New and developing non-adrenoreceptor small molecule drugs for the treatment of asthma

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ABSTRACT

Introduction

Inhaled corticosteroids (ICS) alone or in combination with an inhaled long-acting beta$_2$-agonist (LABA) are the preferred long-term treatment for adults and adolescents with symptomatic asthma. Additional drugs include leukotriene-receptor antagonists, slow-release theophylline and the long-acting muscarinic antagonist (LAMA) tiotropium (approved in 2015). There is a need for more effective therapies, as many patients continue to have poorly controlled asthma.

Areas covered

New and developing long-acting non-adrenoreceptor synthetic drugs for the treatment of symptomatic chronic asthma despite treatment with an ICS alone or combined with a LABA. Data was reviewed from studies published up until November 2016.

Expert opinion

Tiotropium improves lung function and has a modest effect in reducing exacerbations when added to ICS alone or ICS and LABA. The LAMAs umeclidinium and glycopyrronium are under development in fixed dose combination with ICS and LABA. Novel small molecule drugs, such as CRTH2 receptor antagonists, PDE$_4$ inhibitors, protein kinase inhibitors and nonsteroidal glucocorticoid receptor agonists and 'off-label' use of licensed drugs, such as macrolides and statins are under investigation for asthma, although their effectiveness in clinical practice is not established. To better achieve the goal of developing effective novel small molecule drugs for asthma will require greater understanding of mechanisms of disease and the different phenotypes and endotypes of asthma**.**

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KEYWORDS

Asthma; CRTH2 antagonist; CXCR2 antagonist; Inhaled corticosteroid; Long-acting $beta_2$-agonist; Long-acting muscarinic antagonist; Macrolide; Phosphodiesterase inhibitor; Protein kinase inhibitor; Selective glucocorticoid receptor modulator; Statin; Theophylline

1. INTRODUCTION

Asthma is a chronic inflammatory disease of the airways that affects over 300 million people worldwide, of whom 80% are adults and adolescents. The Global Initiative for Asthma (GINA) guideline for the pharmacological treatment of adults and adolescents with asthma recommends a step-wise approach to control symptoms and minimize future risk (Figure 1) [1]. Daily low dose inhaled corticosteroid (ICS) is the preferred treatment option for mild persistent asthma [1, 2] as ICS improves asthma control and lung function as well as reduces the risk of exacerbations and death [3, 4]. At step 3, the combination of low dose ICS and inhaled long-acting beta$_2$-agonist (LABA) is recommended. The safety of LABAs for the treatment of asthma has been a major focus for discussion, although recent new research has provided reassurance that LABAs can be used safely in combination with ICS [5, 6]. Alternative less effective add-on options to a LABA are leukotriene-receptor antagonists and low dose theophylline [7]. At Step 4, the combination of a medium dose ICS and LABA plus as-needed short-acting beta$_2$-agonist or low dose ICS and formoterol combination as maintenance and reliever treatment are recommended as first-line options. Add-on therapies for patients with uncontrolled asthma despite using the combination of a medium or high dose ICS and LABA are leukotriene-receptor antagonists and sustained-release theophylline, although evidence for their efficacy is based on clinical trials in patients receiving ICS alone and not when combined with a LABA. The long-acting muscarinic antagonist (LAMA) tiotropium was included in the 2015 GINA guideline as an alternative add-on therapy for people with a history of exacerbations. After assessment by a specialist, add-on therapies at step 5 include tiotropium, monoclonal antibodies mepolizumab

and omalizumab and low dose oral corticosteroid. The 2016 British Guideline on the management of asthma recommendations on pharmacological treatment are broadly similar to those advocated in the GINA guideline, although the British guideline no longer refers to numerical steps of treatment and uses descriptive terms only for each step [8].

Despite the use of current therapies, surveys indicate that many patients have poorly controlled symptoms and experience frequent exacerbations [9, 10]. Poor asthma control can be due to factors other than uncontrolled disease, such as poor inhaler technique, non-adherence to drug treatment and co-morbidities, and these issues should be identified and managed before adding further treatment. For some individuals, particularly those with severe disease, there is an unmet need for improved therapies. This reviews summarizes the efficacy and safety of new long-acting non-adrenoreceptor synthetic drugs currently used in the clinic or that are under clinical development for patients with poorly controlled chronic asthma despite treatment with ICS alone or combined with a LABA (Table 1). Evidence is obtained from key clinical therapeutic phase III trials, selected phase II trials and studies in 'real-life' populations that were published predominately in the last five years.

2. LONG-ACTING MUSCARINIC ANTAGONISTS

Long-acting muscarinic antagonists (LAMA) competitively inhibit the action of endogenously released acetylcholine at muscarinic (M)3 receptors on airway smooth muscle resulting in prolonged bronchodilation. Additionally, LAMAs may reduce mucus secretion by inhibition of

M3 receptors on submucosal glands and attenuate inflammation by antagonism of muscarinic receptors on inflammatory cells [11]. Antagonising autoinhibitory M2 receptors on vagal nerve terminals could potentially enhance acetylcholine release and thereby increase airway smooth muscle contraction [12], however, slow dissociation of LAMAs from the M3 receptor compared with the M2 receptor preventing LAMAs causing bronchoconstriction [12]. The LAMAs aclidinium, glycopyrronium, tiotropium and umeclidinium are approved for the treatment of COPD [13], whereas tiotropium is the only LAMA currently licensed for the treatment of asthma. Tiotropium (Respimat® SoftMist inhaler) 5 µg daily dose was approved for use in the European Union in 2014 as add-on therapy to maintenance ICS (≥800 µg budesonide or equivalent) plus LABA, in patients aged 18 years who experienced one or more severe asthma exacerbations in the previous year. The Tiotropium Respimat® 2.5 µg daily dose was approved by the US Food and Drug Administration in 2015 for once-daily maintenance treatment of asthma in patients aged 12 years or older. Other countries including Australia, Canada and Japan have approved tiotropium for use in asthma.

2.1 Tiotropium add-on to low and medium dose ICS

A Cochrane systematic review (5 trials, 2563 participants) evaluated the efficacy and safety of adding a LAMA to any dose of an ICS in adults whose asthma was not well controlled by the same dose of ICS and who were not taking a LABA [14]. The addition of tiotropium resulted in 35% reduction in severe exacerbations (odds ratio (OR) 0.65, 95%CI 0.46 to 0.93; 2277 participants; four studies) and an increase in trough forced expiratory volume in 1 second (FEV_1) (140 ml),

but no improvement in asthma control or quality of life scores. The review was not able to conclude whether there were benefits of tiotropium add-on in hospital admissions and all-cause serious adverse events due to the infrequency of these events. Two phase III trials have examined the effects of tiotropium in adolescents with asthma. A 48-week phase III, randomized controlled trial assessed the efficacy and safety of once-daily tiotropium 5 µg or 2.5 µg added to ICS with or without a leukotriene receptor antagonist in 398 adolescents patients aged 12 to 17 years with moderate symptomatic asthma [15]. Tiotropium produced improvements in the primary end-point, peak FEV_1 at 24 weeks (174 ml 95% CI, 76-272 ml) compared with placebo, whereas asthma control questionnaire (ACQ) and asthma quality of life questionnaire (AQLQ) scores were not significantly improved with tiotropium. A 12-week phase III trial assessed the efficacy and safety of once-daily tiotropium 5 µg added to ICS plus one or more controller therapies in 392 adolescents with severe symptomatic asthma [16] and found no significantly improvement in peak FEV_1 or ACQ score compared with placebo [16].

2.2 Tiotropium add-on compared with doubling the dose of ICS

A Cochrane systematic review (1 trials, 210 participants) evaluated the efficacy and safety of adding a LAMA to any dose of an ICS compared with increasing the dose of ICS in adults whose asthma was not well controlled [17]. The review included one cross-over trial of 14 weeks duration [18]. The addition of tiotropium 18 µg once daily (dry powder suspension) compared to doubling low to medium dose of ICS resulted in a significant improvement in the primary outcome, morning peak expiratory flow (PEF) and non-significant reduction in a secondary

outcome, severe exacerbations (OR 0.57, 95% CI 0.22 to 1.43). The addition of tiotropium resulted in an increase in FEV_1 (100 ml) and slight decrease in ACQ score. . Overall, the authors of the systematic review concluded it was not possible to know whether adding tiotropium to ICS is more effective or safer than increasing the dose of ICS [17].

