TREATMENT OF ALLERGIC RHINITIS

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ABSTRACT
Allergic rhinitis (AR) is a symptomatic disorder of the nose, induced after allergen exposure, by an IgE-mediated inflammation of the nasal membranes. The symptoms of AR include rhinorrhoea, nasal congestion or blockage, nasal itching, sneezing and postnasal drip. Treatment of patients with AR includes patient education, allergen avoidance, pharmacotherapy, and immunotherapy. Allergen avoidance may lessen the severity of disease but is seldom sufficient as a single intervention to control rhinitis. Drugs that can be used for the treatment of allergic rhinitis include intranasal corticosteroids, antihistamines, leukotriene receptor antagonists, cromones, anticholinergics and decongestants. Intranasal corticosteroids are the preferred form of pharmacotherapy for AR, being effective against all the symptoms of AR, with a low incidence of adverse effects. Antihistamines are most effective against rhinorrhoea, sneezing and nasal itching. Allergen specific immunotherapy is the only curative treatment for AR.

Allergic rhinitis (AR) is defined as a symptomatic disorder of the nose, induced after allergen exposure, by an IgE-mediated inflammation of the nasal membranes. Symptoms include rhinorrhoea, nasal congestion or blockage, nasal itching, sneezing and postnasal drip. Nasal congestion is the predominant symptom in AR, described as the most troublesome symptom and occurring in up to 90% of patients. The Allergic Rhinitis and its Impact on Asthma (ARIA) expert committee workshop reclassified AR, based on the duration of symptoms as ‘intermittent’ or ‘persistent’, and on the effect on the patient’s quality of life (QOL) as ‘mild’ or ‘moderate-severe’. Intermittent symptoms are symptoms lasting for less than 4 days of the week or less than 4 weeks per year, while persistent symptoms are symptoms lasting for more than 4 days per week and more than 4 weeks per year. Mild AR does not affect the patient’s QOL, while moderate-severe AR causes one or more of the following:
- Sleep disturbance
- Impairment of daily activities leisure and/or sport
- Impairment of work or school
- Troublesome symptoms.

More recently, Valero et al. have proposed that moderate and severe AR be differentiated based on the number of affected items of sleep, daily activities or sport, work or school, and troublesome symptoms, with AR being considered moderate if one to three items are affected and severe if four items are affected. However, because this would not lead to treatment differences, the revised ARIA guidelines proposed continuation of the classification of rhinitis severity as mild or moderate-severe. Most patients with allergic rhinitis have moderate-severe disease. In South Africa, allergic rhinitis is mostly a persistent disease. The diagnosis of AR is based on the history, clinical findings and demonstration of allergen sensitisation by skin-prick tests and/or specific IgE measurements (RASTs). Patients may have allergic mannerisms and have the ‘allergic facies’. The classic findings on rhinoscopy in AR are the presence of bilateral oedematous swelling of the mucosa of the inferior turbinates, which typically appear pale but may be purplish, and the presence of clear nasal secretions. Allergy testing should be guided by the common prevalent allergens in the region.

The ARIA treatment guidelines for the management of AR include: patient education, allergen avoidance, pharmacotherapy, and immunotherapy. Patient education with regard to the condition and treatment is vital to ensuring compliance with treatment and optimising treatment outcomes. It is only by informing the patient as to the chronic nature of AR, allergen avoidance measures and the correct use of pharmacotherapy that symptom control can be achieved.

ALLERGEN AVOIDANCE AND ENVIRONMENTAL CONTROL
Allergen avoidance, based on the results of allergen sensitivity testing, may lessen the severity of disease. These measures are usually insufficient as a single intervention to control rhinitis or asthma as the majority of interventions fail to achieve a sufficient reduction in allergen load to lead to clinical improvement. However they should form an integral part of management plan.

House-dust mites
There are a number of measures that can be taken to reduce house-dust mite (HDM) exposure including:
- Encasing the mattress, pillow and duvet in impermeable covers
- Washing all bedding in hot water
- Replacing carpets with linoleum or wooden flooring or treating carpets with acaricides
- Minimising the use of upholstered furniture
- Keeping dust-accumulating objects in cupboards
- Using a vacuum cleaner with a HEPA filter
- Washing curtains in hot water or replacing curtains with blinds
- Washing soft toys in hot water or freezing them.

