

EXPERT OPINION

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Monoclonal antibodies for asthma and chronic obstructive pulmonary disease

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Introduction: In asthma and chronic obstructive pulmonary disease (COPD), the inflammation in the airways cannot always be controlled with conventional therapies, such as inhaled corticosteroids. Addition of more specific anti-inflammatory therapies, such as monoclonal antibodies, against inflammation pathways might improve the disease outcome.

Areas covered: This review individually discusses the major inflammation pathways and their potential blocking monoclonal antibodies in asthma and COPD.

Expert opinion: The current use of omalizumab in asthma provides a good example on the potential therapeutic role of monoclonal antibodies in both asthma and COPD. There are many other monoclonal antibodies which are currently investigated as possible therapies in these diseases. The identification of the disease subsets in which such antibodies might exert the maximum benefit opens the door for personalized medicine and for targeted biological therapy in asthma and COPD.

Keywords: asthma, chronic obstructive pulmonary disease, cytokines, monoclonal antibodies, T lymphocytes

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1. Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are both chronic diseases of the airways with high prevalence and morbidity with distinct inflammatory patterns and triggers and with common inflammation effectors. In most of the cases, asthma is developed as a result of allergen exposure, whereas COPD is mainly related to smoking or to exposure to other inhalatory fumes.

In asthma, the airways inflammation is driven mainly by the activated Th2 lymphocytes and is the result of complex interactions and crosstalks among various cytokines, chemokines and other proinflammatory mediators, whereas in COPD several inflammatory cell populations such as neutrophils, macrophages and CD8⁺ lymphocytes, are involved [1].

Furthermore, in both diseases various studies demonstrated that some polymorphisms of certain inflammation mediators might make these molecules to play a pivotal role in the disease pathogenesis [2].

Asthma manifests clinically with respiratory symptoms, such as dyspnea, or cough, which are the result of the bronchospasm induced by the various triggers including the allergens, and which in absence of a treatment can last several hours, whereas in COPD similar symptoms are the result of chronic exposure to the noxious inhalant and are progressive and aggravate during the disease exacerbations.

In both asthma and COPD, inhaled corticosteroids are used as the main anti-inflammatory therapy; in asthma it is used in any stage of persistent disease, whereas

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Article highlights.

- Asthma and COPD are chronic inflammatory diseases of the airways with different triggers and different inflammation patterns.
- Inhaled corticosteroids are more effective in asthma and of limited usefulness in COPD.
- There is an unmet therapeutic need in both asthma and COPD, because inhaled corticosteroids are not always able to achieve an acceptable disease control.
- Monoclonal antibodies might represent appropriate therapeutic options in severe asthma and in COPD.
- Omalizumab is currently authorized to be used in asthma and it is the most relevant example of the plausibility of such therapies.
- These therapies can be given in a targeted manner in populations in which the pathways to be blocked are upregulated.
- Such an approach opens the doors of personalized medicine and requires the detection of the therapeutic target.

This box summarizes key points contained in the article.

in COPD it is used only in more advanced stages. The therapeutic efficacy of these drugs is more evident in asthma and rather modest in COPD. In both diseases, there are populations of patients with poor corticosteroid response and severe forms of the disease. In such populations, other anti-inflammatory therapies are needed to be used alone or to be added to corticosteroids in order to achieve a better disease control.

Both asthma and COPD are characterized by a heterogeneity of the airways inflammation and this leads to various inflammatory phenotypes and endotypes [3].

Efforts to identify appropriate therapeutic targets and to develop specific anti-inflammatory therapies were made during the recent years and as a result, therapies, such as omalizumab, were authorized to be used in asthma patients. However, despite demonstrated efficacy and long-term safety, omalizumab is not always able to reduce inflammation in all patients with severe uncontrolled asthma. In COPD the inhaled corticosteroids still remain the main anti-inflammatory therapy and newer therapies such as roflumilast are also efficacious only in certain populations.

