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To cite this article: Enrico Heffler, Luisa Brussino, Stefano Del Giacco, Giovanni Paoletti, Paola Lucia Minciullo, Gilda Varricchi, Guy Scadding, Luca Malvezzi, Armando De Virgilio, Giuseppe Spriano, Francesca Puggioni, Monica Fornero, Giovanni Rolla & Giorgio Walter Canonica (2019): New drugs in early-stage clinical trials for allergic rhinitis, Expert Opinion on Investigational Drugs, DOI: 10.1080/13543784.2019.1571581

To link to this article: https://doi.org/10.1080/13543784.2019.1571581

Published online: 24 Jan 2019.
New drugs in early-stage clinical trials for allergic rhinitis

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\textbf{Abstract}

\textbf{Introduction}: Allergic rhinitis (AR) is the most common allergic disease, and it has a relevant impact on the quality of life of the patient. Treatment of AR includes a combination of strategies of proven efficacy and effectiveness; however, a relevant proportion of patients remain uncontrolled.

\textbf{Areas covered}: This review article summarizes emerging therapeutic approaches to AR; these approaches include nasal sprays, oral drugs, alternative allergen immunotherapy administration routes, and biologic agents.

\textbf{Expert opinion}: The agents discussed require further clinical trials to prove their efficacy in the treatment of AR. Some of these agents, in particular, allergen immunotherapies and biologics, have the potential to form crucial precision medicine approaches to AR. Those that prove their efficacy in clinical trials must also be evaluated from a pharmacoeconomic perspective, possibly in real-life studies; this will define which therapeutic strategies achieve the most convenient and cost-effective ratio, thus yielding a novel opportunity for the most severe and previously treatment-resistant allergic patients.

\section{1. Introduction}

Allergic rhinitis (AR) is the most common allergic disease worldwide \cite{1}, is frequently associated with asthma \cite{2}, and has a relevant impact on health-related quality of life \cite{3}. Treatment of AR includes a combination of different strategies, ranging from allergen avoidance, allergen immunotherapy (AIT), oral antihistamines, mast cell stabilizers, intranasal corticosteroids and/or antihistamines, and short-course nasal decongestants \cite{4}. Despite the availability of well-established effective therapeutic strategies, a relevant proportion of patients are still uncontrolled \cite{5}. Moreover, associated adverse events to drugs for AR, including drowsiness and confusion, bitter taste, epistaxis, headache, somnolence, and nasal burning, have led to greater efforts to identify new medications; additionally, although most corticosteroid nasal sprays have good safety profile \cite{6}, long-term steroid medication is a cause for concern, particularly in children, pregnant and lactating women, and those patients using high and prolonged doses \cite{7}.

Here, we summarize the novel possible therapeutic approach to AR that is emerging (Table 1).

\section{2. Novel nasal sprays}

\subsection{2.1. Barrier agents}

Avoiding allergen and other triggering factor exposure should be the first step in the management of a patient with AR, as recommended by ARIA (Allergic Rhinitis and its Impact on Asthma) guidelines \cite{4}. However, a complete environmental remediation or avoidance of allergen exposure is not always entirely possible.

In this context, creating a mechanical barrier over the sinonasal mucosa can avoid or reduce the contact between allergens, irritants, pathogens, triggering factors, and the mucosa.

In this regard, barrier measures, such as non-pharmacological intranasal cellulose powder (which hygroscopically binds water to form a mucosal gel) \cite{8,9} and lipid microemulsions \cite{10}, have been shown to reduce the symptoms of AR in three double-blind, placebo-controlled studies \cite{8–10}, while an observational study has provided preliminary evidence of the efficacy for a liposomal nasal spray \cite{11}.