A systematic review on HDM avoidance measures for perennial AR found that trials have been small and of poor methodological quality, and it is therefore difficult to offer any definitive recommendations on the role of HDM avoidance measures in these patients. While the use of acaricides and extensive bedroom-based environmental control programmes may be of some benefit in reducing rhinitis symptoms, the isolated use of HDM-impermeable bedding is unlikely to prove effective. The 2010 revision of the ARIA guidelines...
recommended that patients sensitised to HDM do not use currently available single chemical or physical preventive methods aimed at reducing exposure to HDM or their combination.1,14

Moulds
Although the ARIA guidelines suggest that sensitised patients avoid exposure to moulds at home, there are no controlled studies showing that these measures are of clinical benefit.1,14

Cockroaches
Cockroach eradication measures can be instituted in the case of patients with cockroach sensitisation but it is difficult to prevent reinfestation.1 There are no studies that have evaluated the effect of cockroach eradication on AR.1

Pets
Pet allergens are contained in saliva and sebaceous secretions of cats and dogs.1 The only effective measure for avoiding animal dander allergens in the home is to remove the pet and to carefully vacuum clean all carpets, mattresses and upholstered furniture.1 However, most patients are not prepared to do this. Measures that can be taken by sensitised patients who are allergic to their pets include:15

• Confining the pets to uncarpeted rooms (other than the bedroom)
• Use of a vacuum cleaner with a HEPA filter
• Increasing ventilation
• Washing dogs and cats on a frequent basis (one to two times a week); although this reduces airborne allergens, it is effective for a short time only. While these measures may reduce airborne allergen levels, there are no specific environmental interventions that have been shown to reduce symptoms significantly.15

In patients with occupational rhinitis and asthma, the ARIA guidelines recommend immediate and total cessation of exposure to occupational allergen but suggest specific strategies aimed at minimising occupational allergen exposure when total cessation of exposure is not possible.14

PHARMACOTHERAPY

Drugs that can be used for the treatment of AR include intranasal corticosteroids (INCSs), H1 antihistamines, leukotriene receptor antagonists (LTRAs), cromones, anticholinergics and decongestants. The relative effectiveness of these drugs against the symptoms of AR is summarised in Table I. None of these drugs has a persistent effect when stopped; continuous treatment is therefore indicated for persistent AR. Factors that should be taken into account when commencing pharmacological treatment include:2

• Efficacy
• Safety
• Cost-effectiveness of medications
• Patient preference
• Objective of the treatment
• Likely adherence to recommendations
• Severity and control of the disease
• The presence of comorbidities.

Corticosteroids

Intranasal corticosteroids
INCSs that can be used in the treatment of AR include beclomethasone dipropionate, budesonide, triamcinolone acetonide, fluticasone propionate, mometasone furoate, fluticasone furoate and ciclesonide.1,16 Intranasal ciclesonide is not available in South Africa at this stage. INCSs are the single most effective class of medications for AR.1,2,10,14,16 They are effective against all the symptoms of AR, with a low incidence of adverse effects.1,2,10,14,16 The mechanisms of action of INCSs are related to their anti-inflammatory activities.1,16 They offer superior symptomatic relief compared to both oral and intranasal antihistamines, as well as LTRAs, and should be considered the first-line treatment for patients with moderate-severe and/or persistent symptoms.1,14,16–19 A systematic review found that INCSs also have a positive impact on ocular symptoms.20 INCSs have been shown to be the most cost-effective treatment for AR.21 Systemic absorption rates are highest among the relatively older INCSs, viz. beclomethasone, flunisolide, budesonide and triamcinolone, with 30-40% of the intranasally administered dose of these drugs reaching the systemic circulation.16,22 The newer INCSs, fluticasone propionate, fluticasone furoate, mometasone furoate and ciclesonide, undergo rapid and extensive first-pass metabolism after oral administration, contributing to their negligible systemic absorption.10

