New and existing pharmacotherapeutic options for persistent asthma and COPD

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ABSTRACT

Asthma and COPD are chronic inflammatory airway disorders with systemic manifestations. The two diseases have different airway inflammation, features of airway remodelling with subsequent pathophysiology and clinical presentation. The international management guidelines recommend stepwise pharmacotherapy depending on disease control and/or disease stage, comprising *relievers* and overall uniform *controller treatment*, despite the heterogeneity across the conditions and treatment response. Despite effective medications *per se,* still too many patients remain uncontrolled and no treatment can definitely cure either of the conditions. This overview includes currently recommended pharmacotherapeutic options with novel and future treatment targets.

KEYWORDS

Asthma, COPD, pharmacotherapy, anticholinergics, beta2 agonists, xanthines, inhaled corticosteroids, leukotriene modulators, PDE-inhibitors, anti-IgE, anti-cytokines

INTRODUCTION

According to GINA (Global Initiative for Asthma, 2010), there are currently over 300 million people suffering from asthma worldwide; the prevalence is still increasing especially among children.[1] Despite overall effective treatment options and uniform management guidelines, there is apparently still room for improvement. Based on a large cross-sectional study involving Asthma Control Test (ACT) scores in almost 8000 adults and over 3000 children from 29 countries worldwide, still too many asthmatics appeared sub-optimally controlled.[2] A similar conclusion can be drawn from the Gaining Optimal Asthma control (GOAL) study, where approximately 30% of almost 3500 patients failed to reach 'optimal' asthma control, despite sustained maximal therapy with the gold standard combination (inhaled corticosteroids and long-acting beta2-agonists)[3] and from more recent studies which reported up to 59% of asthmatics from primary care failing to reach control.[4,5]

Chronic obstructive pulmonary disease (COPD) is a major cause of premature death with approximately 600 million sufferers worldwide.[6,7] The prevalence is raising mainly due to an increasing number of smokers. Epidemiological surveys previously showed that 0.1 to 1.5% of individuals have severe obstructive lung disease, defined as FEV_1 of <50% of predicted.[8] More recent data, notably the PLATINO[9] and the BOLD[10] surveys, highlighted the prevalence of COPD GOLD stage I and onwards of 7.8 to 19.7% in a population of certain Latin Americans and the prevalence of COPD GOLD stage II and onwards of a mean of 10.1% in smokers of a globally more representative population sample, respectively. Few epidemiological studies exist on the prevalence of COPD GOLD stage IV disease, and therefore it is often the opinion that figures on the number of COPD patients at all stages are significantly underestimated.[11-13]

In the past two decades, the development and validation of several non-invasive inflammometric methods and assays has greatly contributed to our understanding of the pathophysiological backgrounds, disease phenotyping and identification of potential targets for customised therapies.[14-17] In the updated GINA guidelines, this

paradigm became manifest as control-directed disease management in contrast to the previous approach based on symptoms and lung function parameters.[1] For COPD, it appears that the level of clinical, pathological and genetic heterogeneity that exists across patients has undermined potential advances in COPD pharmacotherapy. So far, there is no disease-modifying pharmacotherapy available and smoking cessation is the cornerstone of causal COPD management with additional, stage-dependent, mainly one-size-fits-all, symptomatic pharmacotherapy.[6] Given the multifaceted and heterogeneous aetiologies of asthma and COPD, optimal disease management should consist of customised treatment following accurate phenotyping. Such customised or phenotype-directed therapy should include targeted pharmacotherapy, combined with patient education, lifestyle adjustments, avoidance of noxious airway irritants, co-treatment of comorbidities and (if needed) additional therapies (revalidation, oxygen, etc.) along with adequate monitoring of the effects of disease management.[18]
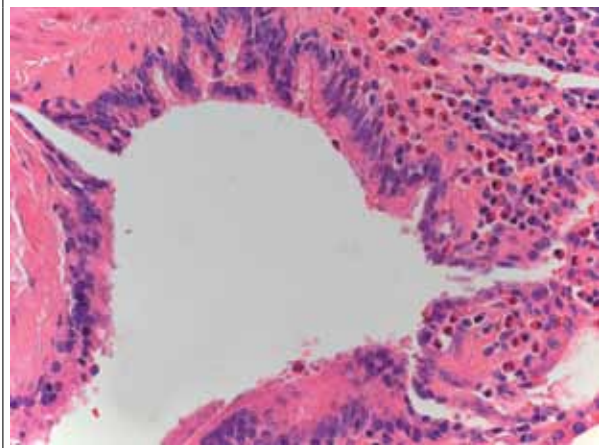
In this review we aim to provide a link between disease subsets of chronic inflammatory (obstructive) airways disease to current treatment options according to international guidelines and to some novel, (targeted) pharmacotherapeutic modalities.
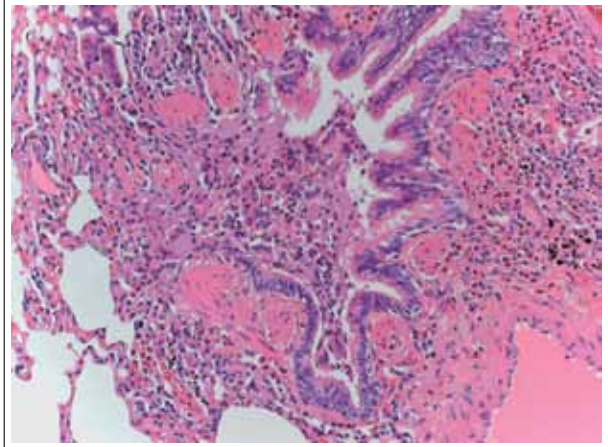
FROM PATHOGENESIS TO TARGETED TREATMENT