An intranasal micronized powder filling hydroxypropyl methylcellulose has been registered in the UK medical devices agency in 1994 \cite{12}. Cellulose powder is sprayed into the nose by
Allergic rhinitis remains uncontrolled in a proportion of patients despite the availability of effective drugs, and sometimes, they suffer from drug-related adverse events. Novel medications for allergic rhinitis, such as intranasal and systemic drugs, are in development. Novel administration routes for allergen immunotherapy are emerging, they may enhance clinical efficacy. Biologic agents already used or in development for severe asthma have the potential to be effective for treating concomitant allergic rhinitis. Novel therapeutic approaches to allergic rhinitis need further testing in clinical trials.

### Article highlights
- Allergic rhinitis remains uncontrolled in a proportion of patients despite the availability of effective drugs, and sometimes, they suffer from drug-related adverse events.
- Novel medications for allergic rhinitis, such as intranasal and systemic drugs, are in development.
- Novel administration routes for allergen immunotherapy are emerging; they may enhance clinical efficacy.
- Biologic agents already used or in development for severe asthma have the potential to be effective for treating concomitant allergic rhinitis.
- Novel therapeutic approaches to allergic rhinitis need further testing in clinical trials.

'This box summarizes key points contained in the article.'

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a small pump. The cellulose moisturizing the nasal mucosa creates an impermeable barrier that hinders the binding of allergens to mucosal cells, thus preventing the release of vasoactive substances from the mucosal cells and the subsequent immunological reactions. In the study conducted by Emberlin et al., this intranasal micronized cellulose powder significantly reduced the severity of rhinitis symptoms compared with placebo [13]. In a more recent single-blind, randomized interventional study [14], the effect of intranasal cellulose powder compared to mometasone has been investigated in patients with AR: the severity of sneezing, runny nose, nasal congestion, itchy eyes, and itchy throat improved significantly both in cellulose and mometasone groups following 14 and 28 days of treatment; ocular symptoms improved only in intranasal cellulose powder group. A similar result had been reported previously by Mohammad Reza Fathololoomi et al., who showed that nasal corticosteroids did not improve eye symptoms [14].

Another novel therapeutic strategy is a medical device containing xyloglucan, a natural hemicellulose extracted from the seeds of the tamarind tree (**Tamarindus indica**). In 2017, De Servi et al. have designed an in vitro study [15] to assess the barrier-preserving properties of xyloglucan spray in the airway tissue model MucilAir (organotypic 3D airway tissue model: pseudostratified cell layer containing mucus-secreting goblet cells and ciliated columnar cells) using Trans-Epithelial Electrical Resistance (TEER), which is related also to tight junction stability, and Lucifer Yellow assay, which is related to the permeability of intercellular tight junctions of epithelial cells. Upon exposure to xyloglucan, TEER values increased in the actively treated model, while with saline solution, TEER values decreased. Moreover, xyloglucan did not alter cell permeability of MucilAir cells, thus reflecting the integrity of the mucosal barrier. In the presence of pro-inflammatory compounds (Tumor necrosis factor alpha - TNF-α - and lipopolysaccharide - LPS), cell permeability in the negative control (saline solution) increased, while cells treated with xyloglucan maintained low permeability levels (comparable to the values observed before the pro-inflammatory cytokine exposure) [15]. Moreover, they compared the effect of xyloglucan with budesonide nasal spray obtaining similar results in favor of xyloglucan. These results confirm that xyloglucan spray is able to create a protective barrier on nasal cells, avoiding the contact of triggering factors with the nasal mucosal layer and preventing the activation of epithelial cells.

