Introduction

Allergic rhinitis (AR) is an inflammatory disease of the nasal mucosa caused by an allergen-IgE interaction in sensitized individuals **(Howarth et al., 2000).** It is the most common type of chronic rhinitis, affecting up to 20% of the population and evidence suggests that the prevalence of the disorder is increasing. Severe allergic rhinitis has been associated with significant impairments in quality of life, sleep and work performance **(Dykewicz and Hamilos, 2010).**

In allergic rhinitis, numerous inflammatory cells including mast cells, CD4-positive T cells, B cells, macrophages and eosinophils infiltrate the nasal lining upon exposure to an inciting allergen (most commonly airborne dust mite fecal particles, cockroach residues, animal dander, moulds and pollens). The T cells infiltrating the nasal mucosa are predominantly T helper (Th)2 in nature and release cytokines (e.g., interleukin IL-3, IL-4, IL-5 and IL-13) that promote immunoglobulin E (IgE) production by plasma cells. IgE production in turn, triggers the release of mediators such as histamine and leukotrienes that are responsible for arteriolar dilatation, increased vascular permeability and symptoms associated with allergic rhinitis **(Small et al., 2007; Dykewicz and Hamilos., 2010)**. The mediators and cytokines released

during the early phase of an immune response to an inciting allergen, trigger a further cellular inflammatory response over the next 4 to 8 hours (late-phase inflammatory response) which results in recurrent symptoms usually nasal congestion **(Small et al., 2007; Lee and Mace, 2009).**

So the IgE plays an important role in the pathophysiology of allergic rhinitis when binding to high-affinity receptors on effector cells, such as mast cells and basophils and subsequent exposure to allergen initiates an inflammatory cascade resulting in release of pro-inflammatory mediators, which contribute to the acute and chronic symptoms of allergic airway diseases **(Holgate, 1998).**

The diagnosis of allergic rhinitis is based on a typical history of allergic symptoms and diagnostic tests **(Bousquet et al., 2008).** When 2 or more symptoms out of watery rhinorrhea, sneezing, nasal obstruction and nasal itching persist for ≥1 hour on most days, allergic rhinitis is strongly suspected and a confirmative diagnosis should be established by the skin prick test or the serum-specific IgE level. skin prick tests are generally considered to be more sensitive and cost effective than allergen-specific IgE tests and have the further advantage of providing physicians and patients with immediate results **(Small et al., 2007; Kim and Kaplan, 2008).** Unilateral nasal stiffness, mucopurulent rhinorrhea, mucoid postnasal drip, pain,

recurrent epistaxis or anosmia is usually not associated with allergic rhinitis.

The treatment goal for allergic rhinitis is the relief of symptoms. Therapeutic options available to achieve this goal include avoidance measures, intranasal corticosteroids, leukotriene receptor antagonists and allergen immunotherapy. Other therapies that may be useful in selected patients include decongestants and oral corticosteroids. If the patient's symptoms persist despite appropriate treatment, referral to an allergist should be considered. Despite using all these therapeutic options for treatment of allergic rhinitis, they are often insufficient to totally control the disease or may be associated with significant side effects.

Therefore, the search for an effective and safe treatment of allergic rhinitis is thus not completed. Because the IgE plays an important role in the pathophysiology of allergic rhinitis so the anti-IgE antibody has also been shown to be effective in seasonal allergic rhinitis **(Small et al., 2007).** Omalizumab, an anti-IgE recombinant humanized monoclonal antibody, interferes with the interactions between mast cells/eosinophils and IgE by binding to the free IgE and hence lowers serum free IgE **(Holgate et al., 2005).** It also suppresses the inflammatory reactions in the blood or the nasal mucosa **(Plewako et al., 2002)** and expression of the receptors located on the surface of mast cells or eosinophils **(Beck et al., 2004).**

Casale et al. (2006) have demonstrated that omalizumab pretreatment (300 mg) just before and during the pollen season for 12 weeks with 3-4 weeks intervals reduces allergic rhinitis symptoms significantly in patients with severe seasonal allergic rhinitis.

Aim of the work

The aim of the work is to assess the effect of using anti-IgE antibodies for treatment of allergic rhinitis. This will be reached by reviewing the recent literatures regarding the use of anti-IgE in treatment of allergic rhinitis with special emphasis upon its efficacy, indications and contraindications, side effects drug-drug interaction and cost effectiveness.

