

Corticosteroids for Allergic Rhinitis

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This article is part of the Topical Collection on *Allergic Rhinitis*

Keywords Allergic rhinitis · Type I allergic reaction · Oral allergy syndrome · Eye symptoms · Allergen immunotherapy · Intranasal corticosteroids · Pharmacotherapy

Opinion statement

Allergic rhinitis (AR) is one of the most common allergic diseases. Globally, it is estimated to affect more than 500 million people. The burden of allergic rhinitis is overwhelming due to costs caused by sickness absence, medication, and suboptimal performance by the affected population. AR is characterized by a type I allergic reaction in the epithelium of the nose including both an acute phase reaction and a late phase reaction. The allergic reaction causes exudation, itching, sneezing, and later blocking of the nose. Very often, the nasal symptoms are accompanied by eye symptoms (itching and hyperaemia) and oral allergy syndrome. The treatment of AR include patient education, allergen avoidance, pharmacotherapy, and in a selection of patients, allergen immunotherapy (AIT). The cornerstone of pharmacotherapy is the intranasal corticosteroids (INS). Intranasal application of corticosteroids is regarded as a very efficient treatment—treating not only the acute phase symptoms but also the late phase reaction. The treatment is safe and causes only a few well-known side effects. The aim of this review is to provide an overview of all aspects of corticosteroid treatment including mode of application (per oral, intranasal, intramuscular), way of action, potency, bioavailability, side effects, and aspects regarding the pediatric population.

Introduction

Allergic rhinitis (AR) is a major chronic respiratory disease affecting approximately 10–25 % of the population worldwide [1]. The financial impact of the disease is substantial due to frequency of appearance, negative effect on quality of life, loss of workdays and school attendance, frequent

coexistence with asthma, conjunctivitis, sleep-disordered breathing, atopic dermatitis, and otitis media [2]. The treatment with corticosteroids is effective for treating AR but oral and intramuscular steroids have frequent and severe side effects [3••]. Thus, use of intramuscular

corticosteroids, although often applied, is not a recommended treatment option for AR [4]. Oral corticosteroids can be used as rescue medication for at short period of time (up to 7 days) for otherwise treatment-resistant AR [4, 5]. The development of INS is a huge advance in treating AR. The intranasal corticosteroids (INS) can be grouped in first-generation and second-generation drugs due to the bioavailability (Fig. 1). The high lipophilicity, potency, and low bioavailability of second-generation INS assure the safety and efficacy of the drugs [6]. The drugs are easy to administer, as one daily application is a possibility with several of the registered sprays (Table 1). As INS is the most effective topical treatment option, it is the drug of choice for moderate to severe intermittent and persistent AR (Table 2).

If treatment with INS mono-therapy is inadequate, it can be combined with other drugs. In therapy-resistant

cases, allergen immunotherapy (AIT) is an effective and well-tolerated treatment option in pollen and house dust mite-induced AR [4, 7••, 8, 9]. Anti IgE (omalizumab) is not FDA-approved for treating AR but several studies have shown a promising effect likewise in combination with AIT [10••].

In the pediatric population, AR is a prevalent and troublesome disease, too [5]. One of the major concerns when treating children with steroids is the risk of growth retardation—a well-known side effect when using long-term systemic treatment with corticosteroids. In general, previous studies show no growth impact in children receiving INS [11–14]. Two recent studies find small (<0.5 cm) but significant growth retardation in children treated for one year [15••, 16••]. The INS treatment is regarded safe and effective treating children with AR above 2 years of age [5].