2.3 Tiotropium add-on compared with LABA

Two 24-week, replicate phase III randomized, controlled trials compared the effects on peak and trough FEV_1 response and ACQ-7 score of daily tiotropium 5 µg or 2·5 µg, twice-daily salmeterol 50 µg, or placebo in 1972 participants with symptomatic asthma and a pre-bronchodilator FEV_1 of 60 to 90% predicted despite use of medium-dose inhaled ICS [19]. The addition of once daily tiotropium improved lung function and asthma control to a similar extent as twice daily salmeterol. A Cochrane systematic review (4 trials, including the two replicate trials described above [19], approximately 2000 participants) evaluated the efficacy and safety of adding a LAMA (tiotropium) to ICS compared with adding a LABA (salmeterol) for adults whose asthma not well controlled on ICS alone [20]. The studies were up to 24 weeks in duration. Severe exacerbations were similar in the two treatment groups (OR 1.05, 95%CI 0.50 to 2.18; 1753 participants; 3 studies). Trough FEV_1 was slightly higher in the LAMA group compared to LABA group (50 ml, 95% CI 10 to 90; 1745 participants, 4 studies). ACQ and AQLQ scores were slightly worse with LABA. Adverse events on LAMA were slightly higher, but the difference with LABA was not statistically significant. Overall, the authors concluded that the evidence was not sufficient to advocate LAMA as an alternative for LABA as add-on therapy.

2.4 Tiotropium add-on to medium and high dose ICS and LABA

Two replicate phase III randomized, controlled trials compared the effects on lung function and exacerbations of tiotropium 5 μg or placebo, both delivered by a soft-mist inhaler once daily for 48 weeks, as an add-on to high-dose ICS (≥800 μg budesonide or the equivalent) plus a LABA in 912 adult patients with severe symptomatic asthma [21]. All participants had chronic airflow obstruction (post-bronchodilator $FEV_1 \leq 80\%$ predicted and FEV_1/FVC ratio ≤ 0.7) and gave a history of one severe exacerbation in the previous year.. The primary end-points were peak FEV_1 within 3 hours of drug administration and trough FEV_1, both at week 24, and the time to the first severe asthma exacerbation during 48 weeks. Baseline characteristics of the participants [mean (SD)] were as follows: age, 53 (12) years, ACQ-7 score, 2.6 (0.7), FEV_1 percent predicted after bronchodilation, 62.2 (12.7) and percent of participants with <3 severe exacerbations in past year, 80.9%]. In both trials, the improvement in peak and trough FEV_1 was significantly greater with tiotropium than with placebo. The time to the first severe exacerbation was increased by 56 days with tiotropium compared with placebo (282 days vs. 226 days), with a risk reduction of 21% (hazard ratio, 0.79; p=0.03 in pooled analysis). The total number of severe exacerbations per patient-year was slightly reduced with tiotropium (0.53 tiotropium vs. 0.66 placebo, p=0.046). A consistent improvement in ACQ and AQLQ scores was not found in both replicate studies. A Cochrane systematic review (3 trials, 1197 participants) evaluated the effects of adding a LAMA (tiotropium) to combination ICS and LABA in adults whose asthma was not well controlled by ICS and LABA [22]. The review included the two

replicate trials described above [21] and one phase III trial in which the primary end-point was the number of patients with drug-related adverse events [23]. The addition of tiotropium resulted in 24% reduction in severe exacerbations (OR 0.76, 95% CI 0.57 to 1.02), although the confidence intervals indicated the possibility of no beneficial effect. Small improvements in lung function and asthma control were found with tiotropium, but no improvement in asthma quality of life score.

2.5 Tiotropium in real-life populations

A retrospective study of 2042 adults with asthma recorded in a United Kingdom primary care practice database that were prescribed tiotropium found that in the year after the addition of tiotropium compared with the previous year there was a decrease in the percentage of patients having at least one exacerbation, defined as an asthma-related hospital emergency department attendance or inpatient admission, or acute oral corticosteroid course (37% to 27%, p=0.001) and a reduction in the percentage having at least one acute respiratory event, defined as an exacerbation or antibiotic prescription with a lower respiratory consultation (58% to 47%, p=0.001) [24]. Lung function was unchanged, but there was a small increase in short-acting $beta_2$-agonist use.

2.6 Predictors of efficacy to tiotropium

Airway obstruction and acute bronchodilator reversibility predicted a positive FEV_1 response to tiotropium in adults whose asthma was not well controlled by low-dose ICS and who were not taking a LABA [18, 25]. In this study, neither gender, body mass index, asthma duration, atopic status, serum IgE, sputum eosinophils or fraction of exhaled nitric oxide were predictive [25]. In two replicate phase III trials that compared the efficacy of tiotropium 5 μg or placebo as an add-on to ICS plus a LABA in adults with severe symptomatic asthma [21], a range of baseline characteristics did not predict a beneficial response to tiotropium, including age, gender, race, body mass index, disease duration, FEV_1 percent predicted, reversibility, serum IgE, blood eosinophils and B16-Arg/Arg genotype [26]. In 388 patients with asthma that was not controlled by ICSs alone and who had a B16-Arg/Arg genotype, tiotropium was non-inferior to salmeterol in the change in PEF during 16 weeks of treatment [27].

2.7 Adverse effects of tiotropium

Data on adverse events pooled from seven phase II and III randomized controlled trials of 12 to 52 weeks' duration of once-daily tiotropium 5 μg and 2.5 μg (Respimat) versus placebo as add-on to different background maintenance therapy was reported in 3474 adults with symptomatic asthma, of whom 2157 received tiotropium [28]. The proportion of participants with adverse events was similar between groups. Dry mouth was reported by 1% of the tiotropium 5 μg daily group, 0.4% of the tiotropium 2.5 μg daily group and 0.5% in the placebo group. Cardiac adverse events occurred in 1.4% of patients and were similar between the study groups. Serious adverse events were comparable: 5% in the tiotropium 5 μg daily group, 2% in

the tiotropium 2.5 µg daily group and 3.3% to 4.9% in the placebo groups. The UK Medicines and Healthcare products Regulatory Agency (MHRA) issued a safety update advising prescribers to take the risk of cardiovascular side effects into account when prescribing tiotropium delivered via Respimat or Handihaler to patients with certain cardiac conditions who were excluded from clinical trials of tiotropium including the Investigators in the Tiotropium Safety and Performance in Respimat (TIOSPIR) Study [29]: recent myocardial infarction < 6 months; any unstable or life threatening cardiac arrhythmia or cardiac arrhythmia requiring intervention or a change in drug therapy in the past year; hospitalisation of heart failure (NYHA Class III or IV) within the past year [30]. Tiotropium should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction.

2.8 Umeclidinium

A phase II study of the LAMA umeclidinium in combination with the ICS fluticasone furoate demonstrated a dose-response improvement in trough FEV_1 in adults with asthma compared fluticasone furoate alone [31], whereas consistent bronchodilation was not found in adults with mild asthma who were not receiving ICS [32]. A 52-week phase III parallel group study is underway, comparing the efficacy and safety and of the fixed dose combination of the fluticasone furoate, umeclidinium and the LABA, vilanterol compared with the fixed dose combination of fluticasone furoate and vilanterol in subjects with inadequately controlled asthma despite ICS and LABA maintenance therapy (ClinicalTrials.gov Identifier: NCT02924688) [33] (Table 2).

2.9 Glycopyrronium

Several phase III 52-week parallel group trials are underway, comparing the fixed dose combination of the LAMA glycopyrronium with an ICS (extrafine beclometasone dipropionate or mometasone furoate) and a LABA (formoterol or indacaterol) in patients with uncontrolled asthma receiving medium or high dose ICS and LABA (ClinicalTrials.gov Identifiers: NCT02676076; NCT02676089; NCT02571777) [33] (Table 2).

3. CRTH2 ANTAGONISTS

The chemoattractant receptor-homologous molecule expressed on Th_2 cells (CRTH2) receptor, also known as the prostaglandin D_2 receptor 2 (DP2), is expressed on Th_2 cells, eosinophils, basophils, airway epithelial cells and type 2 innate lymphoid cells [29, 30]. Prostaglandin D_2 activates the CRTH2 receptor to induce chemotaxis and cell activation. The oral CRTH2 receptor antagonists OC000459 and setipiprant both attenuated allergen-induced late asthmatic responses [34, 35] and reduced the associated sputum eosinophilia [34]. In patients with mild asthma not taking ICS, the administration of OC000459 for 4 to 12 weeks produced modest improvements in lung function and asthma control [36], particularly in those with a blood eosinophilia [36, 37]. The oral CRTH2 receptor antagonist BI 671800 administered for 6 weeks to patients with mild asthma produced small improvement in FEV_1 compared to placebo , but the changes were significantly less than those with fluticasone propionate, 440 µg daily [38]. Four weeks treatment with the oral CRTH2 antagonist AZD1981 failed to improve lung function in

patients with asthma after ICS withdrawal or while receiving ICS [39]. An oral dual antagonist of human DP1 and CRTH2 receptors AMG 853, when added to ICS treatment, did not improve symptoms and lung function or reduce sputum eosinophils in patients with poorly controlled moderate to severe asthma [40]. In a phase II trial undertaken in 157 patients with mild to moderate allergic asthma, the oral CRTH2 antagonist fevipiprant (QAW039) did not improve lung function or asthma control, except in a subgroup with more severe airflow obstruction [41]. A recent 12-week phase II exploratory trial investigated the efficacy of the fevipiprant (QAW039) 225 mg twice per day or placebo in 61 patients with persistent, moderate-to-severe asthma and an elevated sputum eosinophil count (≥2%) [42]. The main finding was that sputum eosinophil percentage (primary end-point) decreased from a geometric mean of 5·4% (95% CI 3·1 to 9·6) to 1·1% (0·7 to 1·9) in the fevipiprant group (a reduction of 4.5 times from baseline) and from 4·6% (2·5 to 8·7) to 3·9% (CI 2·3 to 6·7) in the placebo group (a reduction of 1.3 times from baseline group) (difference between groups 3·5 times, 95% CI 1·7 to 7·0; p=0·0014) [42].