#### 2.2. Resveratrol

Resveratrol (trans-3, 4, 5-trihydroxystilbene) is a natural, non-flavonoid polyphenol, which is found in significant amounts in berries, peanuts, grape (and red wine), and other plant sources. It functions as a phytoalexin (a class of vegetal antibiotics), protecting the plant from environmental stress or infection. The anti-inflammatory properties of resveratrol are thought to depend on NF-κB inhibition, mainly via IkB kinase downregulation, and subsequent reduction of the release of several pro-inflammatory cytokines (IL-8, granulocyte–macrophage colony-stimulating factor) and the activation of enzymes (cyclooxygenase-1, COX-2, inducible nitric oxide synthase). Resveratrol has become very popular due to its anticancer potential, first reported in 1997 (it inhibits the proliferation of multiple cancer cell lines *in vitro* and *in vivo*) [16]. In 2009, Lee et al. [17] demonstrated that resveratrol was able to exert an anti-inflammatory and anti-asthma action in a murine model of allergic asthma by significantly reducing IL-4 and IL-5 both in the plasma and in bronchoalveolar lavage fluid, suppressing bronchial hyperreactivity, lung eosinophilia, and mucus hypersecretion. In 2014, Miraaglia Del Giudice et al. [18] reported that resveratrol reduced nasal symptoms in children with pollen-induced AR. Recently, Lv et al. [19] designed a double-blinded, placebo-controlled, randomized study enrolling 151 adults with moderate-to-severe AR: patients treated with resveratrol 0.1% isotonic nasal spray solution (100 μL/spray), twice in each nostril three times/day for a month, reported a significant reduction in nasal

### Table 1. Drugs in development for allergic rhinitis.

<table>
<thead>
<tr>
<th>Drug name/class</th>
<th>Development stage</th>
<th>Administration route</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micronized hydroxypropyl methylcellulose powder</td>
<td>Phase II</td>
<td>Intranasal</td>
<td>8,9,14</td>
</tr>
<tr>
<td>Lipid microemulsions</td>
<td>Phase II</td>
<td>Intranasal</td>
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<tr>
<td>Resveratrol</td>
<td>Phase II</td>
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<tr>
<td>Sodium pyruvate</td>
<td>Phase II</td>
<td>Intranasal</td>
<td>21</td>
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<tr>
<td>PF-03654746 (histamine H3 receptor antagonist)</td>
<td>Phase II</td>
<td>Oral</td>
<td>26</td>
</tr>
<tr>
<td>Setipiprant (CRTH2 antagonist)</td>
<td>Phase II-III</td>
<td>Oral</td>
<td>29</td>
</tr>
<tr>
<td>OC000459 (CRTH2 antagonist)</td>
<td>Phase II</td>
<td>Oral</td>
<td>30</td>
</tr>
<tr>
<td>Roflumilast (phosphodiesterase 4 inhibitor)</td>
<td>Phase II</td>
<td>Oral</td>
<td>32</td>
</tr>
<tr>
<td>Intralymphatic immunotherapy</td>
<td>Phase II</td>
<td>Intralymphatic</td>
<td>34,37</td>
</tr>
<tr>
<td>Epicutaneous immunotherapy</td>
<td>Phase II</td>
<td>Epicutaneous</td>
<td>38,39</td>
</tr>
<tr>
<td>Intradermal immunotherapy</td>
<td>Phase II</td>
<td>Intradermal</td>
<td>40</td>
</tr>
<tr>
<td>Allergen immunotherapy combined with omalizumab</td>
<td>Phase II</td>
<td>Subcutaneous</td>
<td>44,45</td>
</tr>
<tr>
<td>Dupilumab</td>
<td>Phase II</td>
<td>Subcutaneous</td>
<td>48</td>
</tr>
</tbody>
</table>
symptoms after 2 and 4 weeks, compared with placebo. A significant decrease in serum IgE, IL-4, TNF-α, and eosinophils was also observed in treated patients [19].

2.3. Sodium pyruvate nasal spray

Sodium pyruvate is a keto-acid with anti-oxidation and anti-inflammatory effects [20], which has been investigated in a recent randomized, parallel-group, single-center study [21] enrolling 53 adult patients with seasonal AR caused by Artemisia pollen. In the pollen season, patients received corticosteroid nasal spray at standard dose during the first two weeks, while, in the following two weeks, they were randomized to receive nasal sodium pyruvate or placebo: daily rhinoconjunctivitis symptom score and daily rescue medication score were significantly lower in the treatment group than in controls.