Background

AR is caused by an allergic type I reaction in the nasal mucosa. The acute phase reaction is initiated when a sensitized subject is exposed to an allergen. The allergen is recognized by mast cells in the tissue by specific IgE bound to the surface receptors. When IgE on the surface of a mast cell cross-binds to the allergen, the mast cell degranulates and releases histamine, leukotrienes, and other mediators. This results in an increase in vascular permeability leading to rhinorrhoea and swelling of the nasal mucosa. The neuronal stimulatory effect of the mediators leads to itching and sneezing [6, 17]. Immune cells in the nasal

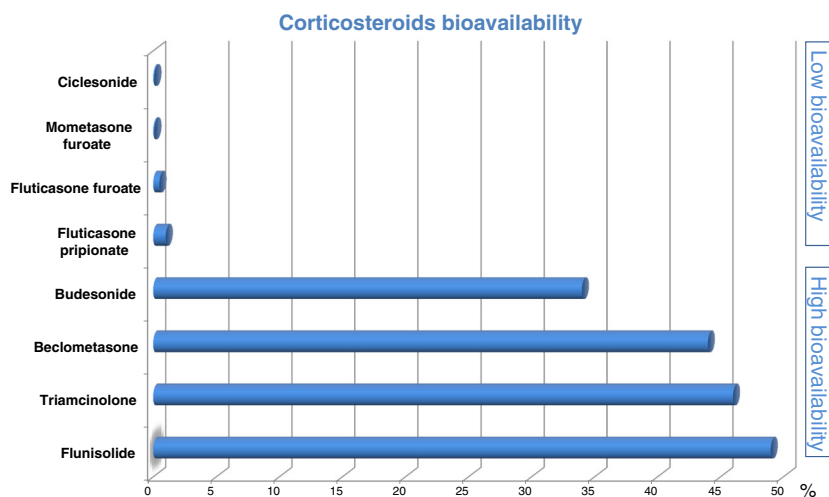


Fig. 1. Bioavailability for corticosteroids. Reprinted with permission by Blackwell Munksgaard from Derendorf H, Meltzer EO. Molecular and clinical pharmacology of intranasal corticosteroids: clinical and therapeutic implications. *Allergy*. 2008;63(10):1292-300., Figure 5.

Table 1. Recommended doses of intranasal steroids

Generic name	µg/dose	Adult dose	Pediatric dose	Preparation
Low bioavailability:				
Ciclesonide	50 µg/spray	Two sprays per nostril once a day	Two sprays per nostril once a day	Aqueous suspension/pressurized aerosol spray
Fluticasone furoate	27.5 µg/spray	Two sprays per nostril once a day	One spray per nostril once a day	Aqueous suspension
Fluticasone propionate	50 µg/spray	Two sprays per nostril once a day/one spray per nostril twice a day	One spray per nostril once a day	Aqueous suspension
Mometasone furoate	50 µg/spray	Two sprays per nostril once a day	One spray per nostril once a day	Aqueous suspension
High bioavailability:				
Beclometasone dipropionate	42 µg/spray	One or two sprays twice daily	One or two sprays twice a day	Aqueous suspension/pressurized aerosol spray
Budesonide	32 µg/spray 64 µg/spray	Two sprays per nostril once a day/one spray per nostril twice a day	Two sprays per nostril once a day/one spray per nostril twice a day	Aqueous suspension
	100 µg/dose	Two sprays per nostril once a day		Nasal powder
Flunisolide	29 µg/spray	Two sprays per nostril twice a day	Two sprays per nostril twice a day	Aqueous suspension
Triamcinolone acetonide	55 µg/spray	Two sprays per nostril once a day	One/two sprays per nostril once a day	Aqueous suspension/pressurized aerosol spray

tissue, not only eosinophils but also T cells and basophils, some hour later, cause the late phase reaction. These cells release immunological mediators including $\text{TNF}\alpha$, $\text{INF}\gamma$, and interleukins (predominately IL-3, IL-4, and IL-5). The process enhances the inflammation and causes tissue damage, mucus production, and oedema resulting in nasal congestion and airflow obstruction [6, 17].

The treatment of AR using INS has a reverse effect on antigen presentation, release of histamine and tryptase from mast cells and eosinophils during the

Table 2. Clinical recommendation

Intranasal corticosteroids are a safe treatment for allergic rhinitis with only minor local side effects.