Therefore, other anti-inflammatory therapies are needed for these two diseases, and currently, various approaches, such as monoclonal antibodies or antisense oligonucleotides, are evaluated for their therapeutic potential. Monoclonal antibodies are currently used in many other chronic inflammatory diseases based on their potent anti-inflammatory effects and might also represent a good therapeutic option in selected populations with severe/uncontrolled asthma or COPD (Table 1).

This review discusses the data on the pathogenic role of various mediators in asthma and COPD and of the effects of their blockade with monoclonal antibodies.

2. Monoclonal antibodies for asthma

In asthma allergen exposure activates Th2 lymphocytes, which in turn stimulate eosinophil infiltration in the airways. Th2 lymphocyte-driven inflammation mediated via complex mechanisms involving cytokines, such as interleukin (IL)-4, -5, -13, represents the pathogenic hallmark of the disease. Other cytokines, such as IL-2, IL-9 or tumor necrosis factor- α (TNF- α), or other proinflammatory molecules also play a role in the amplification of the inflammation.

Monoclonal antibodies can specifically inhibit inflammation and omalizumab is the most relevant example of an available therapy of this kind.

2.1 T cells

CD4⁺(Th2) lymphocytes play a pivotal role in the development and perpetuation of asthma inflammatory response. They are activated via their CD4 receptor, as a consequence of a complex crosstalk of various cytokines, and are involved in eosinophil recruitment, survival and activation in the airways [4]. Therefore the blockade of these cell effectors has a significant therapeutic potential and might be associated with a sustained suppression of the airways inflammation.

Keliximab is a monoclonal immunoglobulin G1 (IgG1) antibody against CD4-receptor which was evaluated in a clinical study performed in patients with steroid-dependent asthma: a dose-dependent improvement in lung function as well as a transient depletion of the Th2 CD4⁺ lymphocytes in blood was reported [5].

2.2 Antibodies targeting cytokine pathways

2.2.1 Interleukin

In asthma, there are various inflammatory pathways which lead to the activation of Th2 lymphocytes, and one such pathway is represented by the IL-2. This cytokine acts via an IL-2 receptor with three subunits, $\alpha\beta\gamma$: the α subunit is also called CD25 which is activated by other proinflammatory molecules, such as NF- κ B, whereas the γ subunit is also found in the structure of other Th2-derived cytokines, such as IL-4 or IL-9 [6,7]. In subjects with severe asthma, an increased expression of the IL-2R was detected on peripheral blood cells, and this was found to regress under anti-inflammatory therapy [8].

Daclizumab is a humanized monoclonal IgG1 antibody against CD25 which is currently approved as a prophylaxis for transplant therapy. This was also evaluated as a potential therapy in asthma in a randomized trial enrolling patients with steroid-dependent asthma: when added to a stable dose of corticosteroids, it improved the lung function and blood eosinophilia [9].

2.2.2 Interleukin-5

IL-5 is expressed and produced by various inflammatory cell populations including Th2-lymphocytes, eosinophils, mast cells, basophils and their CD34⁺ progenitor cells and

Table 1. Investigational monoclonal antibodies evaluated in clinical studies of subjects with severe asthma.