In summary, phase II trials of several oral CRTH2 antagonists in mild to severe asthma have shown limited efficacy in improving lung function or asthma control, although preliminary evidence suggests that blood or airway eosinophilia may predictive a beneficial response to these compounds. Phase II trials are underway to examine the effect of the CRTH2 receptor antagonist OC000459 on eosinophilic airway inflammation and asthma control in adults with severe eosinophilic asthma [ClinicalTrials.gov Identifier: NCT02560610] [33] and in preventing or attenuating the symptoms of an asthma exacerbation after experimentally induced rhinovirus infection [ClinicalTrials.gov Identifier: NCT02660489] [33]. Two replicate 52-week phase III parallel

trial are under way to investigate the efficacy and safety of two doses of fevipiprant (QAW039), compared with placebo, when added to patients aged 12 years and older with severe asthma that is uncontrolled on GINA steps 4 and 5 treatment. The primary end-point is reduction in the rate of moderate-to-severe exacerbations in patients with severe asthma and high eosinophil counts and in all patients with severe asthma [ClinicalTrials.gov Identifier: NCT02563067 and NCT02555683) [33] (Table 2).

4. PHOSPHODIESTERASE INHIBITORS

Phosphodiesterase $(PDE)_4$ inhibitors have anti-inflammatory effects on effector cells potentially relevant to the treatment of asthma [43-45]. In a Phase II allergen challenge study, the oral PDE_4 inhibitor roflumilast attenuated the late phase response and the associated rise in sputum eosinophils and neutrophils numbers [46]. An overview of nine phase II and phase III placebo-controlled studies of roflumilast in asthma with a duration of 4 to 24 weeks found a trend for an improvement in FEV_1, although changes reached statistical significant in only three studies [47]. In two phase III trials included in the review, the addition of roflumilast 500 µg daily to low doses of ICSs [beclomethasone dipropionate (BDP) or fluticasone propionate (FP)] found significant improvements in FEV_1 (71 ml) compared to BDP 400 µg daily, but the changes were not significant compared to FP 250 µg daily. The improvement in FEV_1 with roflumilast and BDP 400 were equivalent to BDP 800 µg daily [47]. A phase II cross-over study of roflumilast combined with montelukast in 64 patients with uncontrolled asthma despite treatment with medium dose ICS and LABA combination produced an improvement in FEV_1 (100 ml) at 4 weeks compared to

montelukast alone [48]. A pooled analysis of one open label and ten phase II and III studies of roflumilast at doses of 125, 250, and 500 µg daily for asthma involving 2851 participants reported that headache was the most frequent adverse effect with an incidence of 50 and 29.2 per 100 patients-years in the 500 µg roflumilast and placebo groups respectively [49]. Nausea and diarrhoea were also often associated with roflumilast use.

Inhaled formulation have been developed that may improve the therapeutic index of PDE_4 inhibitors [50-52]. Inhaled PDE_4 inhibitors GSK256066 and CHF6001 both inhibit allergen-induced late asthmatic responses [53, 54]. An inhaled dual PDE_3 and PDE_4 inhibitor RPL554 has bronchodilator effects and is well tolerated in patients with asthma [55]. A preliminary report of a Phase II trial of nebulized doses of RPL554 compared to salbutamol and placebo on lung function in patients with asthma found that RPL554 caused a dose dependent bronchodilation similar to salbutamol, but with fewer side effects [56].

5. CXCR2 ANTAGONISTS

CXCR2 receptors are expressed on neutrophils as well as on airway goblet cells, fibroblasts and airway smooth and when activated by ligands such as the chemokines CXCL8 (IL-8) induces neutrophil chemotaxis, proteases production, airway goblet cell hyperplasia, collagen deposition and airway smooth muscle contraction and migration [57]. Neutrophilic airway inflammation is found in some patients with asthma although the role of neutrophils in the pathogenesis of asthma is uncertain [58]. A phase II study found that the 4-weeks treatment with

CXCR2 antagonist SCH527123 reduced sputum neutrophil percentage by 36.3% in patients with severe asthma and sputum neutrophils > 40%. [59]. A 26-week phase II randomized controlled trial, investigated the efficacy and safety of a CXCR2 antagonist AZD5069 15, or 45 mg oral twice daily or matched placebo in 640 participants with severe, uncontrolled persistent asthma despite combination treatment with medium-dose or high-dose ICS and LABA. AZD5069 did not reduce the rate of severe exacerbations (primary end-point) at any dose despite a dose-dependent reduction in blood neutrophil counts [60]. No phase III clinical trials of CXCR2 antagonist for asthma are currently registered in the ClinicalTrials.gov website [33].

6. PROTEIN KINASE INHIBITORS

Inhibitors of protein kinases involved in cellular signalling of pro-inflammatory cytokines implicated in the pathogenesis of asthma may have a role in the treatment of severe asthma [61-65]. Several p38 mitogen-activated protein kinase (MAPK) inhibitors restore corticosteroid sensitivity in peripheral blood mononuclear cells (PBMCs) and alveolar macrophages from patients with severe asthma [63, 66]. A phase II trial is registered as investigating the efficacy and safety of the inhaled p38MAPK inhibitor AZD7624 in corticosteroid resistant asthma (ClinicalTrials.gov Identifier: NCT02753764) [33]. A specific c-kit tyrosine kinase inhibitor imatinib attenuates airway inflammation and remodelling in a murine model of asthma [67, 68] and the compound is under development for patients with severe refractory asthma (Phase II trial, ClinicalTrials.gov Identifier: NCT01097694) [33]. A tyrosine kinase inhibitor masitinib improved asthma control in patients with severe corticosteroid-dependent asthma [69]. A phase III clinical

trial of masitinib is registered as underway in patients with severe asthma treated with oral corticosteroids (ClinicalTrials.gov Identifier: NCT01449162; Last verified 2012) [33] (Table 2).

7. SELECTIVE GLUCOCORTICOID RECEPTOR MODULATORS

Non-steroidal selective glucocorticoid receptor agonists and modulators are in development with the aim of improving the therapeutic ratio of corticosteroids by dissociating transactivation, which is associated with the adverse effects of corticosteroids, from the beneficial effect through inhibition of pro-inflammatory gene transcription (transrepression) [70-72]. This concept has been challenged as it does not account for the observations that the production of anti-inflammatory proteins may have a more important role in resolution of inflammation than previously considered [73]. Only a small number of these molecules have been tested in asthma. An inhaled glucocorticoid receptor agonist GW870086 attenuated adenosine induced bronchoconstriction in asthma [74], although chronic dosing did not improve lung function or reduces rescue medication use in patients with mild to moderate asthma [75]. A nonsteroidal glucocorticoid receptor agonist AZD5423 reduced the fall in FEV_1 and sputum eosinophilia during the late asthmatic response induced by allergen challenge [76]. The efficacy and safety of a nonsteroidal glucocorticoid receptor agonist AZD7594 has undergone phase II clinical evaluation in patients with mild to moderate asthma (ClinicalTrials.gov Identifier: NCT02479412) [33], although to date, results of the study have not been published.

8. MACROLIDES

Macrolides possess pharmacological properties that are potentially relevant to the treatment of asthma, such as antibacterial and antiviral activity [77, 78]. Anti-inflammatory properties of macrolides include inhibition of nuclear factor-κB, reduction in neutrophil migration and/or function [79-83] and attenuation of tumor necrosis factor α and interleukin-17 immune responses [84]. Macrolides also restore corticosteroid sensitivity through phosphoinositide 3-kinase (PI3K) pathway inhibition [85-87]. The macrolides most commonly used in clinical trials in asthma include azithromycin, clarithromycin, roxithromycin and troleandomycin [88]. Novel analogues of macrolides have been developed, such as solithromycin (CEM-101) that has enhanced anti-inflammatory properties compared to current macrolides, [83, 86], the non-antibiotic azithromycin derivative CSY0073 that lacks anti-bacterial properties [89] and the oleandomycin derivative MAC5 that has enhanced ant-viral activity [90]. No clinical trials of macrolide analogues in asthma are currently listed in the clintrials.gov. website [33].