Continuously use of intranasal corticosteroids is mandatory for maximal symptom relief.

Intranasal corticosteroids are well tolerated and safe in children above 2 years of age.

Antihistamines and leukotrienes without preferred order are optional in treating mild intermittent allergic rhinitis, and intranasal corticosteroids may be used.

Correct inhalation technique of intranasal steroids is mandatory to obtain maximal efficacy and safety.

The use of intramuscular corticosteroids is not recommended for treating allergic rhinitis due to the risk of severe side effects.

If systematic steroids are needed a short course of oral glucocorticoids (3–7 days) can be used.

Allergen specific immunotherapy can be used in patients with pollen induced seasonal allergic rhinitis and with persistent allergic rhinitis caused by house dust mites resistant to maximal anti-allergic treatment.

acute phase reaction. It also decreases the accumulation of mast cells, basophils, and TH2 cells and the level of interleukins during the late phase response [18].

The action of glucocorticoids is mediated by an activation of the cytoplasmic glucocorticoid receptor. This receptor is inactive in the cytoplasm due to binding to two heat shock proteins. The binding of glucocorticoid to the receptor causes a conformational change and renders the receptor active. The activated receptor-ligand complex is transported to the cell nucleus, here, working as transcriptional factor resulting in down regulation of the allergic response [19].

Evidence-based medicine: current and new preparations

Several systematic reviews have evaluated the use of INS. The ARIA guidelines place INS as the drug of choice for both mild and moderate to severe AR in adults and children. The ARIA guidelines recommend adding an antihistamine if eye symptoms are inadequately treated [4, 20].

“The American Academy of Otolaryngology–Head and Neck Surgery Clinical Practice Guideline for allergic rhinitis” states that INS should be used to treat AR patients with impaired quality of life as INS are more effective in treating AR than antihistamines and leukotrienes. The different preparations of INS are equally effective [2]. “The British Society for Allergy and Immunology guidelines for the management of allergic and non-allergic rhinitis” concludes that INS is first-line therapy in moderate to severe persistent AR and patients with treatment failures to antihistamine, as they are superior to antihistamines [21].

An American evidence-based review “evaluating approved medications to treat allergic rhinitis” demonstrates INS as the most effective drug treating seasonal AR. Concerning perennial AR, the conclusion is that the literature is of variable quality, and for some patients, oral antihistamines might be as effective [22].

The EAACI position paper on pediatric rhinitis concludes that INS is well tolerated and useful in treating AR from 2 years of age. INS should be used if oral and/or nasal antihistamines are not sufficient for controlling symptoms [5].

Efficacy

The potent anti-inflammatory effects of corticosteroids as described make steroids attractive drugs to choose when treating AR.

The most important pharmacodynamics and pharmacokinetic properties are potency, bioavailability, and lipophilicity.

Potency is closely related to the binding capacity to the glucocorticoid receptor. The INS are modifications of the cortisol molecule. Potency can be enhanced by halogen substitution at position 6 and 9. Based on glucocorticoid receptor affinity, some studies rank the potency of the INS as follows: fluticasone furoate > mometasone furoate > fluticasone propionate > budesonide > triamcinolone > dexamethasone [6, 23].

Several other factors contribute to the efficacy of the corticosteroids. The higher the lipophilicity of the corticosteroid, the faster the absorption in the nasal mucosa and the more prolonged the contact with the mucosal cells and

the glucocorticoid receptor. As this is also the case in other tissues, a high lipophilicity may give rise to side effects if the bioavailability is high. The corticosteroids have a relative lipophilicity as follows: mometasone furoate > ciclesonide > fluticasone propionate > beclomethasone dipropionate > triamcinolone acetonide > flunisolide [6, 24].

