



CODEN [USA]: IAJPB

ISSN : 2349-7750

**INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES**

SJIF Impact Factor: 7.187

<http://doi.org/10.5281/zenodo.4277753>Available online at: <http://www.iajps.com>

Research Article

**THE COMPLEX PATHOPHYSIOLOGY OF ALLERGIC
RHINITIS: SCIENTIFIC RATIONALE
FOR THE DEVELOPMENT OF AN ALTERNATIVE
TREATMENT OPTION**¹Dr Sadam Sanwal,²Dr Atika Akbar,³Dr Muhammad Asif Hussain.^{1,3}MBBS, Sahiwal Medical College, Sahiwal., ²MBBS, Frontier Medical College, Abbottabad.**Article Received:** September 2020 **Accepted:** October 2020 **Published:** November 2020**Abstract:**

Globally allergic rhinitis (AR) has created many health issues and its treatment becomes a challenge. For decades various symptomatic treatments have been available for AR but there has been minor amelioration in the life of a patient and to overcome symptoms burden. In this article we explored the pathophysiological gaps for many AR treatments, explained the pharmacological therapies with their mode of action, Moreover, we considered a newer therapy, MP-AzeFlu consist of an intranasal antihistamine (Azelastine hydrochloride) and Intranasal corticosteroids (futicasone propionate) in a single spray and this combination therapy MP-AzeFlu was found to be the best treatment for allergic rhinitis. MP-AzeFlu is simultaneously involved in both phase treatment (first and later phase reaction) in disease and quickly overcome all symptoms of AR. To control the disease in the best way need to discover the prime biomarker and evaluate the disease control parameters.

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Please cite this article in press Sadam Sanwal et al, *The Complex Pathophysiology Of Allergic Rhinitis: Scientific Rationale For The Development Of An Alternative Treatment Option*, Indo Am. J. P. Sci, 2020; 07(11).

INTRODUCTION:

Many diseases are emerging global health issues, allergic rhinitis (AR) has considered one of them immunological disease with its complex pathophysiology. [2] It becomes the most common chronic allergic disorder among the European countries, according to an estimation of 600 million peoples are affected by this disease. The 27% prevalence was measured in Sweden. [1] however, patients suffered through nuisance situations as its quality of life effects badly because of not treated or undertreated symptomatic burdens. [3] It was found in every field of life including school and workplace, that might be linked with inadequate sleep, cognitive and mood disorder. [4] Allergic rhinitis can be a challenge for physicians when patients with the disease having chronic symptoms and polysensitized. Therefore, its treatment is difficult with chronic upper airway disorder and local allergic rhinitis. [5] The amelioration in pharmacological treatments are required to fulfill the challenging condition, few treatments recommended on the base of disorder severity including oral steroids, intranasal corticosteroids, leukotriene receptor antagonists, and antihistamines. [6] Among all of these AR treatments, intranasal corticosteroids have considered better treatment than others. The novel treatments have the same therapeutic response but with lesser systemic bioavailability while no significant reduction in symptoms and no betterment was noticed in the patient's quality of life. The newer formulated MP-AzeFlu (Dymista®), an intranasal antihistamine (Azelastine hydrochloride) and Intranasal corticosteroids (futicasone propionate) in a single spray. [7] Researchers suggested as a first-line treatment choice for patients of AR have a 5 cm score of visual analogue scale followed the recent updates of allergic rhinitis along with its effects on

asthma treatment guidelines. Another publication in support to recommended as first-line treatment during the persistent moderate or severe AR cases. [8]

The vigilance in present management for AR shows the existence of two gaps; the first one is the pathophysiological gap and the second is the control gap (lack of knowledge to control AR). The purpose of this study is to overcome these gaps to explore the advancement of pharmacological and effective use of control assessment.

The complex pathophysiology of allergic rhinitis:

- The complex pathophysiology of AR consists of two phases. The allergens activate the allergic response through the receptors of immunoglobulin on mast cells. In the first phase degranulation of mast cells associated with acute and ocular symptoms e.g. sneezing, rhinorrhoea, and itching redness, and watering which enhances vascular permeability, oedema caused by secretion of histamine with cytokines and eicosanoids. The late-phase reaction response produced after an hour of exposure to allergen associated with tissue remodeling, greater tissue edema, and prolong nasal congestion experience one of the hard symptoms of allergic rhinitis. In this phase, cellular recruitment occurred including the basophils, eosinophils, and neutrophils, T-lymphocytes, and secretion of many mediators produced inflammation of mucosal. As a repercussion inflammatory reaction, tissue reacts more strenuously to the exposed allergen, and changes in tissue are responsible for bronchial hyper-responsiveness. [9]

