Asthma: beyond corticosteroid treatment

Yasser Marandi[1], Neda Farahi[2], Goudarz Sadeghi Hashjin[3]

[1]Department of Pharmacology, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[2]Division of Respiratory Medicine, School of Clinical Medicine, University of Cambridge, Cambridge, UK
[3]Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran

Corresponding author:
Goudarz Sadeghi Hashjin PhD
Faculty of Veterinary Medicine
University of Tehran
P.O. Box 6453, Tehran 14155, Iran
Phone: +98 21 611 171 90
Fax: +98 21 669 332 22
E-mail: gsadeghi@ut.ac.ir

Submitted: 2 May 2011
Accepted: 13 September 2011

Arch Med Sci 2013; 9, 3: 521-526
DOI: 10.5114/aoms.2013.33179

Abstract

Asthma is one of the most common chronic diseases in the world, affecting over 300 million people. It is an inflammatory disorder characterized by bronchoconstriction and airway hyperresponsiveness, followed by inflammatory manifestations in the respiratory system. The prevalence of asthma is rising and there is a clinical need to develop more effective treatments. While corticosteroids (glucocorticosteroids) remain the mainstay of asthma therapy, they have limitations because of their potentially severe side-effects and the presence of corticosteroid resistance in some patients. This review discusses current strategies in the treatment of asthma and considers new therapeutic regimens of asthma in the drug development pipeline.

Key words: asthma, corticosteroids, inflammation.

Introduction

Asthma is defined as a chronic disease characterized by bronchial hyperreactivity and lung inflammation, particularly within the airways. The airway inflammation is characterised by activation of mast cells, infiltration of eosinophils, and increases in the number of activated T helper (Th)2 cells, which mediate allergic inflammation through the secretion of an array of cytokines [1]. Chronic inflammation can lead to structural changes in the airways, including airway smooth muscle cell hypertrophy and hyperplasia. Epithelial cell loss can also occur and expose irritant receptors to potential stimuli such as chemicals or cold air. These structural changes may underlie the irreversible component of airway narrowing that can increase over many years, particularly in patients with severe disease.

Bronchodilators were useful in asthma management in the past but this has changed since the introduction of corticosteroids (glucocorticosteroids). Corticosteroids have the added benefit of treating the underlying inflammatory component of asthma and they have made a significant contribution to asthma treatment by reducing hospitalisation and mortality [2]. Yet, despite the availability of these effective therapies, over half of patients with asthma are poorly controlled [3]. This review discusses the benefits and drawbacks of corticosteroids in current asthma treatment and considers future drug targets.

Current treatment options

Corticosteroids are widely used to treat a variety of inflammatory and immune disorders. The most common use of corticosteroids today is in the treatment of asthma and other allergic diseases. Inhaled corticosteroids have now become first-line treatment in adults and children with persistent asthma. Bronchodilators are important for relieving bronchoconstriction and thus still remain major drugs for asthma. This category includes the β2-adrenoreceptor agonists, xanthines, cysteinyl leukotriene receptor antagonists and muscarinic receptor antagonists. They only treat the bronchospasm and have little effect on the inflammatory phase and these drugs are thus limited to providing symptomatic relief. Mast cell activation through the release of bronchoconstrictor mediators is very important for the symptoms of asthma, and mast cell inhibitors such as cromones (sodium cromoglycate and nedocromil sodium) can also be used. Recently, immunotherapy in the form of an anti-IgE antibody (omalizumab) has proven useful and omalizumab is currently licensed for severe asthmatics in several countries including the USA and UK. Omalizumab is an IgG1 monoclonal antibody that interacts with serum free IgE to generate small complexes [4]. The resulting reduction in IgE has been confirmed in bronchi from patients with mild to moderate asthma treated with omalizumab for 16 weeks as a reduction in high-affinity IgE receptor expression and reduction in eosinophil numbers [5].

Limitations of corticosteroid treatment

Corticosteroids act by diffusing across cell membranes and binding to the glucocorticoid receptors (GR) in the cytoplasm. Cytoplasmic glucocorticoid receptors are normally bound to heat shock protein-90 (hsp-90) and hsp-56 [6]. Two receptors have been described, GRα and GRβ. GRα binds corticosteroids whereas GRβ is an alternatively spliced form that binds to DNA but cannot be activated by corticosteroids. GRβ has a very low level of expression compared to GRα. The GRβ isoform has been implicated in steroid-resistant asthma [7].

All currently available inhaled corticosteroids are absorbed from the lungs and thus have the potential for local and systemic side effects. Corticosteroids inhibit adrenocorticotrophic hormone and cortisol secretion by a negative feedback effect on the pituitary gland. This can produce unwanted systemic effects with large doses or prolonged administration of corticosteroids. The side-effects include suppression of responses to bacterial infection, osteoporosis and Cushing's syndrome. Significant suppression after short courses of steroid therapy is not usually a problem, but prolonged suppression may occur after several months or years. Steroid doses after prolonged oral therapy must also be reduced slowly, otherwise symptoms of steroid withdrawal such as fatigue and musculoskeletal pains may develop.