The systemic effect of the drug depends on the bioavailability and the hepatic first-pass metabolism. Thus, it is appropriate to group the INS in first- and second-generation drugs. First-generation drugs have a bioavailability >30 % (flunisolide, triamcinolone, beclomethasone, and budesonide) and second-generation drugs with an absolute bioavailability <1 % (fluticasone propionate, fluticasone furoate, ciclesonide, and mometasone furoate) (Fig. 1) [25]. As such, an optimal drug would have the combination of high potency, high lipophilicity, and a low bioavailability but so far, no studies have shown significant differences in clinical efficacy among the different drugs.

Onset of action begins after 4 h [26] but for a sustained effect, treatment needs to be continuous. An American study looking at the long-term effect of mometasone furoate and beclomethasone dipropionate in children with perennial AR finds a reduction of symptoms, both subject and physician evaluated from day 8. The effect accumulated during the study and even increased as late as from week 26 to 52. No significant differences between the two drugs were found [27]. The study points out the importance of continuous use for obtaining maximal symptom relief. Nevertheless, some studies conclude that an on-demand treatment might be an alternative. One randomized study includes 60 adults with chronic AR. One group received mometasone furoate once a day for six weeks; the other group received mometasone furoate once daily for one week, every other day during week two and on-demand for the last four weeks. Nasal volume measured by Acoustic rhinometry revealed no significant differences at the end of the study. Overall, the on-demand treatment group have 5 days with a nasal score significant higher than the continuous treated group [28]. Another study examining on-demand treatment in 69 adults with persistent AR concludes that the treatment significantly improves the nasal symptoms and nasal expiratory flow indexes. The study is limited by the lack of a control group [29].

The INS are drugs of choice when treating moderate to severe intermittent and persisting AR having the ability to improve symptom control and quality of life. They reduce the severity of the most bothersome nasal symptoms including nasal congestion, rhinorrhoea, itching, and sneezing. Furthermore, they assure better sleep [2, 4].

Even if there are no significant differences between the different INS according to efficacy, there might be other reasons for choosing one before the other. A placebo controlled randomized study documents that the majority of patients ($P < 0.001$) prefer one formulation of INS to another. The comparison was based on attributes of scent or odor (58 vs. 27 %), aftertaste (60 vs. 18 %), leaking out of the nose and down the throat (59 vs. 21 %), and mist gentleness (57 vs. 26 %) [27].

Systemic administration of glucocorticoid is widely used according to prescription data [30•]. Both oral and intramuscular steroids are often prescribed, but the use of intramuscular injections is not guideline driven. Furthermore, no difference in effect between intramuscular and oral steroid treatment is found [31].

The EAACI position paper on pediatric rhinitis and the ARIA guidelines 2010 revision recommend clinicians not to administer intramuscular corticosteroids due to the risk of side effects. Both guidelines recommend a short dose of oral glucocorticoid as rescue medication for patients with moderate to severe symptoms not controlled on other medications [4, 5]. The severe side effects caused by systemically administered glucocorticoids are well known and beyond doubt [3••]. There is little evidence to support that systemically glucocorticoids are more effective than INS when it comes to treating nasal symptoms. One study reported equivalent effects on nasal symptoms comparing intranasal mometasone furoate 200 µg once daily and betamethasone oral tablets 0.25 mg twice daily for 7 days, and both were significantly better than placebo. The study found a significant improvement in eye itching in the oral betamethasone group compared to the mometasone furoate group, as well as the control group (loratadine treated) [32].

Safety

Several local side effects can occur during treatment with INS and are generally mild to moderate in nature. Frequently observed are nasal mucosa dryness, burning and stinging sensations, headache, nasopharyngitis, pyrexia, nasal ulcerations, and epistaxis [11, 33–35].

In a placebo controlled study following children treated with fluticasone furoate for one year, the overall frequency of adverse events is 14 % (11 % placebo). The most frequently reported adverse event is epistaxis 6 % (placebo 7 %) [15••]. Epistaxis is an often occurring event in children, and because the rate is the same in placebo-treated children, the question is whether the mechanical action of the spray causes local irritation of the mucosa. Epistaxis can be classified in small streaks of blood or severe bleeding. The small streaks of blood from a sensitive mucosa will often be resolved by pausing the medication for some days. It might also help to instruct in proper administration techniques. Severe bleeding is seen with intranasal steroid treatment and placebo, and it might be resolved by correcting application techniques but often treatment needs to be withdrawn.