2.4. Empowering ‘old’ drugs

Research is also focusing on improving the clinical benefits of drugs already used in AR treatment. As budesonide is poorly soluble and the small volume of fluid in the nasal cavity limits the absorption of poorly soluble drugs, in 2017, Pozzoli et al. [22] developed an amorphous solid dispersions/solutions of budesonide combined with a novel polymer (polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer), using a freeze-drying technique, in order to improve dissolution and absorption through the nasal route. This study opens up opportunities in developing new poorly soluble drug formulations for nasal delivery.

In 2018, Jullaphant et al. [23] were able to develop montelukast sodium as a spray formulation for nasal delivery. The formulation was prepared with hydroxypropyl cellulose (HPC) and carboxomer 940 (C940), and its physico-chemical characteristics were evaluated. The suitable formulations were also assessed for their effects on nasal epithelial cells. The formulation containing 0.01% w/V C940 and 0.5–15 µg/50 µL of montelukast exhibited suitable viscosity and rheological properties. Spray droplets were in ranges of 10–40 µm, which are suitable for nasal administration. The solution did not show any cytotoxicity and did not enlarge the tight junction of nasal epithelial cells.

Mometasone furoate nasal spray is available as an aqueous suspension because of the poor solubility in water, leading to a delayed onset of action. For this reason, nasal application of mometasone furoate, as suspension formulation, is not optimal because of the fast elimination of the drug from the nasal cavity by mucociliary clearance (approximately 15 min). In order to avoid the rapid drainage of this formulation and to obtain a prolonged residence time in the nasal cavity, viscosity-enhancing strategy, such as gel, may be applied. A gel could be administered easily by the patients as drops, allowing accurate drug dosing, and it might prolong the contact time between the drug and the nasal mucosa, increasing the drug release.

A phase III, national, multicenter, randomized, single-blind, non-inferiority study (Identifier: NCT02953379) to compare the efficacy of mometasone nasal gel vs mometasone nasal spray in the treatment of persistent or intermittent AR in adults (12–65 years) will start on May 2019.

2.5. A new life for old drugs

Cyclosporine is an immunosuppressive molecule, which decreases the synthesis of inflammatory cytokines, by inhibiting calcineurin in Th cells. A recent study by Senturk et al. [24] reports the effects of cyclosporine in a Sprague Dawley model of ovalbumin (OVA)-induced AR. The authors compared the effects of three different doses of nasal cyclosporine, compared to nasal corticosteroids, in animals with OVA-induced AR, as well as in controls. In the control group, no side effects were observed. Both nasal corticosteroid and cyclosporine obtained a significant decrease of nasal symptoms after OVA challenge, with no difference between the two treatments. Moreover, cyclosporine was found to be as effective as nasal steroids in reducing the eosinophil and basophil/mast cell infiltration both in the lamina propria and in the epithelium. In AR therapy, nasal corticosteroids can inhibit Th2 cytokines, while their effect on Th1 is minimal: being cyclosporine effective in both pathways, it could be useful in steroid-resistant or poor-responder patients.

3. Novel systemic treatments

The main and most commonly used current systemic treatment of AR is anti-H-1 antihistamines that will surely remain the cornerstone of systemic treatment in AR, at least in the near future. However, new drugs belonging to the same or to other classes are under development.

Anti-H3 antihistamines have been proven to increase norepinephrine levels, modulating the vascular contractile responses in human nasal mucosa, and administered alone or in combination with anti-H1 antihistamines, they might provide an effectual action as nasal decongestants [25]. PF-03654746, for example, caused a reduction in allergen-induced nasal symptoms in a double-blind, randomized controlled trial [26].

Anti-H4 antihistamines mainly exert an anti-inflammatory effect, downregulating inflammation in patients with AR (but also asthma, atopic dermatitis, and other chronic inflammatory diseases) [27], again used alone or in combination with anti-H1. JNJ7777120 showed good efficacy in decreasing remodeling and Th2 inflammation in a rat model of AR, with improvements in sneezing and nasal rubbing [28].

