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Review Article

Current treatment options for allergic rhinitis: a review

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ABSTRACT

Allergic rhinitis (AR) is an immunoglobulin E-mediated inflammatory reaction in the nasal mucosa caused by inhaled allergens such as dust, pollen, mold, or animal dander. AR is a common chronic disease that is often ignored, misdiagnosed, and/or mistreated. Clinically, AR is characterized by four major symptoms such as rhinorrhea, sneezing, nasal itching, and nasal congestion. It can be associated with certain co-morbid conditions like asthma and nasal polyposis. AR is diagnosed by taking proper history taking, nasal examination, and allergy tests. A proper understanding of the pathophysiology of AR can lead to improved treatment of this disorder. The treatment for AR should target symptoms to improve the quality of life for patients. Undertreatment of AR often impairs quality of life. The important concern in the treatment of AR is the patient's adherence to the treatment. Novel treatments are needed for cheaper, early, better, and more permanent symptom resolution in AR. Evidence-based guidelines for AR treatment are helpful to improve disease control. The treatment of AR includes avoidance of relevant allergens, appropriate pharmacotherapy, immunotherapy, patient education, and follow-up. Intranasal corticosteroids are the most effective modality of treatment for AR. This review article discusses details of current treatment options for AR.

Keywords: AR, Intranasal corticosteroids, Antihistamines, Immunotherapy

INTRODUCTION

Allergic rhinitis (AR) is a heterogenous disease caused by allergen exposure resulting in an immune-mediated reaction.[1] Many times, the medications for AR may have undesirable side effects that can affect the quality of the patient's life.[2] AR usually manifests with nasal symptoms such as nasal congestion, rhinorrhea, itching, sneezing, and ocular symptoms like redness, puffy lids, teas, and itching.[2] It also cause itching of the palate and pharynx and post-nasal discharge. AR significantly affects the quality of life. Furthermore, AR has some serious co-morbidities such as sinusitis, asthma, nasal polyposis, otitis media, and respiratory infection.[3] Pathophysiology of AR must be clearly understood for appropriate treatment. Pharmacotherapy, allergen-specific immunotherapy, patient education, and environmental control measures are the cornerstones of AR and can significantly reduce the burden of the disease. Nasal surgery can be carried out as an adjunctive treatment in selected cases of AR.[4] Current treatment guidelines for AR include antihistamines, intranasal corticosteroids, oral and intranasal decongestants, intranasal anticholinergics, and intranasal cromolyn and leukotriene receptor antagonists.[5] This review article discusses the current treatment modalities of AR.

METHODS OF LITERATURE SEARCH

Multiple systematic methods were used to find current research publications on the current treatment options of AR and its epidemiology, etiopathology, and current treatment. We started by searching the Scopus, PubMed, Medline, and Google Scholar databases online. A search

strategy using PRISMA (Preferred reporting items for systematic reviews and meta-analysis) guidelines was developed. This search strategy recognized the abstracts of published articles, while other research articles were discovered manually from the citations. Randomized controlled studies, observational studies, comparative studies, case series, and case reports were evaluated for eligibility. There were a total number of articles 68 (17 case reports; 19 cases series; 32 original articles) (Figure 1). This paper focuses only on the details of the current treatment options for AR. This review article describes the epidemiology, etiopathology, and treatment of AR. This analysis provides a better understanding of current treatment options for AR. It will also catalyze further study of current treatment options for AR and the development of newer treatment options for this clinical entity.

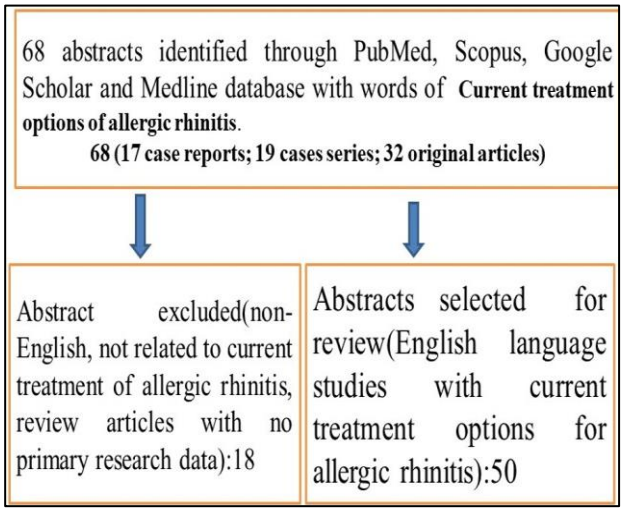

Figure 1: Methods of literature search.