A systemic effect can be measured by impact on the hypothalamic-pituitary-adrenal (HPA) axis. Several methods of evaluating the HPA axis exist. These are thoroughly evaluated in a recent review where the authors conclude that there is no evidence of HPA axis suppression in patients receiving INS in the recommended doses as mono-therapy [36] which is in agreement with several recent studies. However, a note of caution is made concerning the patients receiving different kinds of steroids due to co-morbidities [11, 15••, 33, 35, 36].

The long-term growth (1–2 years) in children is another important parameter used to measure a systemic drug exposure. Recently, the largest randomized, double-blind placebo controlled study to date examines 168 prepubescent children given fluticasone furoate compared to 187 patients in the placebo group and finds a small but significant decrease in growth of 0.27 cm in one year [15••]. This is supported by yet another randomized double-blind placebo controlled study including children aged 3–9 years with perennial AR treated for one year (triamcinolone: 109, placebo: 107). A reduced growth of 0.45 cm

was observed in the triamcinolone group [16••]. Finally, a third randomized double-blind placebo controlled study finds a reduction in growth of 0.9 cm in 51 children aged 6–9 years treated with beclomethasone for one year [37]. In comparison, several other randomized placebo controlled studies have been unable to show reduction in longitudinal growth during one year of treatment with mometasone furoate [11, 12], fluticasone propionate [13], or budesonide [14].

Eye affections such as glaucoma and cataracts are well-known side effects of systemic treatment with glucocorticoids, and it is important to consider whether INS cause ocular side effects. A retrospective study including 286,078 patients in the UK General Practice Research Database concludes that the incidence of cataracts is identical for INS users and non-users [38]. This is supported by a review that carefully looks into the literature on glaucoma and cataract. A higher incidence of side effects in the INS users compared to non-users could not be demonstrated thus concluding that ocular side effects are rare [39•].

Regarding systemic corticoid therapy, side effects are well known and potentially severe. In a comprehensive review, Fardet et al. estimate the incidence of the most often occurring side effects. Weight gain is seen in 10–60 %, lipodystrophy in 35–80 %, diabetes in 4–14 %, dyslipidemia with unknown incidence, hypertension 5–30 %, and cardiovascular events in >6 % of patients treated more than six months [3]. This is in agreement with a Danish study including 47,382 individuals with AR; 55.8 % were treated with an annual intramuscular depot-steroid injection, 37.6 % with immunotherapy, and 6.7 % with both treatments. The authors observed an increased risk of diabetes (RR: 1.5) and osteoporosis (RR: 1.2). The risk was evident already after two years of treatment [30•]. Suppression of the HPA axis and subcutaneous atrophy after depot-steroid injection are documented [40, 41]. Ocular side effects like glaucoma and sub-capsular cataract are also frequently seen in patients treated with systemic steroids [39•].

A short rescue treatment with oral steroid in patients not responding to topical treatment is often administered. A Cochrane review evaluated safety of systemic corticoids for acute respiratory conditions in children and did not find an increased risk for any of the side effect examined (gastro intestinal bleeding, abdominal pain, hypertension, and behavioral reactions) [42••]. These findings support the guideline statements that depot-steroids should be avoided and replaced by short courses of oral steroids in treatment-resistant AR [4, 5].

Quality of life

AR is reported having a major influence on quality of life, cognitive function, and mood disturbances. In an Australian survey including interview with 303 individuals having physician-diagnosed AR, 47 % report unsatisfactory control during the last four weeks, 42 % has interference with school or work performance, around 30 % are moderately-extremely troubled during sleep (difficulty falling asleep, waking up during the night, lack of a good nights sleep), and >45 % report feeling depressed and/or miserable because of their AR. Seventeen percent of the patients has never received INS, and additional 27 % did not use INS for the last year. The individuals receiving INS (64 %) reported that most or all of their symptoms were sufficiently treated [43].