Mode of action of allergic rhinitis pharmacotherapies

Leukotriene receptor antagonists (LTRAs)	Leukotriene receptor antagonists inhibit the production of cysteinyl leukotrienes, a strong inflammatory mediator involved in nasal congestion and mucus secretion in patients with AR, other anti-inflammatory functions such as inactivation of the 5-lipoxygenase, histone acetyltransferase. Further it also, impede the formation of oxygen reactive species. [10]
Oral antihistamines (OAHs)	It includes cetirizine, loratadine, and desloratadine, these hinder the interaction between histamine and H1 receptors and at its high concentration inhibit the various mediators. [13]
Intranasal antihistamines (INAH)	Drugs (azelastine hydrochloride (AZE) and olopatadine) directly deliver to nasal mucosa, enhanced local anti-allergic and anti-inflammatory effects with lesser systemic exposure. Intranasal antihistamines most suitable for AR treatment specifically AZE which stabilizing mast cell, work as multimodal action in patients with AR has neutralized the effect which induced sneezing, nasal pruritus, rhinorrhea. AZE blocked the immunoglobulin E that involved in the regulation of calcium channels

	further responsible for mast cell degranulation results of this mast cell stabilized, inhibit the secretion of histamine and other mediators. [11] Recent study on AZE profile showed that it interferes with immune T-cells and dendrites. [12]
Intranasal corticosteroids (INS)	Late phase allergic reaction of AR can be inhibited through intranasal corticosteroids, also create hindrance in the recruitment of cells into nasal mucosa such as T-cells, mast cells, and eosinophils, bring a reduction in remodeling process, stop the production of inflammatory mediatory contribute in the pathophysiology of the disease. In the case of chronic AR intranasal corticosteroids minimized the hyperactivity of the airway. [14]

Pathophysiological gaps

- Mostly pathophysiological gap linked with choice or availability of treatments of AR, many patients experienced symptoms even after the treatment such cases with severe AR were reported in the United Kingdom, 95.2% actively treated cases with nasal and ocular symptoms and 71.5% treated with multiple therapies. Although patients treated with intranasal corticosteroids were not positively responded. Other additional oral therapies including OAHs or LTRAs could be a better option than INS alone to prevent nasal and ocular symptoms. [15] According to an update of 2016 for guidelines dose recommendation about the allergic rhinitis and its impact on asthma, OAHs or INAH and INS combine treatment may be effective for patients with seasonal AR. [6]
- MP-AzeFlu is considered as filler to narrowing the pathophysiological gap to some extent. It's a signal spray with a novel formulation consist of INAH (AZE) and INS (futicasone propionate). It comprises two agents with different modes of action and has an effect on the first and late phase of an allergic reaction. Currently, it is more effective in the treatment of AR and deemed to be first-line therapy for the treatment of AR. [16]

The control gap

- The main purpose of treatment is to control the disease but the concept of AR control is not well defined. Now European countries priorities the importance of AR controls. Many researchers demonstrated that simple tools can be used to assess AR control.¹⁸ In comparison with other disease states, a visual analogue scale (VAS) can be a potent and simple tool for assessment of control and reaction of treatment. However, VAS study was performed for therapies OLARs INS, INAH, and MP-AzeFlu to determine the effect on disease severity, MP-AzeFlu was found with more effective response. [17]

Discussion

- An efficacy study was attempted to assess the effectiveness of oral antihistamines. The patient

not older than 12 years suffering from moderate AR treated with desloratadine 5mg/day and VAS used with a severity level from 0 to 100 mm. the obtained results indicates that the VAS score failed to meet the clinical threshold as VAS score varies at least 23mm, while the substantial reduction in score from 57.4 mm to 42.2mm after 14 days. [19] One more research followed the same drug for the treatment of patients and the results of 12 week's study shows the reduction in score up 32.4 mm in comparison with the placebo group. [20]

- The studies of intranasal corticosteroids to determine the effect of FP 200 µg/day with oral montelukast (15 mg/day) in 700 patients suffering from seasonal AR and performed VAS for common symptoms such as nasal congestion, itching, sneezing, and rhinorrhea). The 100 score on VAS indicates severity and 0 scores with no symptoms. Significant effective the response of PF to nasal symptoms with 30 mm VAS score within 14 days while 20 mm VAS score was obtained from montelukast for each symptom but many studies reported the variation from baseline in the VASE score not in the actual score. Although the final score was calculated by adding the all symptoms score rather than separate calculation. [21]
- The efficacy study for MP-AzeFlu was conducted in Germany the data was obtained for maximum symptoms of AR, provided rapid relief with recommended drugs such as antihistamines, INSs, and multiple therapies. The baseline score of VAS was 76.4 mm of all patients received AR treatment. Patient treatment significantly reduced the severity and score from baseline. [22]

CONCLUSION:

A combination therapy MP-AzeFlu was found to be the best treatment for allergic rhinitis. MP-AzeFlu simultaneously involved in both phase treatment (first and later phase reaction) in disease and quickly overcome all symptoms of AR. Moreover, the therapy effect also depends upon the patient's disease or inflammatory pattern that varies from patient to

patient. The primary and secondary care management of AR can be facilitated through the use of a visual analogue scale. Besides this, a comparison of corticosteroids alone with combination treatment should be evaluated widely on real-life studies with both AR and non-AR cases. To control the disease in the best way need to discover the prime biomarker and evaluate the disease control parameters.

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