Although corticosteroids are highly effective in the control of asthma, a small proportion of patients do not respond, even when using maximal doses of oral corticosteroids [8]. Steroid-resistant patients present considerable management problems as there are few alternative anti-inflammatory treatments available. There may be several molecular mechanisms for resistance to the effects of corticosteroids and these may differ between patients. Recent work has shed light on the mechanisms which underlie steroid resistance. One mechanism may be due to oxidative stress, as this is increased in patients with severe asthma [9]. Normally corticosteroids bind to GR and recruit histone deacetylase-2 (HDAC2). This reverses the histone acetylation induced by NF-κB and switches off the activated inflammatory genes. In COPD cigarette smoke generates oxidative stress to impair the activity of HDAC2, resulting in amplification of the inflammatory response to NF-κB activation and a reduction in the anti-inflammatory effect of corticosteroids. A similar mechanism may operate in severe asthma where increased oxidative stress is generated by airway inflammation. Other lines of evidence suggest involvement of p38 MAP kinase activation, defective histone acetylation and disruption of the coupling of GR receptor activation to transcription factor inhibition [10-12].

Therapeutics under development

Significant progress has been made in recent years to analyse and understand the myriad of cytokines, chemokines, lipid mediators and signalling cascades underlying asthmatic pathology. This has yielded numerous drug targets but many have shown limited efficacy beyond pre-clinical research. Table I details a selection of compounds/biologics that have reached Phase 2 clinical trial status [13-21].

Following the success of biologics in conditions such as rheumatoid arthritis, monoclonal antibodies targeting Th2 cytokines have been investigated. Anti-cytokine therapies that have been investigated include monoclonal antibodies directed against IL-5, tumour necrosis factor-α (TNF-α), and IL-4/IL-13. Interleukin-5 is the cytokine primarily responsible for eosinophil differentiation, maturation, migration into the circulation and survival [22]. Eosinophils are prominent in the airways of patients with poorly controlled asthma and focusing treatment on reducing their numbers has resulted in fewer severe asthma exacerbations [23]. Mepolizumab, an agent that targets IL-5, demonstrated little benefit in initial studies of mild to moderate asthmatic patients [24]. However, more recently, studies of this agent in severe

Table I. Selection of asthma therapies undergoing clinical trials

Agent	Clinical trial status	Efficacy	References
Anti-cytokine therapies			
IL-4R-α antagonist	Phase 2	Despite initial benefits in severe asthmatics, these compounds have been discontinued	27
Anti-IL-5	Phase 2	Shown to reduce the number of severe asthma exacerbations	24, 25
Anti-IL-5R-α	Phase 2	Reduces circulating eosinophils. Favourable safety, pharmacokinetic and pharmacodynamic profile. Efficacy studies using IV and SC routes of administration still ongoing	13
Anti-IL-9	Phase 2b	Modest improvements reported in patients with mild asthma undergoing allergen challenge. Larger clinical studies underway in severe asthmatics	14
Anti-IL-13	Phase 2	Five anti-IL-13 compounds investigated. Early compounds reduced both early asthmatic response (EAR) and late asthmatic response (LAR) Majority of Phase 2 results yet to be released	15, 16
Chemokine ihibitors			
CCR3 antagonist	Phase 2	Orally active competitive antagonist, currently on trial for mild to moderate asthma	17
Toll-like receptor targets			
TLR7, TLR9 synthetic agonists	Phase 1 and 2	Effective in animal models of asthma, efficacy in human studies yet to be determined	18
Kinase inhibitors			
Syk kinase inhibitor	Phase 2 planned	In Phase 1, reported that the inhaled inhibitor is well tolerated, with an improvement in both the EAR and LAR	19
c-kit/PDGF receptor tyrosine kinase inhibitor	Phase 3	In Phase 2, generated promising efficacy data and good safety profile	20
Phosphodiesterase inhibitors			
PDE 3/4 inhibitors	Phase 2	Reduced EAR and LAR in naive atopic asthmatics in response to inhaled allergen. However, orally administered drugs result in side effects such as gastro-intestinal symptoms	21

steroid-resistant asthma showed that anti-IL-5 reduced asthma exacerbations significantly [25]. In studies of anti-TNF-α, there were no significant improvements in any asthma outcome and, furthermore, the safety profile of this compound was not favourable [26]. Interleukin-4 and IL-13 share many biological functions which play a role in the pathogenesis of asthma [27]. Corren *et al.* used AMG 317, a fully human monoclonal antibody to IL-4R-α that blocks both IL-4 and IL-13 pathways. This antibody improved clinical symptoms in a subgroup of severe asthmatics but not the entire study group [27].