One of the most bothersome symptoms in AR is nasal congestion. It is speculated that congestion leads to obstructive sleep apnea and nighttime

awakening and as a consequence daytime drowsiness. In a review including 18 cases or case-control studies, 12 of these show a statistically significant association between sleep-disordered breathing and AR [44]. Only few studies have looked for a direct causation, but a very recent study elegantly supports the concept. Fifty-five patients with ($n = 34$) or without ($n = 21$) AR were treated with mometasone furoate 200 µg twice daily for 10–12 weeks. Sleep studies, quality of life (QOL) measurements, and nasal biopsies were performed at inclusion and post-treatment. A significant improvement in O_2 -saturation, apnoea-hypopnoea index, and QOL scores is seen in the AR patients, but not in the group without AR [45••].

The negative impact on cognitive function is best documented in children and adolescents. A British case-control study showed that students dropping one or more grades from winter to late summer were more likely to have AR symptoms (OR: 1.4) or taking sedating antihistamines (OR: 1.7) [46]. A Korean study from 2014 looked into attention deficit in 797 children with AR and 239 children with non-AR. The children underwent a computerized comprehensive attention test at inclusion and after a year. The children were followed regularly, and those with AR were continuously treated with INS and per oral rescue medication. The symptomatic treatment within the non-AR group was on demand. At study end, a significant increase in attention was found in the AR group but no difference in attention level was seen in the non-AR group [47]. Studies investigating the second-generation INS find an increased QOL level during treatment [48, 49]. Furthermore, two comprehensive reviews support the above made conclusions and report that reduction of nasal congestion by INS treatment may improve sleep quality and reduce daytime tiredness, improving cognitive function and quality of life [50, 51].

Comparative studies with other drugs

INS are the most efficient treatment for AR—intermittent as well as persistent, and it is first-line therapy in moderate to severe disease. It relieves all of the known symptoms including eye symptoms [2, 4]. However, INS must be used continuously to act sufficient [27].

Oral antihistamines is another drug, which in intermittent or persistent mild disease, might be preferred to INS due to its fast mode of action blocking the acute phase response by binding to the H_1 histamine receptor and as such used for episodic control of symptoms or used prophylactic for persistent disease [52]. H_1 antihistamines can also be grouped into first- and second-generation drugs. The first-generation antihistamines are lipophilic and easily cross the blood-brain barrier leading to side effects such as sedation and decreased cognitive abilities. Also, first-generation antihistamines cause anticholinergic side effects such as dry mouth and accommodation difficulties resulting in blurred vision [52]. The second-generation drugs are lipophobic and less sedating with only mild side effects. The ability of oral antihistamines to treat nasal congestion is less pronounced compared to INS. However, they reduce all other symptoms including eye symptoms [2, 4, 22].

According to most evidence-based systematic reviews, intranasal antihistamines are second-line drugs used when the effect of INS and oral antihistamines is not sufficient [2, 4]. The intranasal antihistamines have a rapid onset of action

(15–30 min), and they have a more pronounced effect on congestion than the oral antihistamines but are less effective in reducing rhinorrhoea. A disadvantage can be the bitter taste [2]. The ARIA guidelines only recommend using intranasal antihistamines in intermittent but not persistent AR [4].

The studies combining oral antihistamines and INS have conflicting conclusions regarding an additive effect. The ARIA guidelines recommend the combination when eye symptoms are observed [2, 20, 22] whereas a recent Cochrane review, including only one study of sufficient quality, could not support combination therapy in children [53].