EPIDEMIOLOGY

AR and asthma are highly prevalent worldwide. AR is a recognized global health issue in the community and it affects at least 10 to 25% of the world's population.[6] Approximately 50% of all cases of rhinitis are caused by an allergy. The reported incidence of AR in India ranges from 20 to 30%.[7] The prevalence of AR has been reported from 1.4% to 39.7% in different Western countries, and in England, it is increased four times during the previous thirty years, in which the exact cause is not clearly known.[8]

ETIOPATHOLOGY

AR is an IgE-mediated inflammatory reaction of the nasal mucosa caused by inhaled allergens. The allergic response occurs in two phases such as early and late. Exposure to allergens leads to allergens cross-linking with immunoglobulin E antibodies attaching to the mucosal mast cells and followed by the release of inflammatory mediators like histamine, prostaglandins, and leukotrienes.[9] The inflammatory mediators attract, recruit, and activate additional inflammatory cells such as eosinophils, neutrophils, and T lymphocytes into the mucosal lining of the nasal cavity. These cells cause the release of more inflammatory mediators and initiate late phase response, which happens several hours after initial allergen exposure. The late response is associated with chronic inflammation and manifests the same symptoms as in the early phase with nasal congestion, nasal discharge/rhinorrhea, itching of the nose and eyes, and sneezing.[10]

TREATMENT OPTIONS

There are several treatment options for AR such as non-pharmacologic and pharmacologic. The goal of the treatment is to eliminate or reduce the present symptoms and prevent future attacks and complications.[11] Appropriate treatment selection should have minimal adverse effects and enable the patient to maintain a normal lifestyle. The treatment options include allergen avoidance, pharmacotherapy, and immunotherapy.

Non-pharmacologic interventions

The non-pharmacological interventions include allergen avoidance. Allergen avoidance is a practical option when the allergens have been identified, either by the patient or by allergy testing.[12] Patients can take measures to reduce exposure to triggers based on specific allergens, whether it is pollen, mold, or animal dander. Allergen avoidance should be part of an overall treatment strategy that includes pharmacotherapy. Pet avoidance shows a clear benefit.

PHARMACOTHERAPY

The selection of appropriate pharmacotherapy is based on efficacy, patient preference, tolerability, adverse effects, and cost. The treatment options are usually administered orally or intranasally. The treatment options available include antihistamines, corticosteroids, decongestants, leukotriene receptor antagonists, and anticholinergics. Immunotherapy is also an important treatment option for patients who are refractory to pharmacotherapy.[13] The most common pharmacologic treatment options include intranasal corticosteroids, H1 receptor inverse agonists (antihistamines), and leukotriene receptor antagonists. These medications are effective in the case of seasonal AR and also in perineal AR.[14]

Intranasal corticosteroid

Intranasal corticosteroid sprays are the first-line treatment for moderate to severe AR and are considered the most effective medication for controlling the symptoms of AR.[15] Intranasal corticosteroids show potent anti-inflammatory action due to their effects on several cell types, including topically on the nasal mucosa.[16] They reduce the release of inflammatory mediators and

cytokines, so reduce nasal mucosal inflammation.[17] These give symptomatic relief when used continuously or as required. However, these are the most effective when used regularly, as the onset of action is 7 to 12 hours, reaching maximum benefit within two weeks[18] Intranasal corticosteroids are highly effective in reducing nasal obstruction and congestion. Intranasal corticosteroids are preferred over all other agents for mild or moderate to severe symptoms of AR. In comparison to antihistamines and leukotriene receptor antagonists, intranasal corticosteroids are superior in decreasing nasal symptoms scores and nasal congestion. The intranasal corticosteroids are beclomethasone propionate, fluticasone propionate, mometasone furoate, fluticasone furoate, and dexamethasone cipecilate. Local side effects of intranasal corticosteroids include epistaxis, drying of the nasal mucosa, and nasal septal perforation.[19] Intranasal corticosteroids rarely show systemic effects of oral corticosteroids-adrenal suppression, bone fractures (particularly in elderly age), growth suppression, and ocular effects. All available intranasal corticosteroids are efficacious in controlling AR symptoms.[18] The product differentiation involves factors like cost, ease of dosing, and sensory issues such as aroma and taste, which can affect patient preference.[20]

