Use of Anti Leukotriens in Treatment of Nasal Allergy

Meta-Analysis Study

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List of Abbreviations

AR	:	Allergic rhinitis
ASIT	:	Allergen-specific immunotherapy
CysLTs	:	Cystienyl-leukotriens
DNSS	:	Day time nasal symptoms score
ECP	:	Eosinophil cationic protein
EPR	:	Early phase response
H1	:	Histamine 1 receptors
HRQL	:	Health related quality of life
IgE	:	Immuno- glubulin E
IL	:	Interleukin
IL-4	:	Interleukin-4
LPR	:	Late phase response
LT	:	Leukotriens
LT As	:	Leukotriene antagonists
MBP	:	Major basic protein
NNSS	:	Night time nasal symptoms score
PGs	:	Prostaglandins
TH	:	T helper cells
UVA	:	Ultraviolet-A
UVB	:	Ultraviolet-B
VCAM	:	Vascular cell adhesion molecule
VIS	:	Visible light
XeCl	:	Xenon chloride

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Introduction

Researches over the past decade have provided information concerning the onset and treatment of allergic diseases, including bronchial asthma, allergic rhinitis and atopic dermatitis. Recent studies also indicate that allergic inflammation is the basic pathophysiology of allergic diseases, and is closely associated with their progression and exacerbation. Our understanding of the mechanism of allergic inflammation with regard to therapeutic agents has improved as a result of immunological and molecular biological studies. While much effort has been paid to developing a new anti-allergic drug, allergic disease has yet to be completely conquered. ***(Nagai et al., 2006)***.

Leukotrienes are inflammatory mediators synthesized in response to many triggers, including receptor activation, antigen-antibody interaction, physical stimuli such as cold, and any stimulation that increases intercellular calcium. These potent inflammatory mediators promote neutrophil-endothelial interactions, inducing bronchoconstriction and enhancing airway hyperresponsiveness. They also stimulate smooth muscle hypertrophy, mucus hypersecretion, and the influx of eosinophils into airway tissues; therefore, theoritically inhibition of leukotrienes activity would potentially play an important role in the treatment of asthma and other allergic conditions such as allergic rhinitis, atopic dermatitis, and chronic urticaria ***(Dean Thomas Scow, et al., 2007)***.

Leukotriene inhibitors are either leukotriene receptor antagonists or leukotriene synthesis inhibitors, which act by blocking 5-lipoxygenase activity. The leukotriene receptor antagonists include zafirlukast (Accolate) and montelukast (Singulair). zileuton (Zyflo) is the only leukotriene synthesis inhibitor. ***(Dean Thomas Scow, et al., 2007).***

Many controversies arose for and against use of anti leukotriens in treatment of allergic rhinitis. (***Dean Thomas Scow, et al., 2007)***.

Aim of the Work

Aim of this work is to find out whether antileukotrien drugs are effective or not in treatment of patients with allergic rhinitis by review of available prospective randomized control trial studies addressing this topic.

Definition:

Allergic rhinitis is an IgE mediated hypersensitivity of the mucous membranes of the nasal airway, eyes, Eustachian tubes, middle ears, sinuses and pharynx. This hypersensitivity can be precipitated by exposure to certain allergens, which may be inhalant, digestant, contactant, drugs, infections or endogenous ***(Allho, 2004)***.

Epidemiology:

Allergic rhinitis is a major chronic allergic disease, the recent estimates that it affects nearly 15 to 20% of the population, so it is the most common allergic disorder ***(Lane, 2001)***.

Onset of allergic rhinitis is common in childhood, adolescence and early adult years, with mean age of onset 8-11 years, but allergic rhinitis can occur at an age ***(Hussain and Kline 2004)***.

Pathophysiology

Allergic rhinitis is an abnormal immunologic response mediated by immuno-globin E (IgE), and it can be classified as seasonal, perennial, or episodic ***(Dykewicz, 1998)***.

The pathophysiologic processes involved in AR have been divided into early-phase and late-phase responses (EPR and LPR, respectively) ***(Togias, 2000)***.

The EPR starts within minutes of allergen exposure and lead to release of inflammatory mediators, including histamine, cystienyl-leukotriens (CysLTs), prostaglandins (PGs), kinins, and neuropeptides. The release of these mediators subsequenty leads to the characteristic symptoms of AR, namely: sneezing, itching, rhinorhea, and nasal congestion. In addition, about 50%of allergic patients have a late response 3 to 12 hours after the EPR ***(Meltzer, 1997)***.

