WPAS Symposium: Rhinitis : mechanisms, endotypes and management

Guideline for allergic rhinitis: medical treatment

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Allergic rhinitis (AR) is a IgE-mediated inflammatory disease of nasal mucosa of which cardinal symptoms are sneezing, watery rhinorrhea, and nasal obstruction. It affects 10% - 30% of all adults and up to 40% of children, and its global socioeconomic burden is substantial. There are several national guidelines for AR which reflect their own specific conditions. 'Allergic Rhinitis and its impact on Asthma (ARIA)' published in 2008 and updated in 2010, has been the most widely adapted as standard of clinical practice guideline for the management of AR. Here, I will summarize the updates of the guidelines for medical treatment of AR.

Classification of AR

ARIA guideline in 2008 suggested a new classification of AR based on frequency and severity of symptoms as these are the major factors involved in determining treatment (Figure 1). A clinical classification of seasonal and perennial rhinitis is also noted in Japanese guideline, and can be used alongside the ARIA classification.

Pharmacotherpy

1. Oral H1-antihistamines

Second generation antihistamines such as ebastine, cetirizine, fexofenadine, loratadine, olopatadine, bepotastine, and levocetirizine, is preferred to first generation antihistamines because of less adverse effects such as sleepiness, impaired performance, anticholinergic effects and dry mouth, and longer duration of drug action. Priority indications are mild to moderate sneezing and rhinorrhea type. Newer second generation antihistamines such as desloratadine, fexofenadine, cetirizine and levocetirizine have modest effects on nasal blockage.

2. Topical H1-antihistamines (Azelastine)

It is recommended for mild to moderate seasonal AR. It can be additional to intranasal steroids for moderate/severe persistent rhinitis uncontrolled on topical intranasal corticosteroids alone. However, they do not improve symptoms due to histamine at other sites, such as the eye, pharynx, lower airways and skin. It is useful as rescue medication due to fast onset of action within 15 min. Major adverse effect is local irritation.

In patients with AR, we recommend new generation oral H1 antihistamines over intranasal H1-antihistamines

3. Intranasal glucocorticosteroids

They are highly effective for sneezing, watery rhinorrhea, and nasal mucosal swelling, and exert their effects within 1-3 days. Meta-analysis shows that intranasal corticosteroids (INS) are superior to antihistamines. They have few systemic adverse effects. A slight feeling of nasal irritation, feeling of dryness, and epistaxis may occur. This is first-line therapy for moderate to severe persistent symptoms and treatment failures with antihistamines alone.

4. Systemic glucocorticosteroids

Systemic glucocorticosteroids is rarely indicated in the management of rhinitis, except for: severe nasal obstruction, short-term rescue medication for uncontrolled symptoms on conventional pharmacotherapy. Oral corticosteroids should be used briefly and always in combination with a topical nasal corticosteroid. A suggested regime for adults is 0.5 mg/kg given orally in the morning for 5-10 days. Injectable corticosteroids are not recommended.

5. Leukotriene receptor antagonists

They are effective for nasal blockage. Their effects are increased by prolonged administration. There is no apparent net clinical benefit of oral leukotriene receptor antagonists over oral H1-antihistamines, or vice versa, in patients with seasonal or perennial AR. Anti-leukotrienes are less effective than topical nasal corticosteroids. ARIA suggests oral leukotriene receptor antagonists in adults and children with seasonal AR and in preschool children with perennial AR. ARIA suggests that clinicians do not administer and patients do not use oral leukotriene receptor antagonists in adults with perennial AR because of cost-effectiveness.

6. Decongestant

Intranasal decongestants can be used for very short course (not longer than five days and preferably shorter) while co-administering other drugs in adults with AR and severe nasal obstruction. Long-term continuous administration causes *rhinitis medicamentosa*.