A Cochrane systematic review (23 trials, 1513 participants) evaluated the effects of macrolides for managing asthma [88]. Macrolides did not improve most clinical outcomes compared to placebo including exacerbations (OR 0.82, 95% CI 0.43 to 1.57), symptoms and asthma quality of life, although there was a modest increase in FEV_1 (80 ml, 95% CI 20 to 140). Two studies suggested that macrolides may have an oral corticosteroid sparing effect. Macrolides have been investigated in non-eosinophilic asthma, suggesting a beneficial effect in never and former smokers with asthma [91], but not in smokers with asthma [92]. A randomized controlled trial investigated low-dose azithromycin or placebo for 6 months as add-on treatment to combination therapy of ICS and LABA

in patients with exacerbation-prone severe asthma [91]. Azithromycin did not improve the primary end-points of the number of severe exacerbations and lower respiratory tract infections. Azithromycin reduced the primary endpoints in a predefined subgroup with non-eosinophilic severe asthma (blood eosinophilia ≤200/µl). In a clinical trial in smokers with mild to moderate asthma, azithromycin 250 mg per day for 12 weeks resulted in no improvements in morning PEF, ACQ score, AQLQ score and methacholine PC_{20} compared to placebo [92]. Common adverse effects of macrolides are nausea and diarrhoea. Drug inhibitors or inducers of the cytochrome P450 3A4 (CYP3A) enzyme that metabolizes macrolides may cause serious interactions. Macrolides prolong the QTc interval that in susceptible individuals can cause ventricular fibrillation and sudden death. Long-term treatment increases the risk of the development of microbial resistance [79].

9. STATINS

The pleiotropic immunomodulatory properties of statins [93] and their ability to restore corticosteroid sensitivity [94, 95] suggest that statins may improve clinical outcomes in asthma [93, 96-99]. A small number of randomized controlled trials in adults with mild to moderate asthma found that short-term statin treatment did not improve lung function or symptom control in non-smokers with asthma [100]. In smokers with asthma, atorvastatin treatment resulted in a small improvement in asthma quality of life and symptoms that were associated with reductions in several sputum cytokines, chemokines and growth factors concentrations unresponsive to ICS treatment [101, 102]. Several observation studies report that statin use in asthma is associated with a reduced risk of asthma-related emergency department visits, oral corticosteroid dispensing or hospital admissions

[100]. Statins treatment in asthma may have modest local anti-inflammatory effects in the airways [100]. A 12-week phase II study is examining the effects of simvastatin on airway inflammation, lung function and exacerbations in patients with severe asthma taking ICS and LABA (ClinicalTrials.gov Identifier: NCT02433535) [33].

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10. ULTRA-LOW DOSE THEOPHYLLINE

Low dose theophylline restores corticosteroid sensitivity *in-vitro,* possibly by increasing histone deacetylase (HDAC)-2 activity, which is suppressed in severe asthma and in smokers with asthma [103, 104]. Theophylline inhibits oxidative stress dependent PI3K-δ activation and restores corticosteroid sensitivity in PBMCs from patients with COPD [104]. A clinical trial of ultra-low dose theophylline, titrated to provide a 'sub-therapeutic' concentration, when added to inhaled beclometasone in smokers with asthma, resulted in increased efficacy as measured by lung function compared to inhaled beclometasone alone suggesting the restoration of corticosteroid sensitivity in those treated with the combination [105]. Clinical trials to date have not investigated the therapeutic effects of a combination of ultra-low dose of theophylline with ICS in severe asthma. The development of fixed combination of ultra-low dose theophylline with fluticasone propionate (SKP-2075) in a dry powder inhaler for the treatment of smokers with asthma and COPD is currently on hold [106].

CONCLUSION

The LAMA tiotropium is the only small molecule drug approved for the maintenance treatment of adults and adolescents with asthma in recent years. Clinical trials of tiotropium in asthma report improvements in lung function and reductions in exacerbations in patients taking ICS alone and the combination of medium to high dose ICS and LABA. The LAMAS umeclidinium and glycopyrronium are under development in fixed dose combination with ICS and LABA in patients with uncontrolled severe asthma. Several novel small molecule drugs are under clinical development for asthma, although none are approved for use in clinical practice. Short-term phase II clinical trials of the CRTH2 receptor antagonists AMG 853, AZD1981, BI 671800, OC000459 and fevipiprant (QAW039) in chronic asthma have produced little or no improvements in symptoms and lung function, except in eosinophilic subgroups. Based on evidence suggesting that blood and/or airway eosinophilia may predictive a beneficial response to these compounds, the CRTH2 receptor antagonist fevipiprant (QAW039) is being investigated in two replicate 52-week phase III parallel trial in patients with severe asthma, including a subgroup with high eosinophil counts, and a phase II trial is underway to examine the effect of OC000459 on eosinophilic airway inflammation and asthma control in adults with severe eosinophilic asthma. The PDE_4 inhibitor roflumilast produces modest improvements in FEV_1 in some studies, including when added to low dose BDP and when compared to the addition of montelukast in patients taking ICS and LABA. The main adverse effects are headache, nausea and diarrhea. An inhaled dual PDE_3 and PDE_4 inhibitor RPL554 has acute bronchodilator effects comparable to inhaled salbutamol. A phase II trial of the CXCR2 antagonist AZD5069 adults with severe, uncontrolled persistent asthma despite combination treatment with medium-dose or high-dose ICS and LABA produced no reduction in severe

exacerbations despite a reduction in blood neutrophil counts. Several protein kinase inhibitors are under investigation including the inhaled p38MAPK inhibitor AZD7624 in corticosteroid resistant asthma, the specific c-kit tyrosine kinase inhibitor imatinib in severe refractory asthma, and the tyrosine kinase inhibitor masitinib in severe asthma treated with oral corticosteroids. The efficacy and safety of a nonsteroidal glucocorticoid receptor agonist AZD7594 has undergone phase II clinical evaluation in patients with mild to moderate asthma, although to date, results have not been published. Exploratory clinical studies of 'off-label' use of licensed drugs suggest that macrolides show efficacy in non-smokers with non-eosinophilic severe asthma and statins and ultra-low dose theophylline may benefit smokers with asthma.

EXPERT OPINION

Surveys of adults and adolescents with asthma report that many people have poorly controlled symptoms despite long-term treatment with an ICS alone or combined with a LABA. For many of these individuals there is an unmet need for improved therapies, particularly for those with severe asthma. Despite the clinical development of many novel small molecule compounds, tiotropium is the only drug approved for the treatment of adults and adolescents with asthma in recent years. The beneficial effects of tiotropium are improved FEV_1 and a modest reduction in exacerbations when added to ICS or the combination of ICS and LABA. At step 4, there is a lack of studies comparing the effectiveness of tiotropium with other add-on therapies, such as leukotriene antagonists and theophylline. The participants recruited to clinical trials of tiotropium may not be representative of real-life populations of asthma, since current smokers,

former smokers with greater than a 10 pack-years and older people aged >75 years were excluded [21]. Fixed dose combinations of LAMAs, umeclidinium or glycopyrronium, with ICS and LABA are undergoing evaluation in patients with uncontrolled severe asthma and these combination treatments are likely to have similar clinical benefits to those found with the addition of tiotropium in this patient group. Novel small molecules drugs, such as the CRTH2 receptor antagonist fevipiprant (QAW039), the PDE_4 inhibitor roflumilast, several protein kinase inhibitors and the nonsteroidal glucocorticoid receptor agonist AZD7594 are under development for asthma, although only a small number of phase III trials are registered on the clinicaltrials.gov website and none of these drugs are currently approved for use in clinical practice. Several drugs licensed for the treatment of medical conditions other than asthma have been investigated for their efficacy in asthma. The 'off-label' use of licensed drugs, such as macrolides, statin and ultralow-dose theophylline are not established for the treatment of asthma and funding for large clinical trials of these drugs in asthma is likely to be difficult. Of the small molecule drugs under development for asthma, the fixed dose combinations of LAMAs, umeclidinium or glycopyrronium, with ICS and LABA are the ones most likely to be marketed for the treatment of severe asthma in the next few years.

Several monoclonal antibodies are approved for the treatment of asthma, including anti-IgE (omalizumab) and anti-IL-5 (mepolizumab, reslizumab) and others are under development [107]. An important aim in the future will be to assess if novel small molecule drugs can replace or complement the use of one or more of the monoclonal antibodies therapies approved or under

development for asthma, possibly at a reduced cost. For example, could an effective CRTH2 antagonist replace monoclonal antibody therapy for severe eosinophilic asthma?