Chapter (1):

Definition and Epidemiology of Allergic Rhinitis

Introduction

Allergic rhinitis (AR) is an inflammatory disease of the nasal mucosa caused by an allergen-IgE interaction in sensitized individuals **(Howarth et al., 2000).** It the most common allergic disease and is associated with a reduced quality of life of the patients, lower work productivity and school learning performance as well as increasing medical costs **(Pawankar et al., 2009).** Its prevalence in the industrialized world is increasing, particularly in urban areas **(Sly., 1999; Von Mutius et al., 1998).**

The Allergic Rhinitis and its Impact on Asthma (ARIA) in 2008 updated document estimates that there are 500 million subjects in this world who suffer from allergic rhinitis, Also suggests that AR is the most common chronic disorder in the pediatric population with up to 40% of children affected (**BOUSQUET et al., 2008).** According to studies done by **Torrance (1997); Bender (2005)**, allergic rhinitis accounts for at least 2.5 percent of all physician visit, 2 million lost school days per year, 6 million lost work days and 28 million restricted work days per year, The disorder results in the expenditure of

2.4 billion American dollars on prescription and over the counter medications and 1.1 billion dollars in physician billings, causing a total indirect and direct cost of several billion dollars per year. It can begin at any age but most affected individuals who develop symptoms are children or young adults. Symptoms typically peak in childhood and again in the thirty or forty and tend to continue with varying severity throughout life, including periods of remission **(Danielsson and Jessen, 1997).**

In childhood, boys with allergic rhinitis outnumber girls, but in general equal numbers are affected during adulthood. Allergic rhinitis results in day-time fatigue and impairment of cognition and memory in children which significantly affect the learning process and thus impacts on school performance and all these aspects upset the family **(Jauregui et al., 2009).**

Risk factors:-

Frew (2004); Watson et al. (1993) identified risk factors for allergic rhinitis which include:-

- Family history of atopy.
- Male sex.
- Birth during the pollen season.
- Firstborn status.

- Early introduction of formula and food.
- Early use of antibiotics.
- Maternal smoking exposure in the first year of life.
- Exposure to indoor allergens such as animal dander.
- Serum IgE > 100 IU/ml before age six years old.
- Presence of allergen specific IgE.

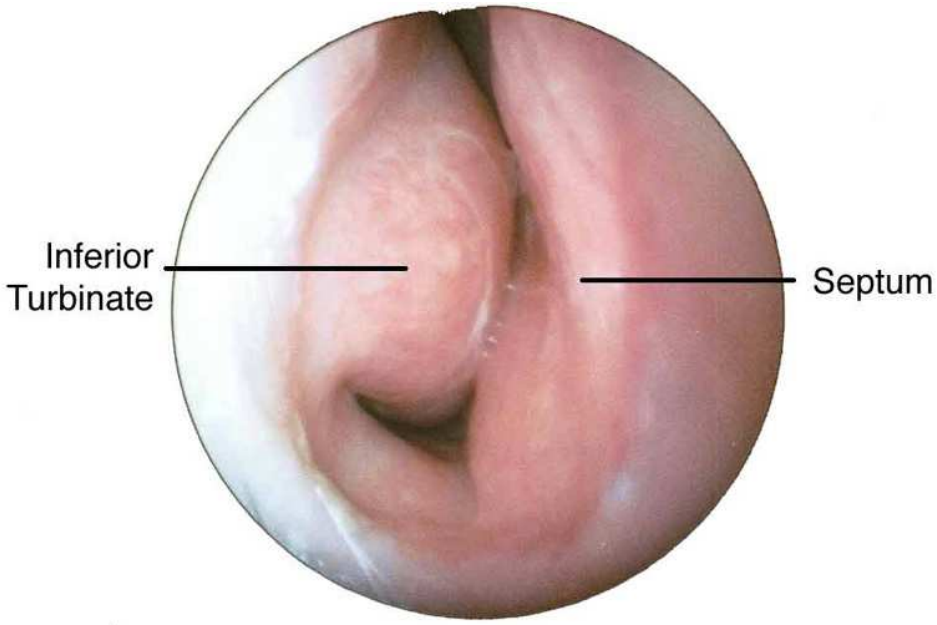

Fig (1): Nasal-allergy

Mucosal swelling, pale and thin secretions.

Chapter (2):

Pathophysiology of allergic rhinitis:-

The pathophysiology of allergic condition and inflammation of the mucous membranes are characterized by a complex interaction of inflammatory mediators but ultimately is triggered by an immunoglobulins E (IgE medaited) response to an extrinsic protein **(Mullol et al., 2005).** The tendency to develop allergic reactions to extrinsic allergen has a genetic component. In susceptible individuals, exposure to certain foreign protein leads to allergic sensitization which is characterized by the production of specific IgE directed against these proteins. Antigen presenting cells such as dendritic cells in the mucosal surface process the foreign protein (allergen) and present some peptides from allergens on the major histocompatibility complex (MHC) class II molecule **(Chaplin, 2006)**. This MHC class II molecule and antigen complex result in differentiation of Naive CD4+ T cells to allergen – specific Th2 cell. Activated Th2 cells secrete several cytokines which induce isotype switching of B cells to produce specific IgE and proliferation of eosinophils, mast cells and neutrophils **(Broide, 2007).** This specific IgE coats the surface of mast cells which are present in the nasal mucosa. On subsequent exposure to the same protein (allergen), it can bind to the IgE on the mast cells

leading to immediate and delayed release of a number of mediators **(Ray et al., 1996; Skoner, 2001).**