When given at recommended doses, even with long-term use, INCSs do not cause clinically significant suppression of the hypothalamic-pituitary-adrenal (HPA) axis.2,22–24 However, suppression of the HPA axis may occur in atopic children with AR who are also receiving topical steroids for treatment of asthma and/or eczema.23,25 While the use of beclomethasone may be associated with slight growth retardation in children, no growth retardation has been reported with use of fluticasone propionate or mometasone furoate.2 Long-term studies have documented a lack of bone metabolism side-effects and a lack of ocular side-effects.26,27 INCSs also do not affect the HbA1c and serum glucose levels in diabetic patients.28 The correct technique of using the nasal spray is very important. Patients should be instructed to direct the nozzle of the spray superolaterally into the nose.10,12

| Table I. Relative effectiveness of drugs on the symptoms of allergic rhinitis |
|---------------------------------|----------------|----------------|----------------|----------------|
|                                 | Nasal obstruction | Rhinorrhea  | Sneezing | Nasal itching |
| Intranasal corticosteroids      | +++             | +++         | ++       | +             |
| Antihistamines                  | +               | +++         | +++      | +++           |
| Intranasal cromones             | +               | +           | +        | +             |
| Intranasal decongestants        | ++++            | –           | –        | –             |
| Anticholinergics                | –               | ++          | –        | –             |
| Leukotriene receptor antagonists| ++              | +           | –        | –             |
While it is traditionally accepted that INCSs should be used for days or weeks to achieve significant benefits, symptomatic improvement with the newer INCSs begins after a few hours of use. There is no clear evidence to show that any INCS is superior to any other in the treatment of AR, although the various preparations may vary in the volume emitted per spray and sensory attributes such as perceived runoff, discomfort, taste, and smell that may affect patient acceptance and adherence.

**Systemic corticosteroids**

Oral glucocorticosteroids should not be considered as a first line of treatment but a short course can be used in patients with moderate-severe nasal symptoms not controlled with other treatments. However, a recent study found that there were no significant differences in the therapeutic effects of INCSs and systemic corticosteroids, suggesting that INCSs should sufficiently improve nasal symptoms without administration of oral corticosteroids. Oral corticosteroids should be avoided in children, pregnant women, and patients with known contraindications. Depot steroid injections should be avoided because the clinical importance of adverse effects and complications outweigh any benefit in AR. Potential complications include fat atrophy, abscess formation, osteoporosis, and necrosis of the femoral head. Intranasal injection of corticosteroids should be avoided because of possible blindness due to ophthalmic artery vasospasm.

**Antihistamines**

**Oral antihistamines**

Antihistamines are inverse agonists at H$_1$-receptors. Depending on the molecule, they may have other properties. Although they relieve nasal and ocular symptoms, they are not consistently effective for nasal congestion and are most effective for rhinorrhea, sneezing and nasal itching. Oral antihistamines are equal or superior to INCSs for ocular symptom relief but less effective than intra-ocular antihistamines and mast-cell stabilisers. Long-term continuous treatment is more effective than on-demand use.

The first-generation (old) antihistamines are poorly selective for the H$_1$-receptor. They have a rapid onset of action and thus provide rapid symptomatic relief, but also have a short half-life. As a result of the lack of action and thus provide rapid symptomatic relief, women, and patients with known contraindications. This may lead to impairment of learning and cognitive processing, increased risk of injury and driving impairment. These drugs may therefore be beneficial in patients who experience somnolence while using oral medication. The 2010 ARIA guidelines suggest use of intranasal antihistamines in adults and children with seasonal AR but suggest that intranasal antihistamines not be used in adults and children with perennial/persistent AR until more data on relative efficacy and safety are available. The guidelines also suggest that new-generation oral antihistamines be used in adults with seasonal AR and perennial/persistent AR and children with intermittent or persistent AR.

**Leukotriene receptor antagonists**

LTRAs are as effective as antihistamines, but less effective than INCSs in improving symptoms and QOL in patients with seasonal AR. The 2010 ARIA guidelines suggest use of oral LTRAs in adults and children with seasonal AR and preschool children with perennial AR but recommend that LTRAs not be used in adult patients with perennial AR as there is no evidence for a clinically relevant benefit in these patients. They also suggest that oral antihistamines be used in preference to oral LTRAs in patients with seasonal AR and preschool children with perennial AR.