The ideal properties of a new small molecule drug for asthma should include once daily dosing, an impact on reducing exacerbations and oral corticosteroid sparing actions. The assessment of new therapies should involve studies that compare novel drugs with current add-on therapies and that reflect real life populations of asthma. To better achieve the goal of developing effective novel small molecule drugs for asthma will require greater understanding of mechanisms of disease and the different phenotypes and endotypes of asthma. International collaborative programmes of research investigating pathogenic mechanism of severe asthma such as the Unbiased Biomarkers for the Prediction of Respiratory Disease Outcome (U-BOPRED) study [108, 109] and the UK Refractory Asthma Stratification Programme (RASP-UK) [110] are designed to identify new phenotypes/endotypes and treatment targets that will hopefully identify new approaches to the treatment of asthma including small molecules drugs that demonstrate effectiveness that would warrant approval for use in clinical practice.

ARTICLE HIGHLIGHTS BOX

- The long-acting muscarinic antagonist (LAMA) tiotropium is the only small molecule drug approved for the maintenance treatment of adults and adolescents with asthma in recent years. Clinical trials of tiotropium in asthma report improvements in lung function and

modest reductions in exacerbations in patients taking ICS alone and the combination of medium to high dose ICS and LABA.

- The LAMAs umeclidinium and glycopyrronium are under development in fixed dose combination with ICS and LABA in patients with uncontrolled severe asthma.

- Novel small molecules drugs, such as the CRTH2 receptor antagonist fevipiprant (QAW039), the PDE_4 inhibitor roflumilast, several protein kinase inhibitors and the nonsteroidal glucocorticoid receptor agonist AZD7594 are under development for asthma, although only a small number of phase III studies are registered on the clinicaltrials.gov website and none of these drugs are currently approved for use in clinical practice.

- Exploratory clinical studies of 'off-label' use of licensed drugs suggest that macrolides show efficacy in non-smokers with non-eosinophilic severe asthma and statins and ultralow-dose theophylline may benefit smokers with asthma, although the effectiveness of these drugs in clinical practice is not established.

- To better achieve the goal of developing effective novel small molecule drugs for asthma will require greater understanding of mechanisms of disease and the different phenotypes and endotypes of asthma**.**

REFERENCES

Papers of special note have been highlighted as:

* of interest

** of considerable interest

1. Global Initiative for Asthma (GINA) 2016 http://www.ginasthma.org/ Accessed 12th December 2016

   ** Comprehensive international guideline covering the assessment and management of asthma

2. Montuschi P, Barnes PJ. New perspectives in pharmacological treatment of mild persistent asthma. Drug Discov Today 2011 12//;16(23–24):1084-91.
3. O'Byrne P, Barnes P, Rodriquez-Roisin R, Runnerstrom T, Sandstrom T, Svensson K, et al. Low Dose Inhaled Budesonide and Formoterol in Mild Persistent Asthma . The OPTIMA Randomized Trial. Am J Respir Crit Care Med 2001;164(8):1392-97.
4. Pauwels R, Pedersen S, Busse W, Tan W, Chen Y, Ohisson S, et al. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. Lancet 2003;361:1071-76.
5. Stempel DA, Raphiou IH, Kral KM, Yeakey AM, Emmett AH, Prazma CM, et al. Serious Asthma Events with Fluticasone plus Salmeterol versus Fluticasone Alone. N Eng J Med 2016;374(19):1822-30.
6. Peters SP, Bleecker ER, Canonica GW, Park YB, Ramirez R, Hollis S, et al. Serious Asthma Events with Budesonide plus Formoterol vs. Budesonide Alone. N Eng J Med 2016;375(9):850-60.
7. Montuschi P. Leukotrienes, Antileukotrienes and Asthma. Mini Rev Med Chem 2008;8(7):647-56.
8. British Guideline on the Management of Asthma. 2016 [cited; www.sign.ac.uk:[Available from:

9. Price D, Fletcher M, van der Molen T. Asthma control and management in 8,000 European patients: the REcognise Asthma and LInk to Symptoms and Experience (REALISE) survey. NPJ Prim Care Respir Med 2014;24:14009.
10. Demoly P, Annunziata K, Gubba E, Adamek L. Repeated cross-sectional survey of patient-reported asthma control in Europe in the past 5 years. Eur Respir Review 2012 March 1, 2012;21(123):66-74.
11. Kistemaker LEM, Gosens R. Acetylcholine beyond bronchoconstriction: roles in inflammation and remodeling. Trends Pharmacol Sci 2015;36(3):164-71.
12. Montuschi P, Macagno F, Valente S, Fuso L. Inhaled Muscarinic Acetylcholine Receptor Antagonists for Treatment of COPD. Curr Med Chem 2013;20(12):1464-76.
13. Montuschi P, Ciabattoni G. Bronchodilating Drugs for Chronic Obstructive Pulmonary Disease: Current Status and Future Trends. J Med Chem 2015 2015/05/28;58(10):4131-64.
14. Anderson DE, Kew KM, Boyter AC. Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus the same dose of ICS alone for adults with asthma. Cochrane Database of Systematic Reviews 2015(8).
    * Systematic review of clinical studies of tiotropium add-on to low and medium dose ICS
15. Hamelmann E, Bateman ED, Vogelberg C, Szefler SJ, Vandewalker M, Moroni-Zentgraf P, et al. Tiotropium add-on therapy in adolescents with moderate asthma: A 1-year randomized controlled trial. J Allergy Clin Immunol 2016 8//;138(2):441-50.e8.
16. Hamelmann E, Bernstein JA, Vandewalker M, Moroni-Zentgraf P, Verri D, Unseld A, et al. A randomised controlled trial of tiotropium in adolescents with severe symptomatic asthma. Eur Respir J 2016;Nov 3. pii: ERJ-01100-2016. doi: 10.1183/13993003.01100-2016. [Epub ahead of print].
17. Evans DJW, Kew KM, Anderson DE, Boyter AC. Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus higher dose ICS for adults with asthma. Cochrane Database of Systematic Reviews 2015 Jul 21;(7):CD011437. doi: 10.1002/14651858.CD011437.pub2..

18. Peters SP, Kunselman SJ, Icitovic N, Moore WC, Pascual R, Ameredes BT, et al. Tiotropium Bromide Step-Up Therapy for Adults with Uncontrolled Asthma. N Engl J Med 2010;363(18):1715-26.
19. Kerstjens HAM, Casale TB, Bleecker ER, Meltzer EO, Pizzichini E, Schmidt O, et al. Tiotropium or salmeterol as add-on therapy to inhaled corticosteroids for patients with moderate symptomatic asthma: two replicate, double-blind, placebo-controlled, parallel-group, active-comparator, randomised trials. Lancet Respir Med 2015;3(5):367-76.
20. Kew KM, Evans DJW, Allison DE, Boyter AC. Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus addition of long-acting beta2-agonists (LABA) for adults with asthma. Cochrane Database of Systematic Reviews 2015(6).
21. Kerstjens HAM, Engel M, Dahl R, Paggiaro P, Beck E, Vandewalker M, et al. Tiotropium in Asthma Poorly Controlled with Standard Combination Therapy. N Engl J Med 2012;367(13):1198-207.
    * Report of two replicate phase III randomized, controlled trials comparing the effects on lung function and exacerbations of tiotropium as an add-on to high-dose ICS plus a LABA in adult with severe symptomatic asthma
22. Kew K, Karen D. Long-acting muscarinic antagonists (LAMA) added to combination long-acting beta2-agonists and inhaled corticosteroids (LABA/ICS) versus LABA/ICS for adults with asthma. Cochrane Database Syst Rev 2016(1):Art. No.: CD011721. DOI: 10.1002/14651858.CD011721.pub2.
    * Systematic review of clinical studies of tiotropium add-on to medium and high dose ICS and LABA
23. Ohta K, Ichinose M, Tohda Y, Engel M, Moroni-Zentgraf P, Kunimitsu S, et al. Long-Term Once-Daily Tiotropium Respimat® Is Well Tolerated and Maintains Efficacy over 52 Weeks in Patients with Symptomatic Asthma in Japan: A Randomised, Placebo-Controlled Study. PLoS ONE 2015;10(4):e0124109.
24. Price D, Kaplan A, Jones R, Freeman D, Burden A, Gould S, et al. Long-acting muscarinic antagonist use in adults with asthma: real-life prescribing and outcomes of add-on therapy with tiotropium bromide. J Asthma Allergy 2015 01/14;8:1-13.

25. Peters SP, Bleecker ER, Kunselman SJ, Icitovic N, Moore WC, Pascual R, et al. Predictors of response to tiotropium versus salmeterol in asthmatic adults. J Allergy Clin Immunol 2013 09/30;132(5):1068-74.

26. Kerstjens HAM, Moroni-Zentgraf P, Tashkin DP, Dahl R, Paggiaro P, Vandewalker M, et al. Tiotropium improves lung function, exacerbation rate, and asthma control, independent of baseline characteristics including age, degree of airway obstruction, and allergic status. Respir Med 2016 8//;117:198-206.