Refs.	Monoclonal antibody	Route of administration	Therapeutic target	Phase	Study design and dosing schedule	Duration of dosing	Endpoints improved
Kon <i>et al.</i> 2001 [5]	Keliximab	i.v.	CD4 ⁺ receptor	II	Randomized placebo-controlled, single dose 0.5, 1.5 and 3 mg/kg		Lung function, blood Th2 cells
Busse <i>et al.</i> 2008 [9]	Daclizumab	i.v.	IL-2R	II	Randomized placebo-controlled 2 and then 1 mg/kg every 2 weeks	20 weeks	Blood eosinophilia, lung function
Kips <i>et al.</i> 2003 [22]	Reslizumab	i.v.	IL-5	II	Randomized, placebo-controlled, single dose, 0.03, 0.1, 0.3 and 1 mg/kg		Blood eosinophilia, lung function
Castro <i>et al.</i> 2011 [23]	Reslizumab	i.v.	IL-5	II	Randomized placebo-controlled study 3 mg/kg every 4 weeks	12 weeks	Disease control, lung function
Halder <i>et al.</i> 2009 al [30]	Mepolizumab	i.v.	IL-5	III	Randomized placebo-controlled study 750 mg every 4 weeks	52 weeks	Severe exacerbations, quality of life, blood and sputum eosinophilia
Nair <i>et al.</i> 2009 [31]	Mepolizumab	i.v.	IL-5	III	Randomized placebo-controlled study 750 mg every 4 weeks	20 weeks	Prednisone sparing, reduction of blood and sputum eosinophilia
Pavord <i>et al.</i> 2012 [32]	Mepolizumab	i.v.	IL-5	III	Randomized placebo-controlled study 75, 250 and 750 mg monthly		Reduction of exacerbations rates
Molfino <i>et al.</i> 2012 [35]	Benralizumab	i.v.	IL-5R α	II	Randomized, placebo-controlled study 0.3 or 1 mg/kg single dose		Reduction of hospitalization risk
Piper <i>et al.</i> 2012 [57]	Talokinumab	s.c.	IL-13	Ila	Randomized placebo-controlled study 150, 300 or 600 mg every 2 weeks	12 weeks	Lung function
Corren <i>et al.</i> 2011 [58]	Lebrikizumab	s.c.	IL-13	II	Randomized placebo-controlled study 250 mg every 4 weeks	24 weeks	Lung function
Wenzel <i>et al.</i> 2009 [65]	Golimumab	s.c.	TNF- α	II	Randomized placebo-controlled study 50 or 100 or 200 mg every 4 weeks	52 weeks	Early study discontinuation

is a major pathogenic cytokine in allergic diseases, such as asthma [10]. Its specific receptor (IL-5R) can be found on surfaces eosinophil, mast cells or their bone marrow precursors and consists of a specific α chain containing the binding site and having no signal transducing function and of the common cytokine β chain which is involved in signal transduction and is shared in common with other cytokine receptors, such as IL-3 or granulocyte-macrophage colony stimulating factor (GM-CSF) [11]. In asthma, it was found that IL-5 is involved in eosinophil differentiation, migration and survival, which clinically translate in sputum eosinophilia and airway hyperresponsiveness (AHR) [12-14].

Inhibitory approaches against IL-5 are currently under investigation and include monoclonal antibodies against the IL-5 and its receptor, antisense oligonucleotides, other receptor antagonists, small interfering RNAs or anti IL-5 vaccines [15,16]. Monoclonal antibodies against IL-5/IL-5R are the most investigated class in asthma and compounds such as mepolizumab, reslizumab or benralizumab were investigated in clinical studies in healthy volunteers and in various asthma subpopulations.

Reslizumab (CTX55700, SCH55700) is a humanized anti-human IL-5 monoclonal antibody (IgG) which in animal studies demonstrated its inhibitory effects on pulmonary eosinophilia and on AHR [17-21]. In the initial clinical study evaluating single doses of reslizumab, significant reduction of the blood eosinophilia and improvement in lung function were reported [22]. A more recent Phase II study evaluating the efficacy and safety found that reslizumab improved the disease control over baseline and the lung function (FEV1 0.18 L with reslizumab vs -0.08 L with placebo, $p = 0.002$) and found that the maximum efficacy on the ACQ scores was exhibited in a subpopulation of asthma patients with nasal polyps. Reslizumab had no influence on exacerbation, rate and was well tolerated, and the most commonly detected adverse events being nasopharyngitis, fatigue and pharyngolaryngeal pain [23].