Another approach to inhibit inflammation is to block the adhesion molecules that are involved in the recruitment of inflammatory cells from the circulation into the airways [28]. Small molecule inhibitors of very late antigen (VLA)-4, which is involved in the recruitment of eosinophils and T cells, were effective in animal models but success has been limited in trials with asthmatic patients [29, 30].

Major efforts have been undertaken to minimise the side-effects of corticosteroids whilst still retaining their valuable anti-inflammatory properties. One approach has been the development of corticosteroids with enhanced specificity towards the GR receptor compared to other steroid receptors (e.g. the androgen receptor or the mineralocorticoid receptor). This approach has yielded compounds such as fluticasone furoate, which has promising efficacy *in vitro* and *in vivo* [31-33]. Fluticasone furoate (combined with a long-acting β agonist) is under Phase III trials to investigate clinical benefit in asthmatics [34]. Corticosteroids can reduce the expression of many pro-inflammatory mediators via transrepression whilst their adverse effects are due to the transcription of genes involved in metabolic processes, known as transactivation. Thus the selective glucocorticoid receptor agonists (SEGRAs) or dissociated steroids are compounds in development to have more transrepression rather than transactivation activity [35, 36]. However, to date, these compounds have not translated into successful therapies in the clinical setting.

Future therapeutic targets

Whilst we await the results of the clinical studies described in Table I, continuing research is still yield-

ing potential anti-inflammatory strategies. A number of potential therapeutic avenues will be discussed. It is also important to bear in mind that although these compounds may show significant promise during *in vitro* and animal studies, this does not necessarily lead to improved outcome in the clinic. In fact, despite their widespread use, there are a number of limitations when using mouse models of asthma such as differences in anatomy and immunology.

The phosphoinositide 3-kinase (PI3K) family of enzymes consists of several closely related isoforms that are thought to have distinct biological roles. While PI3-kinase inhibitors exhibit poor selectivity of different PI3K isoforms, recently published work describes the next generation of PI3K inhibitors, including several that are isoform-selective [37, 38]. This has prompted some researchers to speculate that isoform-selective PI3K inhibitors will provide new avenues for therapeutic applications in a range of inflammatory diseases. In particular, PI3K-γ has a role in chemotactic responses, and selective inhibitors are in development [39, 40]. PI3K-δ activation attenuates steroid responsiveness; thus PI3K-δ inhibitors could potentially reverse corticosteroid resistance in severe asthma [41, 42]. A concern about kinase inhibitors is their potential for side-effects as they target signalling pathways found in many cell types.

Cyclin-dependent kinases (CDKs) are a family of serine/threonine kinases that regulate cell cycle events through the phosphorylation of transcription factors and tumour suppressor proteins required in DNA replication and cell division. Therefore, CDKs are important therapeutic targets for cancer therapy and there are several CDK inhibitors undergoing clinical evaluation for B cell malignancy, non-small-cell lung cancer and breast cancer [43]. The CDKs have been postulated as a target for anti-inflammatory disorders. In particular, Hallett *et al.* have suggested that induction of apoptosis in inflammatory cells by CDK inhibitors may be anti-inflammatory [44]. Indeed the CDK inhibitor R-roscovitine induced human eosinophil apoptosis [45], although animal studies have since suggested that induction of eosinophil apoptosis does not reduce eosinophilic airway inflammation [46]. Cyclin-dependent kinases inhibitors may also have another problem in terms of side-effects due to non-CDK targets of these inhibitors [47].

More recent work has shown that activating transcription factor-3 (ATF-3) is down-regulated in severe asthmatics compared to mild asthmatics [48]. This group also noted that the presence of corticosteroids enhanced the repression of ATF-3. Given that ATF-3 is a negative regulator of inflammation the authors suggest that agonists of ATF-3 may be therapeutically useful in severe and steroid-resistant asthma.

As highlighted above, the therapeutic efficacy of many compounds targeting enzymes and receptors is limited by their off-target effects. One avenue that may circumvent this problem is to target at the level of microRNAs. MicroRNAs are post-transcriptional regulators of gene expression that can promote mRNA degradation or directly block protein translation. Recent studies have demonstrated a role for specific microRNAs in the asthmatic airways (reviewed in [49]). Moreover, Collison *et al.* [50] have shown that by blocking MiR-145 using a specific antagomir, airway hyperresponsiveness and eosinophil infiltration were reduced in a mouse model of allergic asthma. Thus, inhibition of microRNAs is emerging as a method for specific delivery of anti-inflammatory therapy.

Conclusions

Asthma is a very complex disease which is made up of a number of disease variants with different underlying pathophysiologies. Given the numerous mediators that may play a role in asthma, targeting a single cytokine or chemokine is unlikely to provide significant and prolonged clinical assistance. Indeed, corticosteroids are effective because they suppress multiple inflammatory mechanisms in parallel. Therefore, after significant efforts, the challenge to treat asthma still remains and the ultimate goal is to target multiple pathways and mediators without multiple side-effects.

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