No anti-H3 or anti-H4 agents are approved to date.

Selective CRTH2 antagonists represent a new, promising class of systemic drugs potentially useful in AR. CRTH2 shows a high-affinity interaction with PGD2, that is produced during the early phase of the allergic response and has been proposed to contribute to the accumulation and activation of Th2 lymphocytes, eosinophils, and basophils [27,28]. The biological effects of PGD2 are also mediated by DP1 receptors and thromboxane receptor (TP). The inhibition of the PGD2/CRTH2 pathway blocks the activation of these cells and reduces the secretion of cytokines (IL-4, IL-5, and IL-13). Some drugs belonging to this class are involved in phase I, II, and III trials. Setipiprant (ACT-129968), for example, was tested in both phase II and phase III studies, showing
significant efficacy in the daytime eye and nasal symptoms in phase II but not in phase III [29]. Another CRTH2 antagonist (OC000459) demonstrated a reduction of both nasal and ocular symptoms in allergic subjects compared with placebo after challenge with grass pollen in the Vienna Challenge Chamber [30].

The only drug currently available from this class is ramatroban, a dual antagonist against TP receptor and CRTH2, which is currently marketed in Japan for AR patients only. Thromboxane A2 (TXA2), in fact, is an arachidonic acid metabolite and plays an important role in inflammation. It is produced by platelets, mast cells, and eosinophils and is able to induce vasoconstriction, bronchoconstriction, and an increase in vascular permeability and in airway hypersensitivity [31].

Anecdotally, also the phosphodiesterase 4 inhibitor roflumilast, approved for COPD, has been described as effective in the treatment of AR in one study on 25 patients [32]; however, no further studies were made on this molecule and its efficacy in AR, and there are no solid evidences for its use in clinical practice.

4. Novel AIT strategies

There is good evidence for the clinical efficacy of AIT for AR, allergic asthma, and hymenoptera venom allergy [33]. It is considered the only disease-modifying intervention in IgE-mediated allergic disease, with therapeutic and preventive effects. It has the potential to induce immunological changes with a consequent response of immune modification leading to the induction of tolerance towards allergens. Currently, AIT is administered sublingually (SLIT) or subcutaneously (SCIT). New routes of administration of AIT are in development in order to reduce the risk of adverse events (although they are rare and generally not severe with SLIT and SCIT) and to allow more rapid up-dosing while minimizing costs of treatment and inconvenience to the patients related to the number and duration of visits in the clinic.

4.1. Intralymphatic immunotherapy (ILIT)

The injection of allergen directly into lymph nodes is a new studied route of administration for AIT that it is likely to intensify allergen presentation and subsequent generation of local T and B cell responses [34,35]. A randomized open-label trial of alum-absorbed whole grass pollen extract for SCIT over 3 years compared with just three doses of ILIT over 2 months showed a persistent effect of ILIT during the whole 3 years [34]. Results demonstrated the use of slightly less medication in the ILIT group, with similar reductions in symptom score on nasal provocation during the pollen season [34].

A study developed by Martínez-Gómez et al. has evaluated the impact of direct intralymphatic allergen administration, showing that it delivered the allergen more efficiently to subcutaneous lymph nodes than subcutaneous injection [36]. As intralymphatic immunization induced more than 10-fold higher IgG2a responses with 10-fold lower allergen doses than subcutaneous immunization, this approach should allow reducing both the number of allergen injections and the allergen dose, improving both efficacy and safety of AIT [36]. A clinical randomized trial on patients with pollen-induced rhinoconjunctivitis receiving three intralymphatic inguinal injections of active allergen (1000 SQ-U birch- or grass-pollen) or placebo confirmed that ILIT was a safe and effective treatment able to reduce seasonal allergic symptoms by inducing a greater affinity of allergen to specific IgG4 [37]. Senti et al. have shown that direct ILIT into a subcutaneous lymph node markedly intensified protective immune response, suggesting that ILIT may be safer and faster than other forms of immunotherapy [34].