Antihistamines

Antihistamines are most effective against symptoms that are primarily mediated by histamines such as sneezing, pruritus, and ocular symptoms.[1] Antihistamines are less effective for nasal congestion and may require a combination with a decongestant or intranasal corticosteroid.[21] Rhinorrhea can be multifactorial, and individual patients differ in their clinical response to an antihistamine. First-generation oral antihistamines interact non-selectively with other receptors and so associated with sedation and mental impairment as well as potential anticholinergic side effects like dry mouth, dry eyes, urinary retention, and constipation.[21] Second-generation oral H1 antihistamines are more selective and advised as these are equally effective with less sedation and anticholinergic side effects.[18] Second-generation antihistamines can be dosed once daily as opposed to several doses needed for first-generation antihistamines, with a rapid onset of action between one to two hours. Antihistamines are also available in the intranasal form and their efficacy is similar to that of the oral formulation. These work rapidly, and effectively by reducing nasal symptoms in less than 30 minutes.[18] Oral antihistamines are considered a first-line treatment option for patients with mild to moderate intermittent symptoms of AR.[21] First-generation oral forms of antihistamines are usually well tolerated but have sedative, cognitive, and anticholinergic effects that can lead to challenges for some patients. Second-generation oral antihistamines usually have no sedative effects and are well tolerated. Second-generation oral antihistamines such as fexofenadine, loratadine, and desloratadine do not cause sedation at recommended doses. Cetirizine and intranasal azelastine can cause sedation at recommended doses.[18]

Nasal decongestants

Oral and intranasal decongestants cause vasoconstriction, which reduces inflammation and nasal congestion.[18] Intranasal decongestants are more effective for inducing nasal obstruction than oral decongestants.[22] The intranasal decongestant is limited by adverse effects such as insomnia, loss of appetite, raised blood pressure, and tachycardia.[23] Because of the adverse effects and less tolerability of oral decongestants, these should be prescribed for a short period and cautions in populations like elderly patients with hypertension, hyperthyroidism, urinary retention, and closed angle glaucoma.[2] Few adverse effects of intranasal decongestants include a burning sensation in the nasal cavity, stinging, or dryness.[23] Use of intranasal decongestants should be limited to no more than three days in a row, as overuse can result in dependence and the patient can experience rebound nasal congestion due to α-receptor downregulation, or rhinitis medicamentosa.[23] Rhinitis medicamentosa is a condition of nasal hyper-reactivity, swelling, and tolerance induced aggravated by overuse of topical decongestants.[18] This condition is reversed by the use of topical intranasal corticosteroid which causes to resolve the rebound congestion. Decongestants are very effective in giving short-term relief of nasal congestion but do not affect other symptoms of AR such as sneezing, itching, and rhinorrhea.

Leukotrienes receptor antagonists

Leukotrienes (LTs) are synthesized from arachidonic acid by the 5-lipoxygenase pathway. Leukotrienes usually cause constriction of bronchial smooth muscle, which manifests in airway inflammation. Leukotriene receptor antagonists (LTRAs) block the inflammatory effects of the leukotrienes at the Cys-LT4 receptor, which relieves nasal congestion. [21] These can be used alone or in combination with antihistamines or intranasal corticosteroids and may be helpful in patients who have comorbid asthma.[18] LTRAs have shown efficacy in asthma. As there is a significant link between AR and asthma, with similar inflammatory mechanisms, LTRAs have taken a role in the treatment of AR. Among Cys-LT1 receptor antagonists, montelukast is the only drug approved for the treatment of AR. Montelukast provides statistically significant improvement for nasal symptoms; however, topical corticosteroids and oral antihistamines give a greater reduction in nasal symptom scores. It has been observed that montelukast decreases daytime congestion, rhinorrhea, pruritis, and sneezing. There is also a higher treatment effect found in patients with higher pollen levels. It is helpful to relieve the difficulty in sleeping. It also reduces the number of peripheral blood eosinophils due to its anti-inflammatory effect.[24] The effect of montelukast for reducing nasal symptoms appears to be additive with antihistamines.[25] Montelukast

is considered a safe medication as prophylaxis and treatment for airway allergy including in pediatric age. However, one report shows that there is a possibility of association of montelukast use with several adverse psychiatric events such as aggression, agitation, anxiousness, hallucination, depression, and insomnia.[26]

Combination of antihistamines and LTRAs

Antihistamines and LTRAs are commonly used for the treatment of AR. The inhabitation of these two mediators may give additional benefits compared to a single mediator inhibition.[27] LTRA and antihistamine is more effective than antihistamine alone, but inferior to intranasal corticosteroid for treatment of AR.[28]