Background

Both asthma and COPD are chronic inflammatory airways diseases, although there are local and immunological differences (*figures 1A-C*). Apart from

Figure 1B. *Bronchial biopsy from an asthmatic patient showing eosinophilic infiltration and hyperplastic bronchiolar smooth muscle*
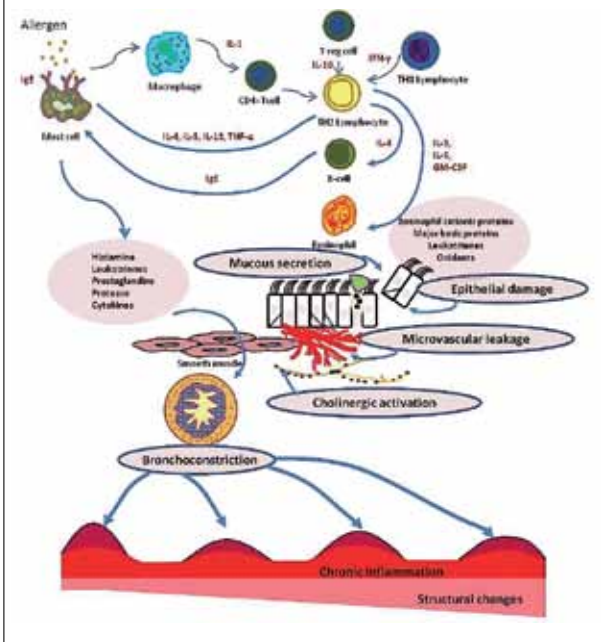

Figure 1C. *Bronchial biopsy taken from a patient with chronic bronchitis, showing epithelium with goblet cell metaplasia and increased number of inflammatory cells, particularly lymphocytes (left corner) and hyperplastic smooth muscle*

Figure 1A. *Bronchial biopsy from a steroid-naive asthmatic patient: Bronchial wall shows extensive eosinophil infiltration and thickening of the basement membrane*
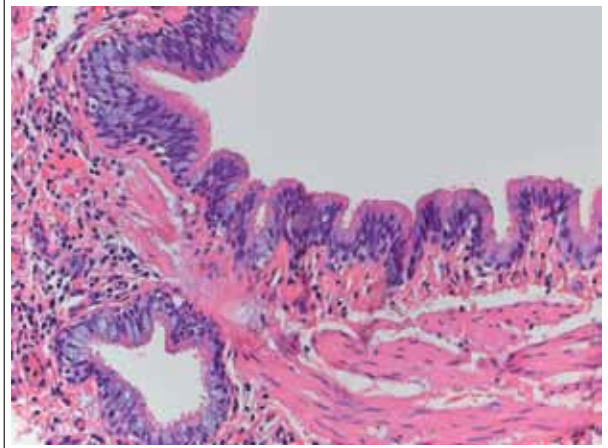
their local presentations, both conditions possess systemic components. Asthma is often associated with allergy. The airway inflammation in allergic asthma is predominantly T-helper 2 cell-driven with mast cells, eosinophils and basophils as the key effector cells (*figure 2*). In more severe asthma other inflammatory mechanisms (Th-1-cells, neutrophils) and structural cell defects (e.g. epithelial and airway smooth muscle cells) may prevail while comorbidities (e.g. obesity, smoking, etc.) often play an important role in its pathophysiology.[14,19-21] In some asthmatics, inflammatory markers, such as allergen-specific IgE, cysteinyl leukotrienes, IL-5 and TNF-alpha, were shown to play a prominent role in the pathophysiology of their asthma.[14] Targeting these

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Figure 2. *Th-2 cell driven airway inflammation in allergic asthma*

inflammatory markers may offer attractive treatment options in some asthma phenotypes.[22] Within the asthmatic airways, inflammatory events along with structural changes ('airway remodelling') have been shown to induce airway hyperresponsiveness to (non) specific stimuli, and if untreated, to produce variable symptoms, exacerbations and pathophysiological signs.[1] Within an asthmatic individual, the degree of bronchoconstriction (generally measured by FEV1 and expressed as % of predicted value or by FEV1/FVC ratio) may vary over time. Depending on asthma control, lung function can be within normal ranges or reduced to some degree, although mostly fully reversible.[1] During the last decade, small airway involvement in uncontrolled asthma and COPD has drawn increasing attention.[23,24] Clinical outcomes that have been found to correlate with uncontrolled small airway inflammation include exacerbations, exercise-induced bronchoconstriction and nocturnal asthma. Targeting the small airways has become part of treatment strategies through the development of small particle formulations inhaled by innovative devices and systemically active compounds along with the introduction of several tools for monitoring of the small airways function and inflammation.[23]

Emphysema and chronic bronchitis are two major subsets of COPD. Tobacco smoking is a major aetiological factor in the pathogenesis of COPD, which clinically presents with progressive dyspnoea, (productive) cough and a fixed, progressive bronchoconstriction and hyperinflation with declining lung function.[6] Clinically, it may be difficult to

discriminate some asthma subsets – especially smoking asthmatics – from full-blown COPD.