The mediators that are immediately released include histamine, tryptase, chymase, kinin and heparin. The mast cells also synthesize other medaitors quickly including leukotrienes and prostaglandin D2 **(Haberal and Corey, 2003; Cates et al., 2003).** Cysteinyl leukotrienes are a family of inflammatory lipid mediators synthesized from arachidonic acid by a variety of cells including mast cells, basophils and macrophages. Cysteinyl leukotrienes play a multi-functional role as mediators in allergic rhinitis (AR), CysLTs play an important role in the maturation, as well as tissue recruitment of inflammatory cells and a complex inter-regulation between CysLTs and a variety of other inflammatory mediators exists **(Benson et al., 2007).**

The mediators released after exposure to the allergen, through various interactions, lead to symptoms of allergic rhinitis such as nasal obstruction, sneezing, itching, tearing and postnasal drip. Mucous glands are stimulated leading to increased secretions. Vascular permeability is increased leading to plasma exudation. Vasodilatation occurs leading to congestion and pressure. Sensory nerves are stimulated leading to sneezing and itching. All these events can occur in minutes so this reaction is called **the early or immediate phase of the reaction**. Over 4-8 hours, these mediators through a complex interplay of events lead to recruitment of other inflammatory

cells to the nasal mucosa such as neutrophils, eosinphils, lymphocytes and macrophages. These leads to continued inflammation termed the **late or delayed phase response**. The symptoms of the late phase response are similar to those of the early phase but less sneezing, less itching and more obstruction and mucous production tend to occur. It may persist for hours or days **(Salib et al., 2004).**

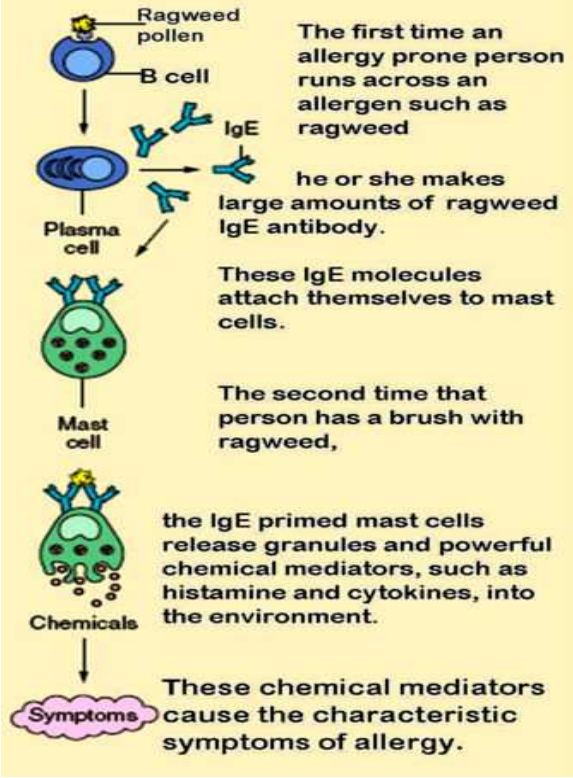

Fig (2): Pathophysiology of allergic rhinitis.

Immunopathogenesis of allergic rhinitis:-

Allergen induces Th2 lymphocytes proliferation in persons with allergies with the release of their characteristic combination of cytokines including IL-3,IL-4, IL-5,IL-9, IL-10 and IL- 13. These substances promote IgE and mast cells production. Mucosal mast cells that produce IL-4, IL-5, IL-6 and tryptase proliferate in the allergic epithelium. Inflammatory mediators and cytokines upregulate endothelial cell adhesion markers such as the vascular cell adhesion molecule-1. Chemoattractants including eotaxin, IL-5 and RANTES lead to the characteristic infiltration by eosinophils, basophils, Th2 lymphocytes, and mast cells in chronic allergic rhinitis **(Rihoux, 2000).** A high degree of cell-to-cell communication is needed to orchestrate this inflammatory immune response. A variety of cytokines and adhesion receptors seem to play an important role in the allergic reaction. Proinflammatory cytokines such as IL-1, IL-8 and TNF-α (tumor necrosis factor-alpha) can be detected in nasal secretions and mucosa. The increased expression of adhesion receptors in mucosal specimens of patients with allergic rhinitis points to their role in regulating the cellular migration and probably represents a key event in allergic inflammation. These findings indicate that proinflammatory cytokines may be key factors for the up regulation of adhesion processes in human nasal mucosa and the activation of various cell populations involved in the