4.2. Epicutaneous immunotherapy

Epicutaneous immunotherapy, by applying an allergen via patches that are kept on the skin for several hours, has been proposed as a possible novel administration route. The process involves no needles and aims to improve compliance, especially in children. In a placebo-controlled randomized trial, grass pollen extract in petroleum was applied to the skin on adhesive tape-stripped skin (n = 48) weekly for 6 months pre-seasonally [38]. There was a 48% improvement in seasonal symptom scores in the first year (placebo 10%) but no significant difference for combined treatment and medication scores [38].

Von Moos et al. have demonstrated that epicutaneous allergen-specific immunotherapy increases the attention because it is safe, needle-free, and potentially self-administrable treatment option for IgE-mediated allergic diseases [39].

4.3. Intradermal immunotherapy

Intradermal administration of allergens increases their local presentation while preventing systemic absorption of the allergen. The intradermal allergen injections, given repeatedly at 2–4-week intervals, have been suggested to suppress late cutaneous allergic responses and induce allergen-specific IgG antibodies [40]. A randomized, controlled phase IIb trial of repeated pre-seasonal low-dose intradermal grass pollen allergen (containing 6 ng of major allergen Phl p 5) was ineffective in improving seasonal outcomes, with a worsening of nasal symptoms compared to placebo and an augmented Th2 response at the site of the intradermal injection. These data suggested that intradermal allergen has the potential to sensitize instead of desensitizing against inhalant allergens and is, therefore, not recommended [41].

5. Biologic agents

5.1. Anti-IgE strategies

Two studies have reported that pretreatment with omalizumab, a fully humanized anti-IgE monoclonal antibody approved for severe allergic asthma and chronic spontaneous urticaria, decreases acute reactions after rush immunotherapy for ragweed-induced AR [42,43].

A double-blind, placebo-controlled multicenter trial tested omalizumab in combination with grass pollen SCIT, obtaining a greater reduction in AR and asthma symptoms during the first subsequent grass season, compared with standard SCIT alone [44].
The approach of combining AIT and omalizumab demonstrated to be safe and well tolerated by patients, as shown by the results of an open-label, 12-week study in 287 patients treated with omalizumab [45].

Moreover, the use omalizumab not associated with AIT was associated with reduced symptoms and decreased intranasal basophil, but not mast cell, response to allergen exposure in patients allergic to cat dander [46].

Finally, an ongoing clinical trial is evaluating the safety and efficacy of omalizumab in adult and adolescent Japanese patients with severe seasonal AR (Identifier: NCT03369704).

5.2. Anti-IL4-receptor-alpha strategies

Dupilumab is a fully humanized mAb that targets the IL-4 receptor α (IL-4Rα) subunit, and thus inhibiting the signaling of both IL-4 and IL-13 (since the IL-13R shares the IL-4α chain), each of which is a key driver of type 2 immune diseases [47].

In a recent randomized, double-blind, placebo-controlled, parallel-group phase IIb clinical trial conducted at 174 study sites in patients with asthma and perennial allergic rhinitis (PAR), dupilumab (300 mg s.c. every two weeks) improved AR-associated nasal symptoms [48]. Dupilumab improved SNOT-22 total score compared to placebo at week 24 including improvement in each of the four SNOT-22 items commonly associated with AR compared to placebo. Interestingly, dupilumab (300 mg s.c. every 2 weeks) improved lung function (FEV1) from baseline to week 24 of the treatment in the subgroup of patients with comorbid PAR. The results of this study suggest that dupilumab improves symptoms of PAR in patients with uncontrolled, persistent asthma and comorbid PAR.

6. Conclusion

Despite the availability of effective drugs to control AR, there is still a relevant proportion of patients with uncontrolled symptoms or who suffer adverse events; hence, there is a need for novel therapeutic approaches. Indeed, new drugs are in development or in early-stage clinical trials; among them, novel nasal sprays, systemic drugs, herbal medicine approaches, novel AIT administration routes, and biologic agents are the most promising.