Regarding the combination of INS and intranasal antihistamines, it seems to be more effective than using either drug separately [2, 22]. A novel formulation of the combination of azelastine and fluticasone propionate is described as fast acting and with a higher grade of relief of all symptoms than the two drugs used separately [54•, 55, 56].

Leukotriene receptor antagonists (LTRA) are not used as first-line therapy, and several studies show less effect compared to INS [57]. Compared to oral antihistamines, the results are conflicting, some studies find the treatments equally effective, and some find LTRA inferior to antihistamines [4]. The combination of INS and LTRA in general is not superior to INS in mono-therapy, but one study including 128 adults with moderate to severe AR treated for 2 month with fluticasone propionate plus placebo ($n = 64$) and with fluticasone propionate plus montelukast ($n = 64$) reports a significant greater improvement in symptom score and QOL with less use of rescue medication (loratadine) in the montelukast group [58].

Cromolyns are mast cell stabilizers used four times daily. They are less effective than INS and antihistamines and should be used continuously as they act by inhibiting the mast cell degranulation [59].

Ipratropium is an anticholinergic with the potential to block rhinorrhoea. It does not ameliorate other symptoms of AR; hence, it is not a first-line drug. Ipratropium is often excellent for treating vasomotor rhinitis [59].

Decongestants are sympathetic α -receptor stimulators with the ability to induce vasoconstriction relieving congestion and rhinorrhea. Use of oral decongestants is not recommended, and use of intranasal decongestants is recommended only in the adult population and in a maximum of 5 days due to the risk of rhinitis medicamentosa [2, 4]. In a recent double-blind placebo controlled study including 60 adults treated for four 4 weeks with fluticasone furoate and oxymetazoline, the two drugs in combination or placebo once a night, the combination therapy resulted in fewer nasal symptoms compared to the two treatments used separately. No rhinitis medicamentosa was detected [60].

Even with the wide range of treatment options, a residual group of people is not obtaining relief from the AR symptoms. A monoclonal antibody against IgE (omalizumab) approved by FDA for moderate to severe chronic persistent allergic asthma has been evaluated as a treatment option for AR in several trials. Severe asthma and AR are often coexisting [10••]. The results are promising consistently finding a reduction in symptoms and an excellent tolerability [10••, 61]. A small study including 34 adults with seasonal AR found the use of omalizumab effective and safe when applied only in the pollen season for two consecutive years [62]. It is suggested that anti IgE prescribed before the peak pollen season can prevent severe symptoms to occur for patients with severe AR [10••]. Thus, although omalizumab is a costly treatment and not approved for

the treatment of AR by FDA, it might be a reasonable alternative for patients with otherwise treatment-resistant AR.

Another option in these patients is the AIT [7••] that routinely can be used as subcutaneous injections every 6th–10th week for 3 to 5 years or as sublingual immunotherapy every day usually for 1–3 years. Numerous well-designed trials have proven the effectiveness of both subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) to ameliorate symptoms, QOL, reducing need of medication use, and inducing immune tolerance [7••, 63••]. Most recently two Cochrane reviews conclude that both SLIT [8] and SCIT [9] are effective and well-tolerated treatment options for otherwise treatment-resistant AR. The ARIA guidelines recommend the use of AIT for pollen-induced seasonal AR and for adults with persistent AR caused by house dust mites [4]. Some studies have estimated duration of efficacy until 10 years after AIT treatment [64]. Furthermore, using AIT as a treatment for AR might have the potential of decreasing the risk of developing asthma and new sensitizations [64, 65]. Very promising trials suggest additional ability to reduce symptoms when combining AIT and anti IgE treatment compared to AIT without anti IgE treatment [66].

Clinical recommendations

In conclusion the following clinical recommendations can be given; see Table 2

Compliance with ethical standards

Conflict of interest

Dr. Agertoft reports personal fees from ALK, personal fees from Novartis, personal fees from Nigaard, and study fees from ALK, outside the submitted work.

Dr. Petersen reports personal fees from Teva Demark A/S and a sponsored study for ALK Abelló.

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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