Mepolizumab (SB-240563) is another anti IL-5 humanized monoclonal antibody which was assessed for its therapeutic potential in diseases, such as asthma or hypereosinophilic syndromes. In preclinical studies performed on monkey asthma model, single dosing was associated with a potent reduction in eosinophil chemotaxis to the lung, and in blood eosinophilia, but failed to impact on the early asthma response, whereas chronic dosing reduced both systemic and pulmonary eosinophil load with no effects on bone marrow precursors [24].

In a clinical study on milder asthma, a single mepolizumab dose of 2.5 to 10 mg/kg reduced sputum and blood eosinophil count, and their increases after allergen challenge and the effect was found to persist up to 4 weeks from dosing. Mepolizumab had no impact on late asthma response [25]. Another study performed again in subjects with milder asthma, mepolizumab given over three months failed to improve lung function or AHR but reduced airways remodeling by reducing collagen deposition in the airways [26,27]. Similar effects were found in

subjects with more severe asthma, uncontrolled with inhaled corticosteroids, with no influence on quality of life, asthma symptoms or use of rescue medication [28]. Chronic mepolizumab administration was however found to reduce airways IL-4 and IL-13 levels and asthma exacerbations rate in various asthma subsets including therapeutic refractoriness or steroid dependence [29-31].

Most recently, a one year placebo-controlled study in subjects with severe eosinophilic asthma and frequent exacerbations found a reduction of the exacerbations rates – the most prominent effect being detected with the highest dosage [32].

Benralizumab (MEDI-563) is a humanized monoclonal antibody against IL-5R α which was found to exert a potent antibody-mediated cell cytotoxicity [33]. In a clinical study performed in subjects with mild atopic asthma and evaluating the safety and pharmacokinetics of MEDI-563, the antibody induced a sustained peripheral eosinopenia lasting up to 12 weeks, reduced the levels of eosinophilic cationic protein and exhibited a dose-proportional pharmacokinetic profile. The most common adverse events were transient increases in C-reactive protein, IL-6 and leukopenia [34]. In a Phase II study benralizumab was assessed for its efficacy and safety in patients with acute severe asthma: a single intravenous infusion of benralizumab added to the standard of care in these patients was associated with a significant reduction in the risk of subsequent hospitalizations for asthma attacks as compared to placebo (0.65 vs 1.62, $p = 0.022$) [35].

2.2.3 Interleukin-4, interleukin-13 and their common pathway

Both IL-4 and IL-13 were known for their major role in allergy and atopy. They exert such activities both individually and in common, due to the common fact that they share in some receptor structures [36-38].

IL-4 contributes to the development of an allergic response in the airways by upregulating the mucin gene and inducing mucus hypersecretion, by triggering the IgE-induced mast cells degranulation, and by stimulating the IgE production by the B lymphocytes [39]. In asthma pathogenesis, IL-4 is also involved in airways remodeling by stimulating the production and release of various profibrogenic mediators, such as eotaxin PDGF or bFGF [40]. IL-4 exerts its effects via a specific IL-4 receptor (type I IL-4R), a heterodimer composed of an α and a common γ which activates STAT6 signaling pathway in various hematopoietic cell lines including eosinophils and mast cells, and can also bind to a type II IL-4 receptor, shared in common with IL-13, having the structure IL-4R α /IL-13R α 1 and being most commonly expressed in non-hematopoietic cell lines, such as Th2 [39,41].

In the airways of subjects with asthma, IL-4 was detected at significantly higher levels compared to healthy controls and its nebulization in asthma subjects resulted in a prompt increase in mucus hypersecretion and sputum eosinophil count [42-44].

IL-13 is also an allergenic cytokine which is released by Th2 lymphocytes, eosinophils or other inflammatory cells,

and has proinflammatory effects which are similar with those of IL-4. These effects are exerted only via the common IL-4R α /IL-13R α 1, because the specific IL-13 receptor, IL-13R α 2 is rather a decoy structure which captures IL-13 and suppresses its related proinflammatory effects [38,41,45]. The IL-13 was also found to be upregulated in the airways of asthma subjects following allergen challenge [46,47].