* Investigation of whether baseline characteristics predict efficacy of tiotropium as an add-on to high-dose ICS plus a LABA in adult with severe symptomatic asthma

27. Bateman ED, Kornmann O, Schmidt P, Pivovarova A, Engel M, Fabbri LM. Tiotropium is noninferior to salmeterol in maintaining improved lung function in B16-Arg/Arg patients with asthma. J Allergy Clin Immunol 2011;128(2):315-22.

28. Dahl R, Engel M, Dusser D, Halpin D, Kerstjens HAM, Zaremba-Pechmann L, et al. Safety and tolerability of once-daily tiotropium Respimat® as add-on to at least inhaled corticosteroids in adult patients with symptomatic asthma: A pooled safety analysis. Respir Med 2016 9//;118:102-11.

29. Wise RA. Tiotropium Respimat inhaler and the risk of death in COPD. N Engl J Med 2013 ;369:1491-501.

30. Tiotropium delivered via Respimat compared with Handihaler: no significant difference in mortality in TIOSPIR trial Drug Safety Update 2015 https://www.gov.uk/drug-safety-update/tiotropium-delivered-via-respimat-compared-with-handihaler-no-significant-difference-in-mortality-in-tiospir-trial Accessed 12th December 2016

31. Lee LA, Yang S, Kerwin E, Trivedi R, Edwards LD, Pascoe S. The effect of fluticasone furoate/umeclidinium in adult patients with asthma: A randomized, dose-ranging study. Respir Med 2015;109(1):54-62.

32. Lee LA, Briggs A, Edwards LD, Yang S, Pascoe S. A randomized, three-period crossover study of umeclidinium as monotherapy in adult patients with asthma. Respir Med 2015;109(1):63-73.

33. https://clinicaltrials.gov/. 2016 Accessed 12th December 2016

** International register of clinical trials including studies in asthma

34. Singh D, Cadden P, Hunter M, Pearce Collins L, Perkins M, Pettipher R, et al. Inhibition of the asthmatic allergen challenge response by the CRTH2 antagonist OC000459. Eur Respir J 2013 January 1, 2013;41(1):46-52.
35. Diamant Z, Sidharta PN, Singh D, O'Connor BJ, Zuiker R, Leaker BR, et al. Setipiprant, a selective CRTH2 antagonist, reduces allergen-induced airway responses in allergic asthmatics. Clin Exp Allergy 2014;44(8):1044-52.
36. Barnes N, Pavord I, Chuchalin A, Bell J, Hunter M, Lewis T, et al. A randomized, double-blind, placebo-controlled study of the CRTH2 antagonist OC000459 in moderate persistent asthma. Clin Exp Allergy 2012;42(1):38-48.
37. Pettipher R, Hunter MG, Perkins CM, Collins LP, Lewis T, Baillet M, et al. Heightened response of eosinophilic asthmatic patients to the CRTH2 antagonist OC000459. Allergy 2014;69(9):1223-32.
38. Hall IP, Fowler AV, Gupta A, Tetzlaff K, Nivens MC, Sarno M, et al. Efficacy of BI 671800, an oral CRTH2 antagonist, in poorly controlled asthma as sole controller and in the presence of inhaled corticosteroid treatment. Pulm Pharm Therap 2015 6//;32:37-44.
39. Kuna P, Bjermer L, Tornling G. Two Phase II randomized trials on the CRTh2 antagonist AZD1981 in adults with asthma. Drug Des Devel Ther 2016 08/31;10:2759-70.
40. Busse WW, Wenzel SE, Meltzer EO, Kerwin EM, Liu MC, Zhang N, et al. Safety and efficacy of the prostaglandin D2 receptor antagonist AMG 853 in asthmatic patients. J Allergy Clin Immunol 2013;131(2):339-45.
41. Erpenbeck VJ, Popov TA, Miller D, Weinstein SF, Spector S, Magnusson B, et al. The oral CRTh2 antagonist QAW039 (fevipiprant): A phase II study in uncontrolled allergic asthma. Pulm Pharm Therap 2016 8//;39:54-63.
42. Gonem S, Berair R, Singapuri A, Hartley R, Laurencin MFM, Bacher G, et al. Fevipiprant, a prostaglandin D2 receptor 2 antagonist, in patients with persistent eosinophilic asthma: a single-centre, randomised, double-blind, parallel-group, placebo-controlled trial. Lancet Respir Med 2016 4(9):699-707.

* Proof of concept clinical trial reported that the CRTH2 antagonist fevipiprant (QAW039) reduced sputum eosinophils in patients with severe persistent eosinophilic asthma

43. Lipworth BJ. Phosphodiesterase-4 inhibitors for asthma and chronic obstructive pulmonary disease. Lancet 2005 2015/01/21;365(9454):167-75.
44. Kim SW, Kim JH, Park CK, Kim TJ, Lee SY, Kim YK, et al. Effect of roflumilast on airway remodeling in a murine model of chronic asthma. Clin Exp Allergy 2016;46(5):754-63.
45. Page CP. Phosphodiesterase Inhibitors for the Treatment of Asthma and Chronic Obstructive Pulmonary Disease. Int Arch Allergy Immunol 2014;165(3):152-64.
** Comprehensive review of selective PDE inhibitors as novel treatments for respiratory diseases including asthma
46. Gauvreau G, Boulet L-P, Schmid-Wirlitsch C, Cote J, Duong M, Killian K, et al. Roflumilast attenuates allergen-induced inflammation in mild asthmatic subjects. Respir Res 2011;12(1):140.
47. Meltzer EO, Chervinsky P, Busse W, Ohta K, Bardin P, Bredenbröker D, et al. Roflumilast for asthma: Efficacy findings in placebo-controlled studies. Pulm Pharm Therap 2015 12;35, Supplement:S20-S27.
48. Bateman ED, Goehring U-M, Richard F, Watz H. Roflumilast combined with montelukast versus montelukast alone as add-on treatment in patients with moderate-to-severe asthma. J Allergy Clin Immunol 2016 7//;138(1):142-49.e8.
49. Chervinsky P, Meltzer EO, Busse W, Ohta K, Bardin P, Bredenbröker D, et al. Roflumilast for asthma: Safety findings from a pooled analysis of ten clinical studies. Pulm Pharm Therap 2015 12;35, Supplement:S28-S34.
50. Chapman RW, House A, Richard J, Prelusky D, Lamca J, Wang P, et al. Pharmacology of a potent and selective inhibitor of PDE4 for inhaled administration. Eur J Pharmacol 2010;643(2-3):274-81.
51. Moretto N, Caruso P, Bosco R, Marchini G, Pastore F, Armani E, et al. CHF6001, a novel highly potent and selective phosphodiesterase 4 inhibitor with robust anti-inflammatory activity and suitable for topical pulmonary administration. J Pharmacol Exp Ther 2015 January 9, 2015;352(3):559-67.

52. De Savi C, Cox RJ, Warner DJ, Cook AR, Dickinson MR, McDonough A, et al. Efficacious Inhaled PDE4 Inhibitors with Low Emetic Potential and Long Duration of Action for the Treatment of COPD. J Med Chem 2014 04/2015/01/16;57(11):4661-76.
53. Singh D, Petavy F, Macdonald A, Lazaar A, O'Connor B. The inhaled phosphodiesterase 4 inhibitor GSK256066 reduces allergen challenge responses in asthma. Resp Res 2010;11(1):26.
54. Singh D, Leaker B, Boyce M, Nandeuil MA, Collarini S, Mariotti F, et al. A novel inhaled phosphodiesterase 4 inhibitor (CHF6001) reduces the allergen challenge response in asthmatic patients. Pulm Pharm Therap 2016 10//;40:1-6.
55. Franciosi LG, Diamant Z, Banner KH, Zuiker R, Morelli N, Kamerling IMC, et al. Efficacy and safety of RPL554, a dual PDE3 and PDE4 inhibitor, in healthy volunteers and in patients with asthma or chronic obstructive pulmonary disease: findings from four clinical trials. Lancet Respir Med 2013 11/1;1(9):714-27.
56. Bjermer L, Stewart J, Abbott-Banner K, Newman K. RPL554, a First-In-Class Dual Phosphodiesterase (PDE)3/4 Inhibitor, Is Equi-Effective as a Bronchodilator to Maximal Doses of Salbutamol in Asthmatics but with Fewer Adverse Events. Am J Resir Crit Care Med 2016;193:A7770-A70.
57. Chapman RW, Phillips JE, Hipkin RW, Curran AK, Lundell D, Fine JS. CXCR2 antagonists for the treatment of pulmonary disease. Pharmacol Ther 2009;121(1):55-68.
58. Thomson NC. Novel approaches to the management of noneosinophilic asthma. Therap Adv Respir Dis 2016 February 28, 2016;10(3):211-34.
59. Nair P, Gaga M, Zervas E, Alagha K, Hargreave FE, O'Byrne PM, et al. Safety and efficacy of a CXCR2 antagonist in patients with severe asthma and sputum neutrophils: a randomized, placebo-controlled clinical trial. Clin Exp Allergy 2012;42(7):1097-103.
60. O'Byrne PM, Metev H, Puu M, Richter K, Keen C, Uddin M, et al. Efficacy and safety of a CXCR2 antagonist, AZD5069, in patients with uncontrolled persistent asthma: a randomised, double-blind, placebo-controlled trial. Lancet Respir Med 2016 10:797-806.
* A phase II randomized controlled trial reported that a CXCR2 antagonist AZD5069 did not reduce the rate of severe exacerbations despite a dose-dependent reduction in blood

neutrophil counts in ptients with severe, uncontrolled persistent asthma despite combination treatment with medium-dose or high-dose ICS and LABA.