Within the chronic airway inflammation of COPD, macrophages, CD8+ T lymphocytes and neutrophils are the key effector cells, releasing toxic mediators contributing to airway destruction and remodelling.[25,26] Destruction of alveolar tissue in emphysema is thought to be caused by the release of proteinases (e.g. matrix metalloproteinase from alveolar macrophages) or as a consequence of an autoimmune response (e.g. CD8+ T lymphocytes).[27,28] Goblet cell hyperplasia and enlargement of submucosal glands contribute to the excessive mucus production especially seen in chronic bronchitis. Peribronchiolar fibrosis within distal airways can induce disruption of the parenchymal attachments to small airways promoting collapse on expiration and hyperinflation.[29]

Asthma severity and phenotypes

Steroid-naive asthma can be classified according to its severity based on variability in symptoms and bronchoconstriction, ranging from intermittent to (mild, moderate and severe) persistent.[1] In general, milder forms are associated with allergy, characterised by a T-helper 2 cell-driven profile with often high levels of specific IgE, airway eosinophilia and increased release of cysteinyl leukotrienes (*figure 2*).[30] In up to 80%, allergic asthma is associated with allergic rhinitis and often becomes manifest at a younger age.[31] This phenotype generally responds well to standard therapy consisting of allergen avoidance and inhaled corticosteroids and/or leukotriene modulators and anti-IgE.[1,31] In contrast, the severe persistent or 'refractory' phenotype is a more heterogeneous disorder, which can be subdivided into several clinical subsets with different (e.g. Th-1 driven, neutrophilic) or more pronounced airway inflammation (small airways) and/or structural cell defects (e.g. epithelial and airway smooth muscle cells), often associated with comorbidities (*table 1*).[14,19-21,23,32]

In view of the heterogeneity in clinical presentation, immunopathology and response to treatment, it may sometimes be helpful to include as many asthma determinants as possible for an adequate evaluation.[15-17,33,34] To aid diagnosis and effective treatment, several classifications for asthma phenotyping have been suggested. Although none are fully standardised, a feasible subtyping has been proposed by Sally Wenzel based on clinical or physiological phenotypes, phenotypes related to triggers and phenotypes related to the predominant inflammatory airway response (*table 1*).[14] Inevitably, there is a substantial overlap across the phenotypes and novel detection techniques in preferably non-invasive airway samplings should help to link the underlying immunological substrates to the clinical and pathophysiological presentation to accurately define an individual's

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Table 1. *Asthma phenotypes and targets, modified from references 14, 21,and 23*

Clinical or physiological phenotypes
Defined by age of onset
Defined by asthma severity
Defined by chronic restriction
Exacerbation prone/brittle asthma
Treatment-resistant/refractory asthma

Phenotypes defined by:
External triggers
Exercise and cold, dry air
Ozone
Environmental allergens, respiratory viruses and irritants
Occupational allergens or irritants
Oxidative stress-inducers: (passive) tobacco smoke, air pollution, airway infections
Aspirin or non-steroidal anti-inflammatory drugs
Interfering drugs (e.g. beta-blocking agents, ACE inhibitors)

Endogeneous factors and comorbidities
Chronic rhinosinusitis
Hormonal (e.g. menses)
Obesity
Gastro-oesophageal reflux disease
Psychosocial and emotional factors (disease understanding and awareness, stress, compliance)

Inflammatory phenotypes
Cellular
Eosinophilic
Neutrophilic
Mixed cellularity
Pauci-granulocytic

Predominant mediators
Cysteinyl leukotrienes
Prostaglandins
IgE
IL-5
TNF-alpha

Important structural determinants
Epithelial cells
Dendritic cells
Glandular cells
Airway smooth muscle cells
Small airways

COPD severity stages and clinical phenotypes

In analogy with GINA, COPD is staged according to the severity of symptoms and (postbronchodilator) lung function impairment in GOLD stages I-IV.[6] Tobacco smoking is the major inducer and therefore smoking cessation is the cornerstone in the management of all COPD stages. Similarly to asthma, COPD also represents a heterogeneous group of airway disorders, with emphysema and chronic bronchitis as the commonly known clinical phenotypes (*table 2*).[6] A recent proposal by a workgroup suggests COPD phenotyping by disease determinants including clinical presentation, response to therapy, frequency of exacerbations, systemic presentation, pathophysiological parameters, radiological characterisation and inflammatory markers to enable identification of prognostic and therapeutic subgroups.[36] This approach awaits validation.

The key COPD characteristics include chronic inflammation of the proximal and distal airways, driven

Table 2. *Major determinants of COPD phenotypes*

Clinical, physiological phenotypes and comorbidities
Emphysema
Chronic bronchitis
Defined by COPD severity
Frequent exacerbator
Bullous emphysema
Concomitant asthma
Respiratory failure (hypercapnia/hypoxia)
Cardiac failure (right/left ventricle)

Phenotypes defined by:
External triggers
Cigarette smoking (history)
Occupational dust, vapours and fumes (e.g. indoor air pollutants, coal, straw, animal dung, crop residues and biomass fuel)
Oxidative stress-inducers: air pollution, airway infections

Endogeneous factors
Alpha1- antitrypsin deficiency

(Systemic) inflammatory phenotypes
Cellular
Neutrophilic
Macrophages
Epithelial cells/fibroblasts/fibrocytes

Soluble inflammatory markers
C-reactive protein
Serum amyloid A
Leukotriene B4
Proteases
Mucines (MUC5AC)
IL-1, IL-6, IL-8, TNF-alpha

phenotype and customised (targeted) therapy.[33,35] Recently, a large international project entitled 'Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes' (U-BIOPRED), initiated by Sterk and colleagues, has started and its aim was to identify, analyse and validate biomarkers for phenotyping and customised treatment of severe refractory asthma.[35]

by several inflammatory cells and mediators and associated with airway remodelling and tissue destruction.[15,37,38] Within a specified COPD phenotype, these features may clinically present as a combination of one or more of the following symptoms and signs: dyspnoea, mucus hypersecretion, chronic cough with sputum production, fixed airway obstruction, hyperinflation and (frequent) exacerbations. Emphysema is characterised by alveolar wall destruction causing irreversible enlargement of air spaces distal to the terminal bronchioles. Chronic bronchitis is clinically defined as daily cough with (excessive) production of sputum for at least three months, two years in a row.[6,39] Histopathologically, there is evidence of mucus gland hyperplasia with mucus hypersecretion leading to chronic cough and sputum production. In addition, chronic bronchitis also presents with inflammation and swelling of the epithelial lining and submucosa of the airways causing narrowing and obstruction of the lower airways and chronic bronchiolitis. These sequelae typically lead to the increased prevalence of bacterial lung infections manifesting as frequent exacerbations.[40] More recently, evidence was provided that the abnormalities seen in COPD are not only restricted to the airways, but often also systemically present.[41,42]

