Available online at www.sciencedirect.com
ScienceDirect
Pharmacology & Therapeutics 113 (2007) 121 – 133
Pharmacology & Therapeutics
www.elsevier.com/locate/pharmthera

Associate editor: A. Trifilieff

Immunoglobulin E: Role in asthma and allergic disease: Lessons from the clinic

Charles E. Owen *

Novartis Institutes for Biomedical Research, Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom

Abstract

The role of immunoglobulin E (IgE) in allergic asthmatic disease is well established. Allergen-specific IgE binds to its cognate receptors, thus triggering a series of cellular events. These events include presentation of antigen by dendritic cells and the degranulation of mast cells and basophils to release numerous factors that play an integral part in potentiating the disease symptoms. Studies in the mouse indicate that a reduction in IgE levels could lead to significant attenuation of the allergic inflammatory response associated with diseases such as asthma, making IgE a target for the development of new therapeutic agents. Omalizumab (Xolair®), a recombinant humanised monoclonal anti-IgE antibody that blocks the interaction of IgE with its receptors, is the first anti-IgE agent to undergo clinical development. Several clinical studies have been performed in adults and children with moderate-to-severe allergic asthma to evaluate the efficacy and safety of this agent, but which have also enabled an insight into the role of IgE in human disease. IgE plays a significant role in a number of allergic conditions including allergic rhinitis and allergies to various substances. Recent data suggests that local IgE production may occur in mucosal tissues and that locally significant concentrations of IgE, not reflected by serum IgE concentrations, indicate that it may play a role in non-atopic as well as atopic disease.

Keywords: Asthma; Immunoglobulin E; Omalizumab; Allergy; Atopy; Anti-IgE

Abbreviations: FcεRI, Fc epsilon receptor RI; IgE, immunoglobulin E; IgG, immunoglobulin G; pDC, plasmacytoid dendritic cell; QoL, quality of life; RAST, Radio-allergo-sorbent Test.

Contents

* Tel.: +44 1403 272827; fax: +44 1403 323353.
E-mail address: Charles.Owen@Novartis.Com.

0163-7258/$ - see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.pharmthera.2006.07.003

1. Introduction

Asthma is a chronic disease of the lung characterised by the reversible obstruction to respiratory airflow caused by excess mucus production, narrowing of the airways and bronchial hyper-responsiveness. The increasing prevalence of asthma and allergy has seen a doubling in patient numbers in 20 years, to the extent that between 10% and 30% of the population in developed countries are likely to suffer from clinical allergy (ISAAC Committee, 1998; Sole et al., 2001). The economic toll of absences from work, missed schooldays and increasing healthcare costs has made allergic diseases, such as asthma, a high priority in terms of finding better forms of treatment.

The allergic asthmatic response to allergen exposure is associated with immunoglobulin E (IgE)-mediated mast cell activation, resulting in the accumulation of leukocytes such as eosinophils and Th2 lymphocytes in the airway (Kay et al., 1997; Umetsu & DeKruyff, 1997). Th2 lymphocytes are believed to play a central role in the allergic inflammatory response. Indeed, the production of the inflammatory cytokines interleukin (IL)-4, IL-5 and IL-13 by such cells has been intrinsically linked to the asthmatic condition and inflammatory cell activation. The aim of this review is to discuss IgE as an important target in the development of future therapies for asthma and other allergy-based inflammatory diseases, a strategy that has led to the development of omalizumab (Xolair®) for moderate–severe allergic asthma and which is beginning to tease open the role of IgE in diseases.

2. Immunoglobulin E and its cognate receptors

IgE is considered to be a key mediator in the pathogenesis of asthma and other allergic diseases. Indeed, the presence of elevated levels of serum IgE has been demonstrated (Fig. 1) to be associated with allergic asthma in several studies (Burrows et al., 1989), while elevated cord blood IgE levels have been linked to a predisposition to develop atopy in young children (Kobayashi et al., 1994).

2.1. Immunoglobulin E

Following its purification and characterisation in 1967, IgE has been identified as being closely associated in mediating hypersensitivity (Ishizaka & Ishizaka 1966; Johansson & Bennich, 1967). IgE is the least abundant antibody class found in the serum of humans. Compared to human immunoglobulin G (IgG), for which concentrations are in the order of 10 mg/mL; serum IgE concentrations in normal individuals rarely exceed 150 ng/mL (King et al., 1991). Between 70% and 80% of patients with atopic dermatitis suffer from the “extrinsic” form, characterised by sensistisation to environmental allergens and often have very highly elevated levels of IgE (Bos et al., 1998; Novak et al., 2003b). Other atopic individuals characteristically have IgE levels up to 10-folds greater than for normals. At the structural level (Fig. 2), IgE is made up of 1 variable heavy chain and 4 constant ε heavy chains (Gould et al., 2003).

The classical allergic inflammatory cascade, whereby allergen-driven presentation by antigen-presenting cells to naïve T lymphocytes promotes their differentiation into T helper 2 (Th2) lymphocytes is traditionally believed to be at the hub of the allergic inflammatory cascade. Th2 lymphocytes release a number of cytokines including IL-5, important for the recruitment and activation of eosinophils and IL-4/IL-13, both of which are critical to the production of IgE by B lymphocytes. IL-4 and IL-13 are the only 2 cytokines able to drive germline ε transcription and subsequent switch recombination to produce IgE in B lymphocytes (Platts-Mills, 2001). Switched B lymphocytes are able to secrete IgE and differentiate to become either memory B cells or plasma cells. Plasma cells reside in the bone marrow and continue to produce IgE (Fig. 3) (Gould et al., 2003). The half-life of IgG immunoglobulins is approximately 20 days, whereas, for IgE, the half-life is a relatively short 3 days in serum. However, a significant amount of IgE resides within the tissue compartment bound to cell surface IgE receptors such that

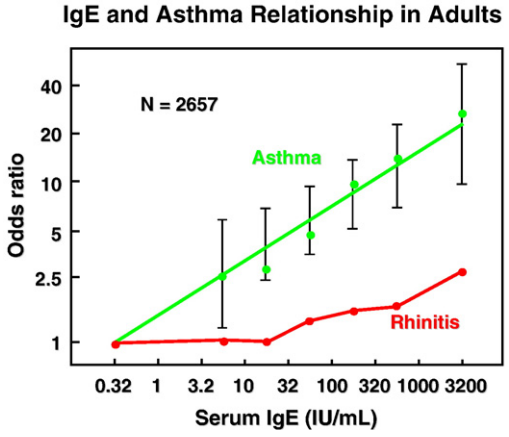

Fig. 1. Relationship between serum IgE concentrations and likelihood of suffering from asthma or allergic rhinitis.