61. Cohen S, Fleischmann R. Kinase inhibitors: a new approach to rheumatoid arthritis treatment. Curr Opin Rheumatol 2010;22(3):330-35
62. Hammaker D, Firestein G. "Go upstream, young man": lessons learned from the p38 saga. Ann Rheum Dis 2010;69, Suppl 1(i77-82).
63. Bhavsar P, Khorasani N, Hew M, Johnson M, Chung KF. Effect of p38 MAPK inhibition on corticosteroid suppression of cytokine release in severe asthma. Eur Respir J 2010 April 1, 2010;35(4):750-56.
64. Guntur VP, Reinero CR. The potential use of tyrosine kinase inhibitors in severe asthma. Curr Opin Allergy Clin Immunol 2012;12(1):68-75.
65. Chung KF. p38 Mitogen-Activated Protein Kinase Pathways in Asthma and COPD. Chest 2011 June 1, 2011;139(6):1470-79.
66. Mercado N, Hakim A, Kobayashi Y, Meah S, Usmani OS, Chung KF, et al. Restoration of Corticosteroid Sensitivity by p38 Mitogen Activated Protein Kinase Inhibition in Peripheral Blood Mononuclear Cells from Severe Asthma. PLoS ONE 2012;7(7):e41582.
67. Berlin AA, Lukacs NW. Treatment of Cockroach Allergen Asthma Model with Imatinib Attenuates Airway Responses. Am J Respir Crit Care Med 2005 01/01 2014/12/07;171(1):35-39.
68. Rhee CK, Kim JW, Park CK, Kim JS, Kang JY, Kim SJ, et al. Effect of Imatinib on Airway Smooth Muscle Thickening in a Murine Model of Chronic Asthma. Int Arch Allergy Immunol 2011;155(3):243-51.
69. Humbert M, De Blay F, Garcia G, Prud'homme A, Leroyer C, Magnan A, et al. Masitinib, a c-kit/PDGF receptor tyrosine kinase inhibitor, improves disease control in severe corticosteroid-dependent asthmatics. Allergy 2009;64(8):1194-201.
70. Schacke H, Schottelius A, Docke W-D, Strehlke P, Jaroch S, Schmees N, et al. Dissociation of transactivation from transrepression by a selective glucocorticoid receptor agonist leads to separation of therapeutic effects from side effects. PNAS 2004 January 6, 2004;101(1):227-32.

71. Cazzola M, Coppola A, Rogliani P, Matera MG. Novel glucocorticoid receptor agonists in the treatment of asthma. Expert Opin Investig Drugs 2015 24(11):1473-82.
** Comprehensive review of novel glucocorticoid receptor agonists in the treatment of asthma
72. Sundahl N, Bridelance J, Libert C, De Bosscher K, Beck IM. Selective glucocorticoid receptor modulation: New directions with non-steroidal scaffolds. Pharmacol Therapeut 2015 8//;152:28-41.
73. Clark AR, Belvisi MG. Maps and legends: The quest for dissociated ligands of the glucocorticoid receptor. Pharmacol & Ther 2012;134(1):54-67.
74. Leaker BR, O'Connor B, Singh D, Barnes PJ. The novel inhaled glucocorticoid receptor agonist GW870086X protects against adenosine-induced bronchoconstriction in asthma. J Allergy Clin Immunol 2015 8//;136(2):501-02.e6.
75. Bareille P, Hardes K, Donald AC. Efficacy and safety of once-daily GW870086 a novel selective glucocorticoid in mild-moderate asthmatics: a randomised, two-way crossover, controlled clinical trial. J Asthma 2013 2013/12/01;50(10):1077-82.
76. Gauvreau GM, Boulet L-P, Leigh R, Cockcroft DW, Killian KJ, Davis BE, et al. A Nonsteroidal Glucocorticoid Receptor Agonist Inhibits Allergen-induced Late Asthmatic Responses. Am J Resp Crit Care Med 2015 12/04 2015/01/16;191(2):161-67.
77. Gielen V, Johnston SL, Edwards MR. Azithromycin induces anti-viral responses in bronchial epithelial cells. Eur Respir J 2010 February 11, 2010;36(3):646-54.
78. Schögler A, Kopf BS, Edwards MR, Johnston SL, Casaulta C, Kieninger E, et al. Novel antiviral properties of azithromycin in cystic fibrosis airway epithelial cells. Eur Respir J 2015 February 1, 2015;45(2):428-39.
79. Cameron EJ, McSharry C, Chaudhuri R, Farrow S, Thomson NC. Long-term macrolide treatment of chronic inflammatory airway diseases: risks, benefits and future developments. Clin Exp Allergy 2012;42(9):1302-12.
80. Culic O, Erakovic V, Parnham MJ. Anti-inflammatory effects of macrolide antibiotics. Eur J Pharmacol 2001;429(1-3):209-29.

81. Fujitani Y, Trifilieff A. In Vivo and In Vitro Effects of SAR 943, a Rapamycin Analogue, on Airway Inflammation and Remodeling. Am J Respir Crit Care Med 2003 January 15, 2003;167(2):193-98.
82. Simpson JL, Powell H, Boyle MJ, Scott RJ, Gibson PG. Clarithromycin Targets Neutrophilic Airway Inflammation in Refractory Asthma. Am J Respir Crit Care Med 2008 January 15, 2008;177(2):148-55.
83. Kobayashi Y, Wada H, Rossios C, Takagi D, Higaki M, Mikura Si, et al. A Novel Macrolide Solithromycin Exerts Superior Anti-inflammatory Effect via NF-κB Inhibition. J Pharmacol Exp Ther 2013 April 1, 2013;345(1):76-84.
84. Essilfie A-T, Horvat JC, Kim RY, Mayall JR, Pinkerton JW, Beckett EL, et al. Macrolide therapy suppresses key features of experimental steroid-sensitive and steroid-insensitive asthma. Thorax 2015 May 1, 2015;70(5):458-67.
85. Spahn J, Fost D, Covar R, Martin R, Brown E, SJ S, et al. Clarithromycin potentiates glucocorticoid responsiveness in patients with asthma: results of a pilot study. Ann Allergy Asthma Immunol 2001;87(6):501-5.
86. Kobayashi Y, Wada H, Rossios C, Takagi D, Charron C, Barnes PJ, et al. A novel macrolide/fluoroketolide, solithromycin (CEM-101), reverses corticosteroid insensitivity via phosphoinositide 3-kinase pathway inhibition. Br J Pharmacol 2013;169(5):1024-34.
87. Hao M, Lin J, Shu J, Zhang X, Luo Q, Pan L, et al. Clarithromycin might attenuate the airway inflammation of smoke-exposed asthmatic mice via affecting HDAC2. J Thorac Dis 2015;7(7):1189-97.
88. Kew K, Undela K, Kotorts I, Ferrara G. Macrolides for chronic asthma. Cochrane Database Syst Rev 2015;15(9):CD002997. doi: 10.1002/14651858.CD002997.pub4.
* Systematic review of clinical studies of macrolides for asthma
89. Balloy V, Deveaux A, Lebeaux D, Tabary O, le Rouzic P, Ghigo JM, et al. Azithromycin analogue CSY0073 attenuates lung inflammation induced by LPS challenge. Br J Pharmacol 2014;171(7):1783-94.

90. Porter JD, Watson J, Roberts LR, Gill SK, Groves H, Dhariwal J, et al. Identification of novel macrolides with antibacterial, anti-inflammatory and type I and III IFN-augmenting activity in airway epithelium. J Antimicrob Chemother 2016 July 25, 2016;71(10):2767-81.

91. Brusselle GG, VanderStichele C, Jordens P, Deman R, Slabbynck H, Ringoet V, et al. Azithromycin for prevention of exacerbations in severe asthma (AZISAST): a multicentre randomised double-blind placebo-controlled trial. Thorax 2013 April 1, 2013;68(4):322-29.

*Randomized controlled trial reporting that azithromycin reducted in exacerbation in patients with severe asthma and non-eosinophilc inflammation

92. Cameron EJ, Chaudhuri R, Mair F, McSharry C, Greenlaw N, Weir CJ, et al. Randomised controlled trial of azithromycin in smokers with asthma. Eur Respir J 2013 November 1, 2013;42(5):1412-15.