PHARMACOTHERAPEUTIC OPTIONS FOR ASTHMA AND COPD

Guidelines
Awareness and avoidance of relevant triggers (e.g. tobacco smoke, occupational and domestic irritants, specific allergens, medications and tobacco smoke) is often the first step in the management of both asthma and COPD. Based on the severity or level of disease control, most guidelines pragmatically recommend a one-size-fits-all, stepwise approach to pharmacotherapy, consisting of relievers (bronchodilators) and controllers (immunomodulator and/or anti-inflammatory agents) in combination with treatment of comorbidities.[1,6,31] Although efficacious in some asthma subsets, allergen-specific immunotherapy will not be discussed in this review given its specific scope and currently ongoing innovations.[43]

Current pharmacotherapy and applications
Anticholinergics
Since the late 1970s, anticholinergic drugs have been developed for the treatment of chronic obstructive airway diseases. Ipratropium (Atrovent®, Iprapropium®, Ipraxa®) and the long-acting tiotropium (Spiriva®), marketed in the beginning of the 2000s, antagonise the effect of acetylcholine at the M1 and M3 muscarinic receptors within the airways, resulting in bronchodilation and a reduction in mucus production. The bronchodilator effect usually starts within 15 minutes post-inhalation and lasts for approximately three to eight hours.

Despite a predominant role in the treatment of COPD, anticholinergics may also benefit asthmatics with congenital adverse responses to beta2 agonists—up to 20% of the asthma population.[44] In addition, during an acute exacerbation when response to SABAs may be poor, a combination with an anticholinergic agent generally provides faster relief.[45] In a recent three-way, double-blind, triple-dummy, cross-over study in 210 patients with inadequately controlled asthma, addition of tiotropium to low-dose ICS during 14 weeks of treatment showed comparable therapeutic efficacy to salmeterol and was superior to doubling of the ICS dose.[46] Similarly, in a double-blind, placebo-controlled, parallel study in B16-Arg/Arg patients with uncontrolled asthma, addition of tiotropium to a moderate dose of ICS was comparably effective to salmeterol in maintaining lung function.[47]

In COPD, a combination of a beta2 agonist with an anticholinergic is often applied as part of the maintenance treatment for optimal efficacy and to reduce the occurrence of any side effects (registered fixed combinations: fenoterol/ipratropium (Berodual®), salbutamol/ipratropium (Combivent®, Ipramol®, Ipratropium/salbutamol FNA).

Both ipratropium and tiotropium have a low systemic bioavailability and hence are associated with few systemic side effects. The most commonly reported side effects include dry mouth, acute urinary retention, gastrointestinal problems, arrhythmias and headache.[48,49] Anticholinergics should be used with caution in patients with prostatic problems and in those susceptible to angle-closure glaucoma. Importantly, during the four years of the UPLIFT study, no evidence of increased (death from) cardiovascular events, arrhythmias or stroke was observed in COPD (stages II-IV) patients treated with tiotropium.[50,51] Presently, several long-acting LAMAs are being developed and are in different developmental phases, e.g. *Aclidinium*, LAS35201, GSK656398, GSK233705, NVA237 (glycopyrrolate), ORM3, CHF5407 and QAT370.

Beta2-adrenoceptor agonists
Soon after its launching in 1968, the short-acting beta2-receptor agonist (SABA) salbutamol became the most widely used fast-acting reliever medication for asthma and COPD.[1] The success of salbutamol initiated the development of several other short-acting beta2 agonists (SABAs), including carbuterol, clenbuterol and fenoterol, with a fast onset (within five minutes of inhalation) and with a duration of action up to six hours. A further step came in the 1980s with the development of long-acting beta2 agonists (LABAs). Salmeterol (a partial beta2-adrenoceptor agonist) with a slow onset and a duration of action up to 12 hours, was first launched followed by formoterol (a full beta2-adrenoceptor agonist)

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combining a similar duration of action with an onset of action comparable to salbutamol. Indacaterol (Onbrez®), a partial beta2-adrenoceptor agonist with a similarly fast onset of action as salbutamol and a 24-hour duration of action, was launched in Europe and the USA in the past year and is currently only registered for the treatment of COPD.[52] In the patient studies so far performed, this ultra-LABA has not shown any tachyphylaxis. Presently, several ultra-long-acting LABAs (ultra-LABAs) e.g. carmoterol, vilanterol trifenatate, olodaterol, GSK-159797 and GSK-642444 with a sustained bronchodilation up to 24 hours are being developed, creating the possibility of once daily dosing.[53] The mechanism of action of beta2 agonists is predominantly bronchodilator through airway smooth muscle relaxation, with modest anti-inflammatory activity encountered in some studies.[54,55]

Current guidelines recommend SABAs as rescue therapy only on (as infrequent as possible) 'as needed' basis.[1] This is based on the insight that asthma is a chronic inflammatory condition and that targeting airway inflammation should be the primary goal in treatment of persistent asthma in contrast to symptom control as the primary focus. Moreover, several studies showed that maintenance therapy with SABAs and LABAs — even if combined with ICS — may potentially mask the airway inflammation.[56,57] In addition, maintenance therapy with LABAs (*plusminus* ICS) has been shown to induce tolerance to their bronchoprotective effects and cross-tolerance to the reliever effects of SABAs.[58-61] Although not a consistent finding,[62] some studies showed a decreased therapeutic response to beta2 agonists in patients with a homozygous variation for arginine (Arg/Arg) at codon 16 of the beta2-adrenergic receptor.[44,63] In patients with this polymorphism, regular treatment with the short-acting beta2 agonist albuterol was associated with a significant decrease in lung function over time.[63] Some of these deleterious effects during long-term use of LABAs with or without an adequate dose of ICS may have resulted in an increased morbidity and even reported asthma deaths.[64] Present guidelines, therefore, recommend maintenance therapy with LABAs only in combination with appropriate doses of corticosteroids in the more severe disease (asthma treatment steps 3-5).[1]