**Cromones**

Sodium cromoglycate has been shown to be effective for the treatment of AR but it is less effective than INCSs and antihistamines. The need for administration four times daily is likely to reduce patient adherence and efficacy. The ARIA guidelines suggest use of intranasal cromones despite limited efficacy as they may be of net clinical benefit for some patients because of mild side-effects but suggest that intranasal antihistamines be used in preference to intranasal cromones.
Decongestants
Intranasal decongestants are very effective in the treatment of nasal obstruction but do not improve other symptoms.1,2,14 There is concern about their safety when inappropriately used for more than 7 days, with prolonged use being associated with the risk of developing rhinitis medicamentosa.1,14 The ARIA guidelines therefore suggest use of a very short course while co-administering other drugs in adults with AR and severe nasal obstruction but suggest that they not be used in preschool children.1,14
Use of oral decongestants is not recommended because, although there is a small benefit from oral pseudoephedrine compared to placebo in relieving symptoms in patients with AR,1,14 a net clinical benefit is unlikely in view of the adverse effects of insomnia, dry mouth and a small increase in systolic blood pressure.1,14
A net clinical benefit in AR from the regular use of a combination of oral antihistamine and decongestant compared to oral antihistamines alone is uncertain as the small improvement in nasal symptoms is counterbalanced with an increased risk of adverse effects.1,14 The ARIA guidelines therefore suggest that a combination of oral antihistamine and oral decongestant not be used compared to oral antihistamines alone.1,14
Anticholinergic compounds
Ipratropium bromide is effective in controlling rhinorhoea but is ineffective against the other symptoms of AR.1,14
As patients usually have other symptoms as well, other drugs are recommended as first-line agents.1 The ARIA guidelines suggest the use of intranasal ipratropium bromide for treatment of rhinorhoea in patients with perennial AR.1,14
Nasal irrigation
Nasal irrigation is a simple and inexpensive non-pharmacological form of therapy for AR that has been shown to improve symptoms and QOL scores and reduce medication requirements.38 The mechanism of action is believed to be a combination of direct physical cleansing by flushing out thick mucus, crusts, debris, allergens and air pollutants, removal of inflammatory mediators and improvement of mucociliary clearance by improving ciliary beat frequency.38 The use of buffered solutions that are mildly alkaline are preferable to non-buffered solutions.39 Buffered hypertonic saline may be superior to buffered normal saline for nasal symptoms.30
Capsaicin
Although capsaicin is effective in the treatment of non-allergic rhinitis,41 a systematic review found that there is currently insufficient evidence to assess the use of capsaicin in the treatment of AR.1,14 One small trial did not find evidence that intranasal capsaicin has a therapeutic effect.42
COMPLEMENTARY AND ALTERNATIVE THERAPY
Although a number of complementary and alternative therapies have been proposed for the treatment of AR, there is no strong evidence to support their use.2,12,14
The ARIA guidelines recommend against the use of homeopathy, acupuncture, butterbur, herbal medicines, phototherapy or other physical techniques for the treatment of AR.2,14 Some of these products may have side-effects and drug interactions.3,12,14
A review of English language articles on rhinophototherapy for AR noted that most studies demonstrated symptomatic improvement and QOL scores but not in objective measures.44 While there were no or mild side-effects and the treatment does not appear to predispose to carcinogenesis, long-term studies are required to verify this.45 The mechanism of action is not clear and the placebo effect is not insignificant.
A recent systematic review on the use of traditional Chinese medication for the treatment of AR that included seven randomised controlled trials with a total of 633 patients found that although there were beneficial effects in patients with persistent AR, the evidence remains weak owing to methodological flaws making it difficult to draw any firm conclusion.46
A systematic review on the use of helminth therapy for AR found that there is currently insufficient evidence on the efficacy, tolerability and likely costs of helminth therapy to support its use in the routine management of AR, although when administered to humans in carefully measured doses, helminths appear to be safe.46
SPECIFIC IMMUNOTHERAPY
Allergen specific immunotherapy (SIT), administered as subcutaneous immunotherapy (SCIT) or as sublingual immunotherapy (SLIT), is an important form of treatment for AR. SIT is the only treatment that may alter the natural course of the disease as it can prevent the development of new sensitisations and can prevent the development of asthma when introduced to patients with only allergic rhinoconjunctivitis.1,12 SIT is indicated in patients with proven IgE-mediated allergy to a single allergen whose symptoms are insufficiently controlled with pharmacotherapy, who do not wish to be on long-term pharmacotherapy or who have undesirable side-effects from pharmacotherapy.1,10
A systematic review on the use of SCIT in patients with AR concluded that in suitably selected patients with seasonal AR, allergen injection IT results in a significant reduction in symptom scores and medication use and that there is a relatively low risk of severe adverse events with no long-term consequences from the adverse events.47 The ARIA guidelines note that while SCIT may be of net clinical benefit in adults with seasonal AR due to pollens, the net clinical benefit in adults with AR due to HDM is uncertain.1,14 The guidelines therefore suggest that SCIT be used in adults with seasonal AR due to pollens and with perennial AR due to HDM.1,14 The net clinical benefit of IT in children with AR is very uncertain but because it may be of some benefit in children with seasonal AR, based on the results of studies in adults, the ARIA guidelines suggest the use of SCIT in children with AR.1,14
With regard to the use of SLIT, the ARIA guidelines suggest its use in adults with AR due to pollen or HDM as there may be a net clinical benefit.1,14 In the case of children with AR, the net clinical benefit is very uncertain, with the small reduction in symptoms being counterbalanced by frequent local adverse effects, although systemic reactions rare.1,14 The guidelines suggest the use of SLIT in children with AR due to pollens but suggest that SLIT not be administered to children with AR due to HDM outside of clinical trials.1,14
A more recent systematic review that included a total of 60 randomised controlled trials found that SLIT results in a significant reduction in symptoms and medication requirements in participants receiving SLIT compared to placebo, with none of the trials reporting severe systemic reactions or anaphylaxis.48 The review
concluded that SLIT is effective for AR and has been proven to be a safe route of administration.