93. Greenwood J, Steinman L, Zamvil SS. Statin therapy and autoimmune disease: from protein prenylation to immunomodulation. Nat Rev Immunol 2006;6(5):358-70.

94. Samson K, Minoguchi K, Tanaka A, Oda N, Yokoe T, Yamamoto Y, et al. Inhibitory effects of fluvastatin on cytokine and chemokine production by peripheral blood mononuclear cells in patients with allergic asthma. Clin Exp Allergy 2006;36(4):475-82.

95. Maneechotesuwan K, Ekjiratrakul W, Kasetsinsombat K, Wongkajornsilp A, Barnes PJ. Statins enhance the anti-inflammatory effects of inhaled corticosteroids in asthmatic patients through increased induction of indoleamine 2, 3-dioxygenase. J Allergy Clin Immunol 2010;126(4):754-62.

96. Hothersall E, McSharry C, Thomson NC. Potential therapeutic role for statins in respiratory disease. Thorax 2006;61(8):729-34.

97. Yeganeh B, Wiechec E, Ande S, Sharma P, Moghadam A, Post M, et al. Targeting the mevalonate cascade as a new therapeutic approach in heart disease, cancer and pulmonary disease. Pharmacol Ther 2014;143(1):87-110.

98. McKay A, Leung BP, McInnes IB, Thomson NC, Liew FY. A Novel Anti-Inflammatory Role of Simvastatin in a Murine Model of Allergic Asthma. J Immunol 2004;172(5):2903-08.

99. Zeki AA, Franzi L, Last J, Kenyon NJ. Simvastatin Inhibits Airway Hyperreactivity: Implications for the Mevalonate Pathway and Beyond. Am J Respir Crit Care Med 2009 October 15, 2009;180(8):731-40.

100. Thomson NC. Clinical studies of statins in asthma and COPD. Curr Mol Pharmacol 2016;9:1-12.

* Comprehensive review of clinical studies of statins in the treatment of asthma

101. Braganza G, Chaudhuri R, McSharry C, Weir CJ, Donnelly I, Jolly L, et al. Effects of short-term treatment with atorvastatin in smokers with asthma - a randomized controlled trial. BMC Pulm Med 2011;11:16

102. Thomson NC, Charron CE, Chaudhuri R, Spears M, Ito K, McSharry C. Atorvastatin in combination with inhaled beclometasone modulates inflammatory sputum mediators in smokers with asthma. Pulm Pharmacol Ther 2015 31:1-8.

103. Barnes PJ. Role of HDAC2 in the Pathophysiology of COPD. Annu Rev Physiol 2009;71(1):451-64.

104. To Y, Ito K, Kizawa Y, Failla M, Ito M, Kusama T, et al. Targeting phosphoinositide-3-kinase-delta with theophylline reverses corticosteroid insensitivity in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2010 Oct 1;182(7):897-904.

105. Spears M, Donnelly I, Jolly L, Brannigan M, Ito K, McSharry C, et al. Effect of low-dose theophylline plus beclometasone on lung function in smokers with asthma: a pilot study. Eur Respir J 2009 May 1, 2009;33(5):1010-17.

106. http://www.vectura.com/news/results-annual-general-meeting/. 2016 Accessed 12th December 2016

107. Fajt ML, Wenzel SE. Asthma phenotypes and the use of biologic medications in asthma and allergic disease: The next steps toward personalized care. J Allergy Clin Immunol 2015;135(2):299-310.

108. Shaw DE, Sousa AR, Fowler SJ, Fleming LJ, Roberts G, Corfield J, et al. Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort. Eur Respir J 2015 2015-11-01 00:00:00;46(5):1308-21.

109. Gaga M, Brand PLP, Thomson NC. The quest for the grail: multidimensional efforts for understanding and targeting severe asthma. Eur Respir J 2015;46(5):1227-31.
110. Heaney LG, Djukanovic R, Woodcock A, Walker S, Matthews JG, Pavord ID, et al. Research in progress: Medical Research Council United Kingdom Refractory Asthma Stratification Programme (RASP-UK). Thorax 2016 July 23, 2015;71(1):187-89.

TABLE 1: NEW AND DEVELOPING NON-ADRENORECEPTOR SMALL MOLECULE DRUGS FOR THE TREATMENT OF ASTHMA

Long-acting muscarinic antagonists (LAMA)

CRTH2 antagonists

Phosphodiesterase (PDE) inhibitors

PDE_4 inhibitors

Dual PDE_3 and PDE_4 inhibitors

Protein kinase inhibitors

p38 Mitogen-activated protein kinase (MAPK) inhibitor

Tyrosine kinase inhibitor

CXCR2 antagonists

Selective glucocorticoid receptor modulators

Macrolides

Statins

Ultra-low dose theophylline

TABLE 2: PHASE III CLINICAL TRIALS OF NON-ADRENOCEPTOR SMALL MOLECULE DRUGS AS ADD-ON THERAPIES UNDERWAY IN ASTHMA*

Small molecule drug and study title	ClinicalTrials.gov Identifier:	Status, estimated enrolment	End-points	Estimated Completion Date	Sponsor
LAMA: Umeclidinium A 52 week, parallel group study, comparing the efficacy, safety and tolerability of the fixed dose combination of fluticasone furoate (FF) + umeclidinium bromide UMEC) + vilanterol (VI) (FF/UMEC/VI) with the fixed dose combination of FF/VI in subjects with inadequately controlled asthma	NCT02924688	Recruiting, n=2250	Primary: trough FEV_1 at week 24 Secondary: include the number of moderate and severe exacerbations up to week 52.	February 2018	GlaxoSmithKline
LAMA: Glycopyrronium A 52-week, parallel group trial comparing a fixed dose combination of extrafine beclometasone dipropionate 100 µg plus formoterol 6 µg plus glycopyrronium 12.5 µg (CHF 5993) with fixed dose combination of extrafine beclometasone dipropionate 100 µg plus formoterol 6 µg (CHF 1535) in patients with uncontrolled asthma receiving medium dose ICS and LABA - TRIple in asthMA With uncontRolled pAtient on Medium streNgth of ICS + LABA (TRIMARAN)	NCT02676076	Recruiting, n=1148	Primary: trough FEV_1 at week 26 and reduction of moderate and severe asthma exacerbations rate up to week 52	June 2018	Chiesi
A 52-week, parallel trial comparing a fixed dose combination of extrafine beclometasone dipropionate 200 µg plus formoterol 6 µg plus glycopyrronium 12.5 µg (CHF 5993) with fixed dose combination of extrafine beclometasone dipropionate 200 µg plus formoterol 6 µg (CHF 1535) alone or plus open-label tiotropium 2.5 µg Respimat® in patients with uncontrolled asthma receiving high dose ICS and LABA - TRIple in Asthma hiGh strenGth vErsus	NCT02676089	Recruiting, n=1435	Primary: trough FEV_1 at week 26 and reduction of moderate and severe asthma exacerbations rate up to week 52	July 2018	Chiesi

Ics/Laba hs and tiotRopium (TRIGGER)).					
A 52-week, parallel group trial comparing the efficacy and safety of two different doses of a fixed dose combination of indacaterol, mometasone furoate and glycopyrronium (QVM149 150/50/80 µg and QVM149 150/50/160 µg) over two respective doses of indacaterol and mometasone furoate (QMF149 150/160 µg and QMF149 150/320 µg) in patients with poorly controlled asthma receiving medium or high doses of ICS and LABA	NCT02571777	Recruiting, n= 3155	Primary: trough FEV_1 at week 26 Secondary: include asthma exacerbation over 52 weeks	October 2018	Novartis
CRTH2 receptor antagonist: fevipiprant (QAW039) Two replicate 52-week, multicenter, randomized, double-blind, placebo-controlled studies to assess the efficacy and safety of fevipiprant (QAW039) when added to existing asthma therapy in patients with uncontrolled severe asthma	NCT02563067 and NCT02555683	Recruiting, n=846 each study	Primary: Moderate-to-severe asthma exacerbations in patients with severe asthma and high eosinophil counts and in all patients with severe asthma	November 2018	Novartis
Protein kinase inhibitor: tyrosine kinase inhibitor masitinib A 36-week study to compare the efficacy and safety of masitinib to placebo in treatment of patients with severe persistent asthma treated with oral corticosteroids	NCT01449162	Recruitment status unknown, n=300	Primary: asthma exacerbation rate at week 36	Unknown (status has not been verified in more than two years)	AB Science

*Information obtained from ClinicalTrials.gov website [33]

Abbreviations: LAMA, long-acting muscarinic antagonist; FEV_1, forced expiratory volume in 1 second

FIGURE LEGEND

Figure 1: Stepwise approach to control symptoms and minimize future risk

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