allergic inflammation. They, therefore, represent a main target for new therapeutic strategies **(Rihoux, 2000).** The type and amount of inflammation in allergic rhinitis are regulated by cytokines. Therefore, the production of the Th2-cytokines,IL-4, IL-5, IL-13, of the Th1-cytokines, IFN-γ and IL-12 and of the regulatory cytokine IL-10 that is capable of down regulating their synthesis was investigated. It was found that the production of IL-4, IL-5, and IL-13 was significantly elevated in allergics; the number of IL-12 and IFN-γ- producing cells was significantly elevated as well. IL-10 was also significantly higher in allergics. This investigation of cytokine production during natural allergen exposure demonstrates that the synthesis of both Th2 and Th1-cytokines is increased in allergic rhinitis **(Baraniuk, 1997).** When allergen challenges are given repeatedly, the amount of allergen required to induce an immediate response decreases, this referred to as the priming effect. This priming effect is thought to be a result of the influx of inflammatory cells during ongoing, prolonged allergen exposure and repeated late-phase responses. The priming effect demonstrates the importance of knowing the full spectrum of aeroallergens to which a patient responds and seasonal variations in allergic symptoms, and provides the rationale to consider initiating effective anti-inflammatory therapies before the pollen season or before other chronic or repetitive aeroallergen exposures **(Bradding et al., 1995).**

When respiratory epithelium is destroyed and nerve endings are exposed by cytotoxic proteins from eosinophils, sensory nerve fibers are excited by nonspecific stimuli and stimulate both sensory afferent and surrounding efferent fibers, the so called retrograde axonal reflex. This makes the sensory nerve fibers secrete neuropeptides such as substance P and neurokinin A, which induce contraction of smooth muscles, mucous secretion of goblet cells and plasma exudation from capillaries. This process is called **neurogenic inflammation (Togais, 2000).**

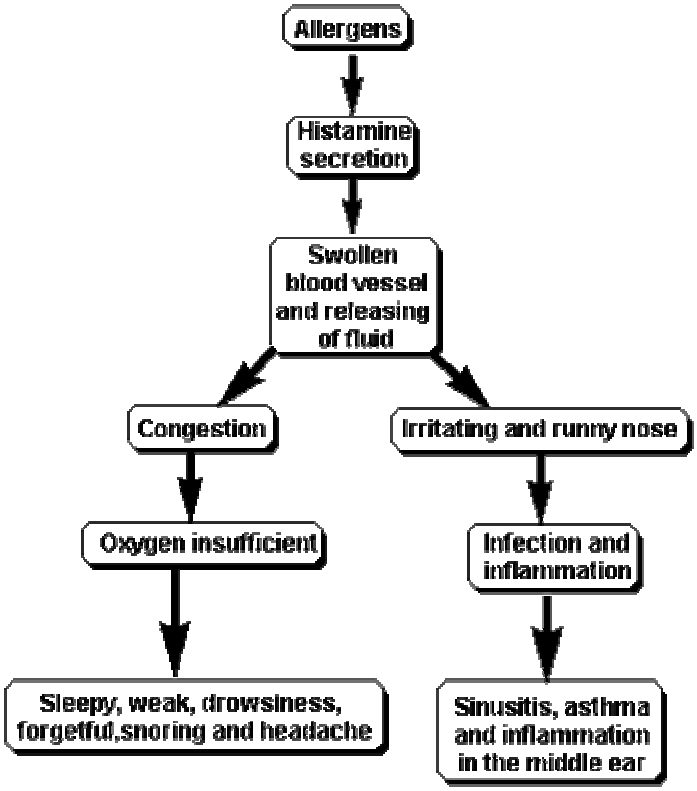

Fig (3): Summary of the nasal allergy pathophysiology

Role of immunoglobulin E in the pathophysiology of Allergic Rhinitis:

Immunogloblin E (IgE) is considered to play a key role in the pathogenesis of allergy **(Holgate et al., 2005)** and the level of circulating IgE to common inhalant allergens is a strong risk factor for emergency admissions with allergy and asthma **(Pollart et al., 1989).**

Structure of immunoglobulin E:-

IgE exists as monomers consisting of two heavy chains (ε chain) and two light chains, The IgE heavy chain has four constant region domains (C epsilon 1-4). The major site of interaction with the high affinity IgE receptor is C epslon 3. The biological activity of IgE is mediated through the action of two types of IgE receptors.