7. Expert opinion

AR is a common chronic disease affecting a relevant proportion of subject, and the need of novel therapeutic approaches to better control the disease is now translating into the clinical research and the development of new drugs or more effective administration routes of already commonly used drugs. Topical treatment remains one of the cornerstones of AR therapy, and novel nasal sprays are in development; among these, different strategies have been investigated to obtain better clinical outcomes, including barrier agents in order to reduce the exposure of nasal mucosa to environmental irritants or allergens, and immunomodulatory and anti-oxidant approaches to reduce the abnormal immunological response to allergens. Moreover, novel formulations of intranasal corticosteroids are in development with the aim of improving their delivery and efficacy on the inflamed nasal mucosa.

The other treatment cornerstone of AR is the use of anti-H1 antihistamines; these drugs proved to be effective, but they may still have relevant adverse effects. This is one of the reasons that is leading researchers to develop systemic drugs able to inhibit other histaminergic pathways and other inflammatory components. Moreover, herbal medicine approaches to AR are widely studied, particularly in Asian countries, as a possible alternative to commonly used treatment; despite not being synthetic drugs, some of them have been tested through Randomized-Controlled trials (RCT), and the obtained results have been also often summarized in metaanalysis studies, giving them the dignity of drugs in early-stage clinical trials for AR.

Intranasal administration of drugs for AR, in our opinion, is still the first choice when developing novel pharmaceutical compounds, as they generally combine a good safety profile with efficacy. However, in a context of precision medicine [49], where after having identified a molecular target, a single drug acting towards it may have an impact on more diseases sharing the same endotype [50], and the opportunity of using such novel systemic therapeutic approaches is fascinating. These drugs aim to reduce or better control AR symptoms and can effectively change the natural history of the disease. AIT and novel biologic agents (mainly those already in use or in advanced-stage trials for severe asthma) have the characteristics to interfere directly to the underlying immunological mechanisms involved in the pathogenesis of the disease. AIT has strong evidence of efficacy and effectiveness in AR patients, but novel administration routes are under clinical investigation in order to further increase its effect in reducing adverse event frequency. Biologic agents, for their intrinsic characteristics, the strong efficacy in other diseases sharing similar inflammatory pathways (severe asthma and chronic rhinosinusitis with nasal polyps), and the excellent safety profile, seem to be the most promising future approach also to the most severe forms of AR [50,51].

The drugs discussed in this review will need further and more specific clinical trials before concluding that their efficacy is proved in AR. The need for new drugs for AR becomes more urgent in consideration of the fact that patients often have asthma as associated comorbidity; this association, particularly in patients with more severe disease, may lead to an overexposure of corticosteroids (intranasal + inhaled ± systemic) that is the predisposing condition to develop relevant glucocorticoid-related adverse events [52]. Novel drugs able to reduce the need or the systemic availability of intranasal and systemic corticosteroids are, therefore, an emerging need also in AR.

The new drugs that prove their efficacy in clinical trials must be evaluated from a pharmacoeconomic perspective (possibly in real-life studies), in order to define which therapeutic strategies will achieve the most convenient cost-effectiveness ratio, therefore becoming a real novel opportunity for the most severe allergic patients.

The introduction of novel drugs will provide new insights into the underlying mechanisms involved in the pathogenesis of AR.

Funding

This paper was not funded.
Declarations of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

• Interesting data on the efficacy of resveratrol nasal spray in patients with allergic rhinitis.
• Preliminary data from a mouse model of allergic rhinitis, showing clinical effects of intranasal cyclosporine.
• Data coming from advanced trials on setipiprant in seasonal allergic rhinitis.

**Novel administration route for allergen immunotherapy (intralymphatic) proved its efficacy in patient with seasonal allergic rhinitis in this double-blind placebo-controlled trial.**


**Anti-IL4-receptor alpha monoclonal antibody is effective in both asthma and allergic rhinitis.**


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