Oral decongestants also can be used for severe nasal obstruction as a rescue or as needed medication. It is not recommended oral decongestants to be taken regularly. Combination drug containing an antihistamine (fexofenadine, levocetirizine) and an oral decongestant (pseudoephedrine) is now available. However, the priority indication for this combination drug is limited to the moderate to severe nasal blockage type of pollinosis and the severe nasal blockage type of perennial AR.

7. Intranasal cromones

Intranasal cromones have mild effects. To achieve sufficient clinical effects, 2-week prolonged administration is required. Adverse effects, such as sleepiness and dry mouth, do not occur. ARIA recommanded intranasal H1-antihistamines over intranasal chromones in patients with AR. Chromones require administration 4 times daily that may limit patient adherence to treatment and reduce efficacy.

8. Intranasal anticholinergics (Ipratropium bromide)

Intranasal ipratropium bromide is effective for rhinorrhoea but has no effect on other nasal symptoms.

Allergen-specific Immunotheray

Immunotherapy is recommended to those subjects with IgE-mediated disease in whom allergen avoidance is either undesirable or not feasible and who fail to respond to optimal treatment. Allergens such as house dust mites, cat, dog, pollens (trees, grasses, weeds) are indicated in allergen-specific immunotherapy. Subcutaneous specific immunotherapy (SCIT) has been used over the past century. Its demonstrated effects may be exerted via immunological mechanisms. Of note, local mast cells are decreased, the Th1/Th2 balance is altered, and regulatory T cells are increased. The duration of allergen immunotherapy is at least for 3 to 5 years. Then, the therapeutic effects often continue for several years after discontinuation of allergen immunotherapy. Sublingual immunotherapy (SLIT) has been noted as effective as SCIT in treatment of AR.

AR in pregnancy

Rhinitis affects at least 20% of pregnancies and can start during any gestational week. Although the pathogenesis is multifactorial, nasal vascular engorgement and placental growth hormone are likely to be involved. Informing the patient that pregnancy-induced rhinitis is a self-limiting condition is often reassuring.

Regular nasal douching may be helpful. It is a good practice to start treatment with drugs. Beclomethasone, fluticasone and budesonide appear to have good safety records as they are widely used in pregnant asthmatic women. Chlorphenamine, loratadine and cetirizine may be added but decongestants should be avoided. Chromones have not shown teratogenic effects in animals and are the safest drug recommended

in the first 3 months of pregnancy although they require multiple daily administrations. Patients already on immunotherapy may continue if they have already reached the maintenance phase but each case must be considered individually. However, initiation of immunotherapy and updosing is contraindicated.

Biologicals

Many biologicals have been developed and tried in various phenotypes of severe asthma. However, clinical trials of biologicals in the treatment of AR are limited. Recently, meta-analysis have shown that anti-IgE antibody (Omalizumab) is generally well-tolerated and associated with a statistically significant symptom relief, decreased rescue medication use, and improvement of quality of life in patients with inadequately controlled allergic rhinosinusitis. CRTH2 (chemoattractant receptor-homologous receptor expressed on Th2 cell) is one of prostaglandin D2 receptors by which PGD2 recruits inflammatory cells such as Th2 cells and eosinophils. Blockage of CRTH2 had beneficial effects on rhinoconjuctivitis symptoms in patients that received an allergen challenge with grass pollen.

Step-wise approach for treatment of AR, Modified from ARIA 2008

ARIA recommended step-wise approach for treatment of AR according to symptoms severity and frequency of AR (Figure 2).

Unmet needs

Thus, various practical guidelines for AR have been developed and updated to improve the management of AR, however, up to 40% patients remain symptomatic. The unmet needs for the management of AR is one of the greatest public health problems in the world. The gaps between guidelines and real-world practice may be attributed to the differences among the region, culture, and medical environments. Recently, unmet needs for existing AR guidelines were surveyed from Korean primary physicians. Therefore, new practical guidelines which reflects our own environment and our unmet needs is needed to be developed in Korea.

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