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Immunomodulators and immunotherapy

Chris J Corrigan

Introduction: the clinical need

Asthma affects 10% of children and 4% of adults, with an overall prevalence of 6% (3.6 million patients) in the UK. Mortality from asthma is relatively low (1,680 deaths in the UK in 1994). However, considerable morbidity arises from the disease in that minority of patients whose symptoms are inadequately controlled by conventional therapy such as inhaled glucocorticoids and long-acting β_2 agonists, even when optimal delivery has been assured, compliance has been verified and the effects of other exacerbating factors minimised (Woolcock 1993). In these patients, oral glucocorticoids are often employed, but even then patients may remain symptomatic. Furthermore, an important minority of patients appear to be resistant to the clinical anti-asthma effects of glucocorticoids, which may partly reflect resistance of their T cells to glucocorticoid inhibition (Corrigan *et al.* 1991a). No existing therapy for asthma is preventive, curative or clearly disease modifying. For all these reasons, alternative modalities of therapy, particularly for chronic, severe, glucocorticoid-dependent asthma, are urgently required.

Immunomodulatory therapy in asthma

It is increasingly recognised that asthma is associated with chronic, cell-mediated inflammation of the bronchial mucosa in which eosinophil-active cytokine products of activated T cells play a prominent role. Eosinophils are considered to be 'end-effector' cells. Their products (granule basic proteins and cysteinyl leukotrienes) are thought to produce much of the damage to the bronchial mucosa that results in the clinical features of asthma (variable airway obstruction and bronchial hyper-responsiveness). Acute release of mast cell mediators (histamine and leukotrienes), IgE mediated or otherwise, may also result in exacerbation of symptoms on this background of T-cell-mediated chronic inflammation. Evidence suggests that glucocorticoids ameliorate asthma at least partly through inhibition of T cells and elaboration of their asthma-relevant cytokine products, particularly interleukin 5 (IL-5) (Corrigan *et al.* 1993, 1995; Doi *et al.* 1994). For this reason, there has been interest in the investigation of other immunomodulatory agents for their possible therapeutic effects in asthma. As many of these agents have potentially serious unwanted effects, attention has generally been focused on those asthmatic individuals who continue to have severe disease despite properly administered, maximal topical

Table 9.5 Shortcomings in hospital management of acute/severe asthma in Birmingham and Manchester in 1985 and in Edinburgh in 1988

	<i>Edinburgh prospective study Bucknall et al. (1988) (patient no. 139) (%)</i>	<i>Birmingham and Manchester retrospective study Baldwin et al. (1990) (patient no. 192) (%)</i>		
	<i>All</i>	<i>Respiratory</i>	<i>General</i>	<i>All</i>
<i>Hospital physicians</i>				
Prior clinic attenders	40		35	
Peak flow monitoring	60	81	55	
Arterial blood gases	84	68	44	
Nebulised β_2 agonists	100			79
Oral corticosteroids	82	86	61	79
Intravenous aminophylline	34	20	30	
Antibiotics	69			
Discharge inhaled steroids	85	74		
Clinic follow-up	77	94	74	
<i>Post-discharge interview</i>				
Able to recognise a bad attack	81			
No management plan	34			
Knew to start steroids	15			
Regular sleep disturbance	39			
Actually taking inhaled steroids	72			
Actually taking oral steroids	47			
Actually taking inhaled β_2 agonists	94			