In COPD from GOLD stage II onwards where sustained bronchodilation is required, maintenance therapy with long-acting beta2 agonists is recommended, either alone or in combination with a LAMA.[6] The development of ultra-LABAs represents a promising advance in the treatment of COPD, enabling (future) combinations with a LAMA, and providing superior efficacy through improved patient convenience and compliance.

Xanthines

Several xanthines are known to positively affect the breathing function, including aminophylline and to a lesser extent caffeine and theobromine. From the late 1930s until the 1970s, theophylline, a weak and nonselective phosphodiesterase (PDE) inhibitor, became the most widely prescribed reliever for obstructive airway disease.[65,66] Although theophylline is known to offer a substantial bronchodilation within the (narrow) therapeutic range (approximately 10 to 20 µg/ml), serious side effects inevitably occur at higher plasma levels.[66] The most common adverse reactions include cardiovascular side effects (arrhythmias), gastrointestinal (nausea) and CNS symptoms (headache, seizures).[66,67] These disadvantages and the advent of the superior beta2 agonists and tiotropium resulted in theophylline's relegation to second/third line (asthma and COPD) treatment option in developed countries during the 1980s.[68-70] In recent years, interest in the xanthine derivatives has revived due to their oral formulation, low cost and the discovery of the PDE-receptor subtypes. Moreover, some evidence pointed to potential anti-inflammatory activity,[71,72] partly through the suppression of the inflammatory gene transcription by activation of histone deacetylase2 (HDAC2), which is the key target for corticosteroids.[73] This mechanism may explain the beneficial effects on asthma control reported by several investigators when combining (low-dose) theophylline with inhaled corticosteroids (ICS).[74,75] Recently, additional anti-inflammatory effects have been reported, including the acceleration in eosinophil apoptosis and the decrease in recruitment of lymphocytes and neutrophils into the airways.[71,76] These properties may be promising in the treatment of severe asthma and COPD. Although initially classified as a nonselective PDE inhibitor, the pharmacological effects of theophylline appear much broader and include, among others, antagonism of adenosine and phosphoinositide-3 kinase (PI3K).[77,78] Oral slow-release tablets (theolair) are the commonly available formulation of xanthines, usually prescribed in a twice daily maintenance dose. In parallel with the renewed interest in theophylline and the discovery of several PDE (receptor) subtypes, there has been development of more specific PDE inhibitors for the treatment of chronic inflammatory/obstructive airway disease in the last decade – see section below.[79] Targeting PDE-3 has been shown to produce bronchodilation.[80] Future studies in asthma applying combined PDE inhibitors (e.g. PDE3/4) should demonstrate their putative superior effectivity.[80]

Inhaled corticosteroids

In the early 1970s, the first topically active, aerosolised corticosteroid, beclomethasone dipropionate (BDP), was registered for treatment of inflammatory airways diseases.[81,82] This inhaled ICS showed efficacy in the treatment of asthma without the adverse effects associated with systemic corticosteroids. However, the widespread

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use of ICS came some 20 years later, most likely as a result of the paradigm switch that asthma is an inflammatory disease and the subsequent effect on the concurrent guidelines for asthma treatment.[1]

Presently, inhaled corticosteroids are the first-choice controller agents for the treatment of persistent asthma.[1] The beneficial effects are mediated through interaction with intracellular corticosteroid receptors present within several cells, resulting in suppression of inflammatory gene transcription and activation of anti-inflammatory gene transcription.[83,84] Prolonged treatment with ICS produces sustained anti-inflammatory efficacy with subsequent improvement in asthma control both in adults and children.[85,86] However, ICS are less effective in patients with severe asthma and in COPD, partly due to the different inflammation (neutrophilia) and extensive structural changes within the airways, inability to (sufficiently) reach all parts of the airways, comorbidities or exogenous factors.[23,87] Particularly, tobacco smoke is known to induce oxidative stress with subsequent airway neutrophilia and the down-regulation of histone deacetylase (HDAC2) activity, thus contributing to corticosteroid resistance.[88]

In COPD, guidelines recommend ICS as maintenance therapy from GOLD stage III (with frequent exacerbations) and onwards in spite of their questionable long-term efficacy.[6] The dry powder and pressurised metered-dose inhalers contain either a mono-compound (beclomethasone, fluticasone, mometasone, ciclesonide or triamcinolone) or a combination with a LABA. The (fixed) combination of a corticosteroid with a LABA has prompted a number of studies which showed notable improvements in FEV1[89-92] and HRQoGRL, including a reduced decline in FEV1 and exacerbations in COPD patients (GOLD stages II-III) over time.[93-95] Although most studies have been unable to demonstrate a significant or clinically meaningful reduction in the FEV1 decline in the long term, two recent large studies, TORCH[96,97] and GLUCOLD[98], examining the long-term clinical efficacy of the fixed combination ICS and LABA in COPD (stages II-III), came close to challenging this premise. In contrast to placebo and both monotherapies, the TORCH data suggest a synergy between fluticasone (FP) and salmeterol reflected in superior efficacy on several disease-related parameters including the FEV1 decline; however, the primary parameter, i.e. reduction in mortality after long-term use of the combination, failed to reach statistical significance.[96,97] In addition, the GLUCOLD study clearly showed that corticosteroids with or without LABA effectively reduced inflammatory cells in sputum and bronchial biopsies while slowing down the decrease in FEV1 in some COPD subsets.[98] A subanalysis[99] showed that different inflammatory phenotypes within COPD may respond differently to (gold standard) pharmacotherapy.

