possibly, with concomitant asthma and conjunctivitis, developing upon contact with an allergen, often in a seasonal fashion;
- The common cold is characterized by the swelling of the nasal mucosa and serous discharge, without other symptoms, but with marked systemic complaints, such as fever, muscle aches, increased sweating, headache;
- Acute bacterial sinusitis presents primarily with local symptoms: a very pronounced purulent discharge, pain in the sinus projection, nasal congestion, and distension within the interorbital area, and is often accompanied by fever.

The mechanisms underlying the aforementioned conditions are very different. In a nutshell, AR is associated with a Th2-dependent immune response, giving rise to histamine secretion and eosinophilic inflammation. In the common cold and acute sinusitis, the immune response is Th1-dependent, leading to a completely different set of cytokines present within the mucosal lining. Among other things, the dominating prostaglandin and neutrophil reactions proceed without the involvement of mediators impacted by the use of olopatadine and mometasone. Therefore, GSP301 should be administered only in the first case, i.e. in allergic rhinitis.

**SUMMARY**

GSP301 is an effective and safe intranasal preparation with a rapid and long-lasting effect. It is recommended for all AR-related conditions, including those with comorbidities. The treatment is initiated and continued before the expected contact with the allergen or at the first symptoms of itching, sneezing, serous discharge, or conjunctivitis of allergic origin. According to the recent ARIA guidelines, GSP301 is the drug of choice in patients in whom previous monotherapy with INCS or anti-H1s failed to afford the expected therapeutic effect. The presented treatment is expected not only to bring relief in patient’s condition, but also to reduce the risk of complications, including sinusitis.
REFERENCES