A meta-analysis of data comparing SLIT and SCIT in patients with AR due to grass and/or tree pollens, found the effectiveness to be virtually equal but favoured the use of SLIT because of the advantageous safety profile and the lower level of burden on the patients’ daily life.49

CONCLUSION

The management of patients with AR includes patient education, allergen avoidance, pharmacotherapy, and immunotherapy in selected cases. Although a variety of drugs can be considered for the pharmacological treatment of allergic rhinitis, INCSs are the single most effective class of medication in the treatment of allergic rhinitis.

Declaration of conflict of interest

Prof Seedat has been sponsored by Aspen Pharmacare to attend international congresses and has given talks for MSD.

REFERENCES


Surgery

The inferior turbinates are the first points of contact for allergens in the nasal cavity, with allergen deposition in these areas resulting in inflammation stemming from submucosal structures. The goal of surgery of the inferior turbinate is to minimise allergen effects by reducing bulky inflammatory tissue or inducing scar formation, while enhancing patency of the nasal fossa.50 Mechanisms accounting for symptomatic improvement in patients are a combination of factors: the net mucosal surface may be slightly decreased after volume reduction of the turbinates thereby reducing available contact points for allergens; scar tissue develops within the submucosal layer after surgical manipulation destroying vasculature and glandular structures while impeding regrowth through fibrosis; and the reduced volume of the inferior turbinate results in increased nasal patency.50 Because of the risk of atrophic rhinitis and empty nose syndrome, total turbinectomy as practised in the past has been replaced by other surgical techniques such as lateral outfracture of the inferior turbinate, submucosal resection, submucosal electrocautery, radiofrequency ablation, coablation, and laser resection.50 Although there are a number of case series reporting on the effectiveness of the various surgical procedures for inferior turbinate hypertrophy, there is a need for randomised controlled trials to evaluate the role of inferior turbinate surgery for nasal obstruction in allergic rhinitis after failed medical treatment.51

The nasal septom is not a major contributor to the disease process or to nasal obstruction due to AR, but anatomical deformities such as bony spurs or cartilaginous deviation may worsen subjective nasal obstruction in patients with AR.50 In these patients, septoplasty may improve the nasal obstruction and allow intranasal preparations to be more effective. Similarly, although endoscopic sinus surgery does not have a direct role in treating AR, it is of indirect benefit in patients with AR who also have chronic rhinosinusitis or polyposis.50

The vidian neurectomy is now seldom performed because of the development of effective medical treatments and the adverse effects, the most frequent and long-term one being keratoconjunctivitis sicca.50 However, a recent large study showed that bilateral endoscopic vidian neurectomy was an effective and safe technique in the management of moderate to severe persistent AR, being superior to both partial inferior turbinatectomy and/or septoplasty and pharmacotherapy with long-term follow-up.52 The procedure was safe, with no major complications reported. Although dry eyes occurred in 30.6% of patients, this symptom resolved within 1 month of treatment with sodium hyaluronate eye drops.

Conjunctivitis and Asthma

Intraocular antihistamines or intraocular cromones should be used to treat coexisting conjunctivitis.14 All patients should be assessed for the presence of asthma.2 As patients with rhinitis are at a higher risk for developing asthma, they should also be assessed for the presence of asthma on follow-up.

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