Pharmacology & Therapeutics 132 (2011) 333–351

Contents lists available at SciVerse ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Associate editor: M.G. Belvisi

Monoclonal antibodies for the treatment of asthma

Matthew C. Catley *, Julie Coote, Mohamed Bari, Kate L. Tomlinson

UCB Pharma, 216 Bath Road, Slough SL1 3WE, United Kingdom

ARTICLE INFO

Keywords:
Asthma
Monoclonal antibodies
Anti-inflammatory
Cytokine
Novel therapies

ABSTRACT

Asthma is a chronic inflammatory disease of the airways which can have a detrimental effect on quality of life and in extreme cases cause death. Although the majority of patients can control their asthma symptoms with a combination of steroids and beta agonists there is still a group of patients whose asthma remains symptomatic despite the best available treatment. These severe asthmatic patients represent the unmet medical need in asthma and are the focus of those developing novel monoclonal antibody based drugs. The complex networks of cytokines and cells involved in the pathology of asthma provide plenty of scope for intervention with monoclonal antibody based drugs which are able to block cytokine or chemokine receptor interactions, deplete cells expressing a specific receptor or block cell/cell interactions. At present anti-IgE (Xolair©) is the only monoclonal antibody based drug approved for the treatment of asthma. However, a number of other antibody based drugs have been clinically tested in asthma including anti-IL-5, anti-IL-4, anti-IL-13, anti-TNFα, anti-CCR3, anti-CCR4 and anti-OX40L. This review will examine the development of these monoclonal antibody based therapies. Since many of these therapies have targeted key pathways in asthma pathology these studies provide information on patient stratification and asthma pathology.

Contents

1. Introduction

The word asthma is derived from Greek, meaning 'to exhale with open mouth', to pant. Its symptoms are shortness of breath, wheezing and a tight feeling of the chest, often worse at night and exacerbated by respiratory infections and other environmental triggers (Global Initiative for Asthma, 2008).

Asthma is one of the most common chronic diseases in the world. It is estimated that around 300 million people in the world currently have asthma and 250,000 die each year because of this disease. In the US, an estimated 8.9% of children (6.5 million) and 7.2% of adults

Abbreviations: Ig, immunoglobulin; IL, interleukin; TNF, tumor necrosis factor; CCR, CC chemokine receptor; CD, cluster of designation; TSLP, thymic stromal lymphopoietin; AHR, airway hyperresponsiveness; mAb, monoclonal antibody; Th, T helper; FcεRI, high affinity IgE receptor; PG, prostaglandin; EAR, early asthmatic response; LAR, late asthmatic response; PC, provocative concentration; FEV1, forced expiratory volume in 1 second; BALF, bronchoalveolar lavage fluid; PEF, peak expiratory flow.

* Corresponding author. Tel.: +44 1753 80 7493; fax: +44 1753 447603.
E-mail address: matthew.catley@ucb.com (M.C. Catley).

0163-7258/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.pharmthera.2011.09.005

(15.7 million) had asthma in 2005. In the US an estimated 14.7 million outpatient visits, 1.8 million visits to emergency departments and 497,000 hospitalizations took place in 2004 because of asthma. In 2003, ~12.8 million school days and 10.1 million work days were missed and 4055 people died from asthma (Akinbami, 2010).

There is an interesting trend in the epidemiology of asthma which indicates that its prevalence is increasing in industrialized countries (Asher, 1998; Crane, 2002). Industrialization however does not explain the entire difference in prevalence of asthma between countries. The disparities may also be affected by differences in genetic, social and environmental risk factors (Gold & Wright, 2005). Mortality however is most common in low to middle income countries (World Health Organization, 2010).

The pathophysiologic hallmark of asthma is chronic inflammation leading to remodeling of airways, mucous hypersecretion and airway hyper-responsiveness (AHR) (Murphy & O'Byrne, 2010). The mechanisms involved in persistence of inflammation in asthma are still poorly understood. At least three pathological phenotypes of asthma have been proposed on the basis of involvement of predominant cell type: eosinophilic, neutrophilic, and paucigranulocytic. These phenotypes are becoming increasingly associated with distinct clinical and physiological inflammatory and repair processes (Wenzel, 2006). However, it is clear that asthma is a heterogenic disease with a range of phenotypes that have not yet been well defined, although considerable effort is now being focused on defining asthma subpopulations. The chronic inflammation is often punctuated by acute inflammatory episodes which correspond to exacerbations of asthma (Wark & Gibson, 2006; Sykes & Johnston, 2008). Exacerbations of asthma are the most common cause of asthma related hospitalizations and have a detrimental effect on patient quality of life. In addition exacerbations impose a financial burden on health care providers. There are currently very few options for the treatment of these exacerbations and considerable effort is being focused on understanding the pathophysiology of asthma exacerbations in the hope that this will lead to novel treatments for this aspect of asthma (Sykes & Johnston, 2008).

The first mAb, Orthoclone OKT3 (muromonab), an anti-CD3 monoclonal antibody used for the treatment of renal, cardiac and hepatic transplant rejections was launched in 1986 (Norman, 1988). Since then, the wider mAb technology has undergone a significant development and antibody based therapeutics are now delivering considerable benefit to patients. The beneficial effects of antibody therapeutics can be delivered through a range of functions such as neutralization of soluble cytokines, blocking of receptors, inducing cell death (depleting) or modulating cell function. These different functions are dictated by the antibody isotype (Salfeld, 2007; Hansel et al., 2010).