These findings warrant characterisation of inflammatory phenotypes within COPD to enable customised (targeted) treatment modalities.

In the past two decades, modification of the initial compounds and inhalers increased their potency and first-pass metabolism in combination with an improved lung deposition. Presently, available ICS differ little in clinical efficacy and side effects: fluticasone and budesonide being the most widely used alone or in combination with a LABA in one inhaler device. The most recently launched innovative ICS is ciclesonide, which is delivered as an inactive prodrug.[100] The pharmacological properties of ciclesonide in combination with the inhaler properties (solution-based HFA MDI) and small particle size result in an optimal lung deposition and distribution including the small airways with an overall low systemic bioavailability.[101] Based on its pharmacokinetic and pharmacodynamic properties, ciclesonide combines the advantages of a prolonged activity (once daily use) with less (local and systemic) side effects which may positively affect patient compliance.[100,102,103] Like most of its competitors, ciclesonide produces comparable improvement on asthma control and QoL across all disease severities.[103]

ICS-related side effects can manifest both locally and systemically. The most commonly reported local side effects comprise of oral candidiasis, hoarseness and dysphonia,[104] while systemic side effects, such as easy bruising, cataract and osteopenia, are usually restricted to chronic use of high ICS doses.[87,105]

Although ICS cannot cure chronic inflammatory airway diseases, they are the mainstay of anti-inflammatory therapy for these conditions. Addition of a LABA may potentiate anti-inflammatory activity of ICS.[106,107] The currently available fixed ICS/LABA-combinations include: fluticasone propionate/ salmeterol (Seretide®/Advair®/Adoair®) budesonide/formoterol (Symbicort®) and beclometasone/formoterol (Foster®).

Future compounds in this drug class presently under development now focus on a favourable therapeutic index including small airway deposition and once daily dosing. The novel once-daily combination of fluticasone furoate/ vilanterol trifenatate (Revolair™), now in phase III, is aimed to eventually supplant Seretide.

Targeted pharmacotherapies
Leukotriene modulators
Leukotrienes (LTB4, LTC4, LTD4, LTE4) are pro-inflammatory mediators, synthesised from arachidonic acid via the 5-lipoxygenase (5-LO) metabolic pathway. Especially the cysteinyl leukotrienes (CysLTs: LTC4, LTD4, LTE4), synthesised by activated mast cells and eosinophils, have been shown to play an important role in the pathophysiology of several asthma phenotypes, including 'asthma rhinitis' and aspirin-exacerbated airway

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disease (AERD).[108,109] CysLTs possess pro-inflammatory, broncho and vasoactive properties and have been shown to induce several features of asthma, including airway inflammation and airway hyperresponsiveness, both in healthy subjects and in asthmatics. These observations have driven the development of several anti-leukotriene agents in the 1980s-1990s as the first systemically active, targeted therapy for asthma.[110] Two main categories of leukotriene modulators have been developed and mainly evaluated in asthmatics: leukotriene synthesis inhibitors (LTSI), i.e. 5-LO-inhibitors and 5-LO activating protein (FLAP) inhibitors that block the synthesis of all leukotrienes at the 5-LO level and leukotriene receptor antagonists (LTRA) that inhibit the effects of CysLTs at the CysLT1 receptor.[108] As opposed to the gold standard (ICS) controller therapy, leukotriene modulators possess targeted activity that acts throughout the entire bronchial tree, which is from the upper airways down to the small airways, thereby combining anti-inflammatory (mainly anti-eosinophilic) properties with (modest) bronchodilator and bronchoprotective effects against nonspecific and specific stimuli.[111,112] So far, zileuton (Zyflo™) is the only LTSI licensed for the treatment of asthma in USA only. Due to its modest potency and potential liver toxicity, this four times daily oral drug has now been largely superseded by the more potent, LTRAs (zafirlukast (Accolate®) and montelukast (Singulair®), respectively) with more favourable safety and pharmacokinetic profiles.

To date, montelukast is the most widely used leukotriene modulator for the treatment of asthma and has been prescribed to over 25 millions of patients including approx. 6.5 millions of young children. Both as monotherapy and in combination with inhaled corticosteroids, montelukast showed clinical efficacy in asthmatic patients, improving symptoms, lung function, exacerbation rates and quality of life in both adults and children.[109,113] Several studies provided evidence that addition of an LTRA can improve several aspects of asthma especially in CysLT-driven asthma-phenotypes, such as with asthmatic patients with concomitant allergic rhinitis.[114-116]

The most commonly described side effects are generally mild and comprise headache, flu and gastrointestinal complaints. Neuropsychiatric events, including anxiety, depression and suicidality, were reported in rare cases but appeared unrelated to montelukast.[109] In addition, Churg-Strauss syndrome (CSS) has been mentioned in relationship to treatment with montelukast; however, the incidence is similarly low to that in the general population and often associated with tapering off of oral corticosteroids in the more severe asthma.[109]

GINA guidelines recommend low-dose ICS or a leukotriene modifier as controller therapy in step 2 of the asthma management in adults and children older than 5 years.[1] In the subsequent treatment steps 3 and 4,

a leukotriene modifier is included as add-on therapy to ICS.[1] Similar recommendations are made by paediatric GINA guidelines, advocating a leukotriene modifier as an alternative to low-dose ICS for the first controller step and as add-on therapy for the subsequent treatment steps in children aged 5 years and younger.[117] According to Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines, LTRA should also be considered in patients with allergic rhinitis with or without concomitant asthma.[31]

