Airway inflammation in asthma: Challenge of gaining asthma control when inhaled corticosteroids fail

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The last several decades have witnessed significant advances in the understanding and treatment of asthma. The introduction of inhaled corticosteroids (ICS) and the application of asthma guidelines have enabled many patients to achieve asthma control, remain out of hospital, and reduce the number of asthma exacerbations. Coupled with these successes is the growing awareness that not all patients can achieve control with ICS despite adherence to therapy. Indeed, a number of studies suggest that upwards of 40–45% of asthmatics fail to achieve asthma control on ICS, patients referred to as steroid–refractory or steroid–insensitive. In part, this failure to respond may relate to the nature of the inflammatory cells which accumulate in the lung tissue and airways. Neutrophil–driven pathways and disease may be relatively steroid–insensitive compared to those pathways which result in eosinophilic inflammation. Upstream, the type of inflammatory pathway activated may be the consequence of exposure to a specific asthma trigger. Allergen exposure in a sensitive individual elicits a response characterized by IgE, airway eosinophilia, and Th2 cytokine responses such as IL–4 and IL–13. In contrast, viruses, which are major causes of asthma exacerbations tend to trigger a neutrophilic and Th1 cytokine responses (IFN–α, IFN–β, IFN–γ). Of perhaps even greater importance, the allergen–driven responses are associated with CD4 + T cells whereas the virus–driven responses are linked to CD8 + T cell infiltration. This paradigm provides a framework for understanding steroid–sensitive and –insensitive asthma as CD4 + T cells and eosinophils are steroid–sensitive, whereas CD8 + T cells and neutrophils are relatively unresponsive to corticosteroids. Moreover, there is now increasing evidence for the role of CD8 + T cells in experimental models of asthma and in asthmatics who have a suboptimum response to ICS. In addition, in a given patient, the exposure to different triggers is dynamic, so that effective treatment at one stage of their disease may not persist at other times. Thus, the nature of the lung inflammatory response, that which is driven by a specific asthma trigger, may dictate the response to ICS and the ability to reduce the burden of asthma. As a result, specific therapeutic targeting will be required beyond ICS if we are to increase our effectiveness in achieving asthma control in the majority of patients exposed to different triggers.