The launch of omalizumab in 2003 opened up respiratory diseases as a new therapy area for mAb developers (Buhl, 2005; D'Amato et al., 2007). The identification of a range of targets thought to play a significant role in the etiology of asthma and the developments of mAbs to these targets have produced a large body of data on pre-clinical and clinical trials of these mAbs.

This review presents detailed study of monoclonal antibodies for treatment of severe asthma from exploratory development perspective.

2. Cellular pathophysiology

This section gives a brief description of some of the concepts that underlay our understanding of the cellular pathology of asthma. For a more detailed description of the current understanding of the cellular pathology of asthma there are a number of recent reviews (Lloyd & Hessel, 2010; Kaiko & Foster, 2011; Koyasu & Moro, 2011).

There is a paradigm that inflammation in asthma is driven by a distinct set of T helper 2 (Th2) cells which promote the eosinophilic allergic inflammation associated with asthma (Epstein, 2006; Durrant & Metzger, 2010; Levine & Wenzel, 2010). However recent research has indicated that clinical asthma has a mixed T helper (Th) cell profile with involvement of Th1, Th9 and Th17 cells (Heaton et al., 2005; Traves & Donnelly, 2008; Alcorn et al., 2010).

The greater involvement of Th1 and Th17 cells in asthma could drive the neutrophilic inflammation in the lungs of some severe asthmatics whose disease is less responsive to treatment with corticosteroids (Green et al., 2002; Alcorn et al., 2010). Neutrophilic inflammation can also be associated with some acute viral and bacterial exacerbations of asthma, another unmet medical need for asthma therapies (Wark et al., 2002; Pallan et al., 2008). Moreover, patients who die suddenly of asthma have large numbers of neutrophils in their airways, although this may reflect the rapid recruitment of neutrophils when compared to eosinophil recruitment (Carroll et al., 1996; Lamblin et al., 1998; de Magalhaes et al., 2005). The presence of neutrophils in severe asthma may also be a consequence of high doses of corticosteroids which inhibit neutrophil apoptosis and promote survival of these cells (Cox, 1995; Liles et al., 1995; Meagher et al., 1996). However, it is highly likely that neutrophils are actively recruited to the airways and play a role in the pathophysiology of severe asthma in some patients. This does not exclude the role of eosinophils in severe asthma and asthma exacerbations and it is clear that some patients seem to have a disease which is characterized by persistent sputum eosinophils despite high dose corticosteroid treatment (Haldar et al., 2009; Nair et al., 2009). Exacerbations can also be associated with increased eosinophils indicating that there may be different mechanisms driving their pathology of neutrophilic and eosinophilic exacerbations (Di et al., 2006; DeMore et al., 2009).

IL-9 has been considered as a Th2 cytokine until recent data has indicated that there may be an additional subset of IL-9 producing cells which express the transcription factor PU.1 (Lloyd & Hessel, 2010; Xing et al., 2011). These cells have been called Th9 cells and there is evidence that they may play an important role in allergic inflammation in the airways of some asthmatics. However, the exact role of these Th9 cells is currently not clear and it appears that IL-9 may also be produced by Th2 and Th17 cells (Nowak et al., 2009; Noelle & Nowak, 2010). Clinical trials of antibodies targeting IL-9 should provide information on the role of IL-9 in asthma. Data from the Th-17 driven experimental autoimmune encephalitis (EAE) model indicates that IL-9 is produced by Th17 cells and drives the production of IL-17A and IL-6 in this model (Nowak et al., 2009). In contrast, in skin transplant models IL-9 production from T regulatory cells may recruit and activate mast cells to suppress inflammation in the periphery (Lu et al., 2006). Thus it appears that IL-9 may function as a regulatory cytokine.

Although there has been considerable focus on the role of T cells in asthma, it is clear that structural and resident lung cells such as the fibroblasts, smooth muscle, epithelium, dendritic cells, mast cells and macrophages may also have a role in the pathogenesis of asthma (Barnes, 2008). Allergens entering the lung are taken up by dendritic cells and also activate pathogen associated molecular pattern receptors and protease activated receptors on epithelial cells. The activated epithelial cells released cytokines such as IL-25, IL-33 and thymic stromal lymphopoietin (TSLP) which appear to fully activate dendritic cells and drive Th2 skewing (Soumelis et al., 2002; Paul & Zhu, 2010). In particular, epithelial derived TSLP causes dendritic cell maturation and the upregulation of costimulatory molecules such as OX40L. TSLP activated dendritic cells then migrate to the lymph nodes where they interact with naive T cells and drive their differentiation to allergen specific inflammatory Th2 cells which express high levels of IL-4, IL-5, IL-13 and TNFα (Wang & Liu, 2007).

Several recent findings have shed further light on the mechanisms involved in priming Th2 responses. The central role of airway dendritic cells (DC) in sampling allergen and subsequently migrating to draining lymph nodes to presenting allergen and prime the Th2 response has been well demonstrated by Lambrecht et al. (van Rijt & Lambrecht,