So far, no leukotriene modulators have been implicated in the treatment guidelines of COPD.[6] In COPD, LTB4 plays a more prominent role than CysLTs, and hence, LTSI may be more effective in COPD than LTRA.[118,119] Presently, there is an interest in leukotriene modifiers and there are several compounds under development, e.g. the FLAP inhibitor GSK2190915 (AM103) and the 5-LO-inhibitors Setileuton and MK-0633 aimed for treatment of conditions including (severe) asthma and COPD.[120-122]

Selective PDE inhibitors

Phosphodiesterases form a superfamily of at least 11 isoenzymes (PDE1-11), which are involved in several biological and inflammatory processes within the human body. Each iso-enzyme has a unique tissue subdivision and different properties allowing targeted therapy with potentially fewer systemic side effects especially when compared with nonselective PDE inhibition.[123] In the past two decades, there is increasing interest in the development of selective PDE inhibitors for potential treatment in asthma and/or COPD.[124] Especially the PDE4 isoenzyme seems a promising target for anti-inflammatory and disease-modifying therapy as it regulates the function of several immune, inflammatory (neutrophils, macrophages) and structural cells (e.g. airway smooth muscle) involved in the pathophysiology of chronic inflammatory and obstructive airways disease.[123] So far, the majority of the clinical COPD studies have been performed with the second-generation oral PDE4 inhibitors cilomilast and roflumilast, of which roflumilast combines a superior pharmacological profile (once daily dosing) with a favourable therapeutic index.[124] In several preclinical studies, selective roflumilast reduced neutrophilic inflammation and features of airway remodelling (see Rabe and the references therein).[125]

Although the result of the early phase III findings showed consistent but small improvements in lung function, the effects on exacerbations remained inconclusive.[126] A post-hoc analysis of these studies revealed a defined subset of COPD patients likely to benefit from roflumilast, with severe COPD associated with chronic bronchitis.[127] This hypothesis was subsequently tested in two randomised, controlled one-year phase III studies of identical design.[128] In these studies, in patients with chronic bronchitis, severe airway flow limitation and a history of frequent

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exacerbations, treatment with roflumilast significantly reduced moderate to severe exacerbations and was again superior to placebo on lung function parameters. This efficacy was independent of concomitant treatment with LABA.[128]

In two supplementary six-month studies in patients with COPD with moderate to severe airway flow limitation, roflumilast (500 µg once daily) provided incremental improvements in pre- and post-bronchodilator FEV1 when given on top of salmeterol or tiotropium, respectively.[129] The most commonly reported roflumilast-related side effects include headache, insomnia, nausea, diarrhoea and weight loss (mean 2.1 kg). The majority were mild to moderate in intensity, appeared early but resolved over time.[128,129]

So far, no studies have compared the efficacy of roflumilast versus ICS. However, a recently published post-hoc analysis of the sub-group of patients concomitantly treated with ICS in the early phase III trials showed a significant incremental effect of roflumilast on both exacerbations and lung function.[127] Given the presence of a (relative) corticosteroid resistance in COPD, mainly caused by the reduction of HDAC2 activity by oxidative stress,[130] it seems logical that restoring the HDAC2 activity with PDE inhibitors, phosphoinositide-3 kinase-delta (PI3Kδ) inhibitors and macrolides could reverse the corticosteroid resistance and result in synergistic activity.[130]

So far, roflumilast (Daxas® (Europe), Daliresp™ (USA)) has been approved in several countries including the European Union (EU), USA and Canada. Presently, roflumilast (500 µg once daily) is recommended for COPD stages III and IV with a history of chronic bronchitis and frequent exacerbations as add-on therapy.[6]

Targeting other PDE isoenzymes (combinations) for application in chronic inflammatory airway disease is presently being studied. PDE3 inhibition produces bronchodilation.[131] Future studies with combined PDE3/4 inhibitors should demonstrate their putative effectivity in asthma and COPD.[132]

Anti-IgE

Immunoglobulin E (IgE) plays a pivotal role in the allergic inflammation and mediates its effects through binding to a high affinity IgE receptor (FcεRI), primarily found on mast cells, basophils and dendritic cells. Alternatively, IgE may be linked to a low affinity receptor (FcεRII, CD23) on T cells, B cells and monocytes.[133] Cross-linking of the FcεRI receptor causes the release of a number of potent inflammatory mediators, while the low-affinity receptor is mainly involved in regulation of the immune response. Several studies have shown a close relationship between increased serum IgE levels and the prevalence of bronchial hyperresponsiveness and/or asthma.[134]

Omalizumab is a humanised, monoclonal IgG1 antibody (moAb) directed to the site of the Fc portion of free IgE, thus preventing the interaction with the human IgE receptors and the subsequent IgE-facilitated allergen uptake and inflammation. Applying total serum IgE (combined with body weight) for dose selection and frequency makes omalizumab the first asthma treatment based on a biomarker approach. In a large number of studies in both adult and paediatric patients with moderate to severe persistent allergic asthma, omalizumab (subcutaneously every two to four weeks) effectively reduced serum IgE levels resulting in sustained improvements in disease control and quality of life (see Di Domenico et al., and the references therein).[135] Apart from allergic asthma, omalizumab showed clinical efficacy in several other IgE-driven conditions including rhinosinusitis, conjunctivitis and bronchopulmonary allergic aspergillosis.[136]

Omalizumab (Xolair®) was first registered in Australia (2002) and subsequently in most countries worldwide. Its clinical indications and applications for persistent allergic asthma vary between countries, largely driven by economic factors. Substantial treatment efficacy is achieved in approximately one third of the patients, while one third show little or no response. Presently, it is unknown what distinguishes responders from non-responders and hence, efficacy should be evaluated after an initial trial of 16 weeks (see Di Domenico et al., and the references therein).[135] The most currently reported side effects ascribed to omalizumab include local symptoms (pain, bruising), while anaphylaxis has been reported in up to 0.2% and may occur within 24 hours of injection.[137]

Current guidelines recommend omalizumab as add-on therapy in step 5 for the treatment of patients (≥12 years) with moderate to severe persistent allergic asthma, with or without concomitant allergic rhinitis, uncontrolled despite optimal pharmacological treatment in combination with appropriate allergen avoidance.[1,31] Recent evidence also suggests some efficacy in non-allergic asthma,[138] which is in line with previous observations but requires further exploration. Another potential application includes combined use of the anti-IgE moAb with allergen-specific immune therapy for increased safety and efficacy.[139] Presently, developments to improve the efficacy of anti-IgE approaches are ongoing (see Holgate and the references therein).[22].