Anticholinergics

Anticholinergics can decrease the watery rhinorrhea in AR, but it does not affect other nasal symptoms.[18] These can be used in combination with an antihistamine or intranasal corticosteroid in patients who have primary symptom is rhinorrhea or is refractory to other treatment.[22] These are usually given as an intranasal spray with minimal absorption, thus with minimal systemic anticholinergic effects.[18]

Saline douching

Normal saline douching reduces the symptoms of AR and enhances the effect of intranasal corticosteroids and is effective for rhinosinusitis. Isotonic solutions are well tolerated, inexpensive, easy to use, and have no side effects. [29] Steam inhalation is also an option to clear the nasal pathway in case of AR.[30]

Immunotherapy

While pharmacotherapy acts by suppressing AR, allergen-specific immunotherapy can be used to cure AR.[31] It causes relief of the symptoms of the patients with long-lasting preventative effects. Subcutaneous immunotherapy is effective in decreasing the symptoms and minimizes the medication requirement in long term. It is reserved for patients with a severe type of AR whose symptoms are not sufficiently treated by pharmacotherapy.[31] Immunotherapy includes repeated subcutaneous injections containing allergens and patients are at little risk of having systemic allergic reactions.[32] Sublingual immunotherapy is also available for a few allergens. The first dose of immunotherapy is usually given at the physician's office, and the patient must be monitored for 30 to 60 minutes for observation of any allergic reactions.[21] If the patient tolerates the first dose, subsequent doses of sublingual immunotherapy can be given at home, repeated from three days per week to daily. The sublingual administration is thought to be better tolerated than the subcutaneous route. The common side effects are often limited to the respiratory and gastrointestinal tracts. However, the allergens considered are currently limited to a few grasses and pollens.

Probiotics

Probiotics are living microorganisms used as supplementary foods and have been utilized for the prevention and treatment of different immunological disorders. It has been proposed that probiotics enhance intestinal microbial balance and may modulate immune responses. One systematic review and meta-analysis revealed the impact of probiotics on patients with AR.[33] Study has shown that probiotics may be very helpful for the treatment or prevention of AR in the pediatric age group.[34] Probiotics promote an improvement to the immune response of the human body and there is satisfactory action on the modulation of the allergic response more as compared to conventional treatment.

AR in pregnancy

Women with AR during pregnancy can be treated by the number of pharmacological agents without concern of untoward effects on their unborn child. Although the choice of pharmacological agents should be based on evidence of fetal safety, the issue of efficacy needs to be addressed to optimally manage AR.[35] Intranasal corticosteroids are not associated with an increased chance of congenital malformations in humans.[36] These should be considered as first-line therapy in treating AR based on their superiority to oral antihistamines, decongestants, and mast cell stabilizers with respect to efficacy.[37] The first-generation antihistamines have not been incriminated as human teratogens. The teratogenicity of second-generation antihistamines has not been studied completely. The fetal safety of loratadine and fexofenadine has not been established in controlled trials and so, their use for AR cannot be used unless first-line therapies have been tried and have failed.[38]

AR in children

Pediatric AR should be adequately dealt with in primary care, using medications along with avoidance of known precipitating factors.[39] children with AR should be looked for asthma, and if present, treatment should be done. Mometasone furoate and fluticasone propionate have been studied in children and found no adverse effects on cortisol levels, the hypothalamic-pituitary-adrenal axis, or growth. Nasal douching with isotonic saline solution can reduce the symptoms of children and adults with seasonal rhinitis and is safe and inexpensive. Ipratropium bromide nasal spray reduces rhinorrhea but does not affect other nasal symptoms.[40] The major side effects of ipratropium bromide nasal spray are dry nose and epistaxis.

Surgical treatment

Nasal blockage in AR is often caused by deviated nasal septum, hypertrophic rhinitis, and nasal polyps.[41] In this

case corrective surgery of the nasal cavity can be performed to relieve the nasal obstruction. Corrective surgery to relieve nasal obstruction includes submucosal turbinectomy, septoplasty, inferior turbinectomy, and nasal polypectomy.[42] Vidian neurectomy is helpful to control rhinorrhea.[43]

CONCLUSION

AR is a heterogeneous disease caused by exposure to an allergen, leading to an immune-mediated reaction. Undertreatment of AR impairs quality of life and exacerbates asthma. The treatment of AR involves avoidance of relevant allergens along with pharmacotherapy for most of the sufferers. The treatment options for AR include non-sedating antihistamines, anti-leukotrienes, saline nasal sprays, intranasal corticosteroids, and immunotherapy. If pharmacotherapy fails, allergen-specific immunotherapy is considered.

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