Chapter 19

The Use of Glucocorticoids in the Treatment of Acute Asthma Exacerbations

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Additional information is available at the end of the chapter

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1. Introduction

1.1. Pathophysiology of asthma and acute asthma exacerbations: Brief overview

Asthma is a chronic respiratory disease that is prevalent worldwide. It is considered as a major cause of morbidity and a main contributor to the high health care expenditure especially in developed countries (Subbarao et al, 2009). There are two major pathological features in asthmatics' airways, inflammation and hyperresponsiveness. These features are interrelated but not totally dependent on each other. Airway inflammatory changes include increased airway mucus secretions, airway wall edema, inflammatory cellular infiltrates, epithelial cell damage, smooth muscle hypertrophy, and submucosal fibrosis (Bergeron et al, 2009). The cellular infiltrates are mainly composed of eosinophils, neutrophils, mast cells, lymphocytes, basophils and macrophages. The ratio of these cells may widely vary between patients pointing to asthma heterogeneity (Holgate, 2008). Overall, asthma can be divided into eosinophilic, neutrophilic, and pauci-granulocytic phenotypes. The eosinophilic phenotype is characterized by predominant eosinophilic infiltration of the airways. Patients tend to be allergic, have asthma triggered by exposure to allergens and tend to respond well to glucocorticoids. The neutrophilic phenotype is characterized by predominant neutrophil infiltration of the airways. Patients tend to have severe, more aggressive, poorly controlled asthma, or acute asthma triggered by viral infection. They usually do not respond to glucocorticoids as good as the eosinophilic type. In the pauci-granulocytic phenotype neutrophils and eosinophils are almost absent (Holgate, 2008).

Triggers of acute asthma exacerbation include allergens like pollens, animal dander, dust mites and mold; viral respiratory tract infections; irritants like smoke and dust; cold air and exercise. When pollens, for instance, are inhaled by an allergic individual, the allergenic protein is taken up by antigen presenting cells (dendritic cells) in the airway. It is then presented to naïve T-helper (Th) cells that develop into Th2 cell phenotype. These cells respond by secreting Th2 cytokines like IL-4 and IL-13 that cause allergen specific B-cells to

switch from IgM producing to IgE producing cells. These cytokines could also contribute to epithelial cell damage, increased mucus secretion and airway hyperresponsiveness. Th2 cells also secrete IL-5 that stimulates eosinophil development, release from the bone marrow and their recruitment to the site of inflammation. IgE antibodies bind to their receptors on the surface of mast cells. Cross linking of adjacent IgE molecules leads to degranulation and release of mediators like histamine and tryptase that are key to features of immediate hypersensitivity reaction. Activation of mast cells and eosinophils will also stimulate the synthesis and release of lipid derived mediators like prostaglandins and cysteinyl leukotrienes that are very potent bronchoconstrictors. Moreover, activation of eosinophils leads to the release of mediators like eosinophil cataionic protein and major basic protein, which can cause airway epithelial cell damage and submucosal fibrosis. New evidence suggests that Th1 cells contribute to chronic changes in the airways including epithelial cells damage and smooth muscle cells activation. Regulatory T cells (Treg) inhibit Th2 cells by secreting IL-10 and tansforming growth factor β (TGFβ). Also, antigen specific Th17 cells were found to play an important role in neutrophilic airway inflammation and the process of airway remodeling (fixed changes to the airway) through the secretion of IL-17A and IL-17F (figure 1). This is a very quick overview, but many other changes take place during this process that are beyond the scope of this chapter.

Figure 1. Major immunopahtologic processes that take place in the bronchial airways of patients with asthma. Please see the text for detailed description. FcεRI, high-affinity receptor for IgE; IFNγ, interferon-γ; TCR, T-cell receptor; TNF, tumour-necrosis factor. Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Immunology. Stephen T. Holgate and Riccardo Polosa. Treatment strategies for allergy and asthma. Vol. 8(3):Page 220, Copyright 2008.