Nasal congestion is the primary symptom of this LPR, which is also characterized by an infiltration of inflammatory cells (including eosiophils and basophils and additional release of inflammatory mediators) thus creating a state of chronic inflammation in nasal mucosa. This chronic inflammation makes the nasal mucosa more responsive to further allergen exposure (priming) as well as to nonspecific environmental stimuli (nonspecific hyperresponsiveness) ***(Skoner, 2001)***.

Sensitization and immune response

Before developing of a full allergic state, individuals undergo sensitization, which involves production of allergen specific IgE antibody by way of a low- dose allergen exposure through a primary humoral response (broody, 1999). The allergen is engulfed by antigen presenting cells (macrophages, dendritic cells, langhans cells) and is partially degraded within these cells, Portions of the processed allergen are then exteriorized on the surface of the antigen presenting cells and are recognized in conjunction with class II major

histocompatibility complex molecules, by T helper cells (TH), especially the TH_2 subtype that are important in allergic diseases, subsequently release cytokines including interleukin-4(IL-4), which leads to isotype switching of B cells and the resultant production allergen-specific IgE antibody. Sensitization is then completed by attachment of the specific IgE molecules to numerous cells, the most important of which are mast cells and basophils ***(Naclerio, 1991)***.

In early-phase response: when allergens deposit on the nasal mucosa of the now-sensitized individual, they are recognized by the IgE receptors on the mast cells. Allergens lead to cross linking of the IgE receptors and immediate release of performed and newly synthesized mediators such as histamine, tryptase, leukotrienes, and PGs. These mediators are responsible for the stimulation of nerves, mucus glands, and blood vessels, causing the classic symptoms of AR ***(Yong, 1998)***.

In late- phase response several hours after the initial allergen exposure, many allergic subjects experience a recurrence of their symptoms without being exposed to more allergen. This is the LPR, which is characterized primarily by nasal congestion and, to lesser extent by rhinorrhea and sneezing. During the LPR, neutrophils, eosinophils, and mononuclear cells infiltrate nasal secretions and tissues ***(White, 1999)***.

Challenge studies have shown that the release of more mediators during the LPR such as albumin, some cytokines, eosinophilic cationic protein, histamine and leukotrienes. The circulating leukocytes become adherent to the post capillary endothelial cells by the effect of vascular cell adhesion molecule (VCAM) which is promoted by mast cell derived mediators. Chemoattactant cytokines such as IL-5 promote the infiltration of the mucosa with eosinophils, neutorophils, and basophils, T lymphocytes, and macrophages ***(Bjornsdottir, 1999)***.

Eosinophil-derived mediators such as major basic protein (MBP), eosinophil cationic protein (ECP) and leukotriens (LT) have shown to damage the epithelium, leading ultimately to the clinical picture of chronic allergic disease ***(Bjornsdottir, 1999)***.

Modalities of treatment

(I) Avoidance therapy:

Complete avoidance of an allergen results in a cure when there is only a single allergen. For this reason, attempts should be made to minimize contact with any important allergen, regardless of what other mode of treatment is instituted ***(Dykewicz, 1998)***.

(II)Pharmacological therapy

Antihistamines:

Antihistamines are the foundation of symptomatic therapy for allergic rhinitis and are most useful in controlling the symptoms of sneezing, rhinorrhea and pruritis that occur in allergic rhinitis. They are less effective, however, against the nasal obstruction and eye symptoms in some patients ***(Massy, 1990)***.

The first-generation antihistamines were defined by their H1 receptor blocking activity, and despite pronounced unwanted side-effects they are still widely used, The problems with systemic side effects, especially sedation and dry mouth, stimulated the pharmacological research to develop a second generation of drugs that were ostensibly free of these properties and more efficacious, e.g. chloropheniramine ***(Nagai et al,2006)***.

The second-generation antihistamines are called non-sedating H1 antagonists because of their low penetration through the blood-brain barrier. Compared with the first generation agents, they are known for their minimal central nervous system effect. e.g. cetrizin, fexofenadine and loratadine ***(Nagai et al,2006)***.

Sympathomimetic agents:

Sympathomimetic drugs are used as vasoconstrictors for the nasal mucous membranes, so the edema of the nasal