Anti-cytokines

Several cytokines have been implicated in the inflammatory cascades within the different asthma and COPD phenotypes. Some cytokines are disease enhancers while others attenuate the disease.[140] The cytokine network is complex and includes a substantial overlap and redundancy. Th2-pathway derived cytokines, including IL-4, IL-5 and IL-13, play an important role in allergic asthma associated with eosinophilic airway inflammation,

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while e.g. TNF-α prevails in severe persistent asthma and COPD characterised by airway neutrophilia is linked to corticosteroid refractoriness.

In the last decade, an increasing number of anti-cytokine approaches have been explored, but so far, none of these strategies have fulfilled the criteria of clinical applicability.[22]

Interestingly, after initial conflicting results in allergic asthma,[22,141] the anti-IL-5 moAb mepolizumab (750 mg i.v. monthly), showed treatment efficacy in patients with severe refractory asthma with persistent sputum eosinophilia by significantly reducing the number of exacerbations along with improvement of other asthma endpoints and by allowing their oral corticosteroids to be tapered off.[142,143] Large clinical trials testing anti-IL-5 approaches in severe persistent asthma are presently ongoing and should provide a conclusive answer on this treatment strategy in this disease subset.[22]

Other novel cytokine targets include IL-9, IL-13, IL-17, IL-25 and thymic stromal lymphopoietin. Presently, an increasing number of approaches directed against these cytokines are being tested in several clinical trials of severe persistent asthma.[22,140]

Apart from offering an innovative treatment approach, anti-cytokine therapy has several drawbacks: (often) a limited efficacy as a result of substantial overlap within the inflammatory cascade, potentially hazardous side effects in the case of more upstream or multi-functional targets and high production costs. Perhaps targeting more than one (downstream) cytokine pathway can offer sufficient treatment efficacy along with an acceptable safety. In addition, more cost-effective antibody production strategies include peptide-based vaccination or the induction of neutralising antibodies requiring lower doses.[144,145]

Future treatment strategies

Treatment options for asthma and COPD are evolving rapidly with the increasing insight into the basic mechanisms of both disorders. Several biologicals directed against different components of the airway inflammation, currently in various clinical stages, are expected to offer alternative treatment options for patients unresponsive to conventional therapies. CRTH2 (chemoattractant receptor-homologous molecule expressed on T-helper type 2 cells) blockade represents a novel upstream anti-inflammatory approach that may provide an alternative to inhaled corticosteroids. Presently, many orally active CRTH2 receptor antagonists are in various clinical development stages and the first results in (eosinophilic) asthma appeared promising.[146,147]

Furthermore, approaches targeting disease-related mechanisms other than the airway inflammatory process have been proposed. In particular, preventive strategies aimed at increasing airway resistance to environmental insults and their subsequent interaction with the airway epithelium may have sustained clinical efficacy.[22] Alternatively,

prenatal factors shaping pro-asthmatic phenotypes could help to identify critical pathways for customised therapy.[22] Modulation of various (patho)physiological processes, including lung ageing,[148,149] tissue repair,[150] proteolysis,[151] airway smooth muscle hyperproliferation[152] and fibrosis[153] could also contribute to future treatment options. To date, there have been several advances in anti-infective and anti-oxidant approaches to supplement existing treatments of asthma and COPD, especially, addressing mechanisms which suppress inflammatory genes – independently of HDAC2 - thereby dealing with corticosteroid insensitivity in certain phenotypes.[154] Targeting cell signalling pathways and transcription factors by inhibition of e.g. p38 mitogen-activated protein kinase (p38 MAP-kinase), nuclear factor-kappaB (NFκB), inhibitory factor-kappaB kinase (IKK-2) or phosphoinositol-3-kinase (PI3K) δ may offer potentially effective treatment alternatives, although systemic inhibition of these ubiquitous molecules is anticipated to induce serious side effects, which precludes their systemic application.[155-158] The majority of these novel treatment strategies are in preclinical phase and await clinical validation.

SUMMARY

Both asthma and COPD are highly heterogenic, chronic inflammatory airway diseases.[159] Although corticosteroids, often combined with long-acting bronchodilators, represent the mainstay pharmacotherapy in milder disease, they are much less effective in severe persistent asthma and COPD. In addition, ICS do not cure any of these conditions. So far, targeted approaches through anti-mediator drugs, including leukotriene modulators and selective PDE4 inhibitors, have shown clinical efficacy in specified disease phenotypes only. Biologicals, except for anti-IgE, so far, have not met the general expectations in clinical studies as predicted from animal models and human in vitro tests. As part of future customised treatment strategies, accurate phenotyping should help to identify key (inflammatory) components within a certain disease subset both as targets and for monitoring of innovative therapies. The evidence of asthma and COPD as potentially systemic conditions calls for the development of systemically active drugs without intolerable side effects. Overall, integrated approaches may be needed to combat the conditions at a more multifaceted level, potentially implying combinations of different treatment strategies.

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