IL-4 pathway suppression with specific monoclonal antibodies directed against the cytokine or against its receptor was attempted in both preclinical and clinical studies, but the overall efficacy of the approach was found to be rather modest due to the fact that IL-13 pathway remains uninhibited. Pascolizumab is a humanized anti-IL-4 monoclonal antibody which in preclinical studies demonstrated potent blocking effects, whereas in a Phase II clinical study it failed to meet the endpoints of efficacy [48]. IL-4R blockade with monoclonal antibodies was only experimented in preclinical studies [49,50].

Vaccines directed against IL-4, such as conjugate IL-4/hepatitis B virus, were also experimented as approaches to actively induce the blocking antibodies production but their development was not advanced further [51].

IL-13 pathway blockade with monoclonal antibodies was found to be more effective in both preclinical and clinical studies. Anrakinumab (IMA-638) is a humanized anti-IL-13 antibody binding on the IL-13 epitope that attaches to IL-4R α /IL-13R α 1, which was evaluated in a primate model of parasite-induced AHR and was found to reduce airways inflammatory cell count and BAL eotaxin levels as well as the amplitude of the early asthma response [52,53]. Furthermore, anrakinumab was also found to exert its blocking effects without interfering with the effects of IL-13R α 1/2 [54]. In a Phase II study performed in subjects with mild atopic asthma, IMA-638 given subcutaneously twice at a dosage of 2 mg/kg subcutaneously at 1 week interval was found to significantly attenuate both the early and the late asthma responses after 14 days but not after 35 days and had no effect on AHR [55]. Another Phase II study was performed in subjects with persistent asthma, but their results are not available [48]. IMA-026 is another anti IL-13 antibody which binds to the IL-13 epitope specific for the IL-13R α 1/IL-13R α 2 and which was investigated in parallel with IMA-638: unlike the latter, IMA-026 was found to interfere with the neutralizing effects of the specific receptor and probably this was one of the reasons for which its efficacy was found to be more modest in patients with asthma [48,54].

CAT-354 (tralokinumab) is a humanized IgG4 anti IL-13 antibody which is in clinical development for uncontrolled asthma: *in vitro* it was found to block the IL-13 without blocking the IL-4, *in vivo* in animal models of asthma it was found to reduce AHR and eosinophil count [56]. CAT-354 was evaluated in a Phase IIa study over 24 weeks in which it was found to increase the lung function in a sustained manner without significantly influencing the quality of life; furthermore, it was found to exhibit the maximum therapeutic

benefit in subjects with the heaviest eosinophil load in the airways [57]. Tralokinumab is currently investigated in a Phase IIb study.

Lebrikizumab is another humanized anti IL-13 monoclonal antibody of IgG4 which is also under development as an asthma therapy and which was found to improve lung function over placebo, the maximum therapeutic benefit being found in a subset of patients characterized by a high periostin level [58].

Vaccination to induce production of anti IL-13 antibodies was experimented in murine model of asthma and was found to mount an effective IgG production, but no data on clinical efficacy exist yet [51].

Other antibodies, such as QAX-576 or R1671, are also under investigation in clinical studies in asthma [48].

2.2.3.1 Common IL-4/IL-13 pathway

Common IL-4/IL-13 pathway exerts its downstream effects via the type II IL-4 receptor and is a major factor contributing to the amplification of allergen-induced Th2-driven inflammatory response in the airways. AMG-317 is a human IgG2 antibody blocking the IL-4R α and consequently the IL-4/IL-13R α function. In a Phase II study, AMG-317 exhibited a rather modest efficacy, which however was more significant in patients with a more impaired disease control at the time of randomization [59].

2.2.4 Interleukin-9

IL-9 is another Th2-related cytokine which was found to be involved in asthma pathogenesis: in a transgenic mice model, IL-9 overexpression was found to be associated with atopic asthma phenotype traits, such as airways eosinophilia, mucus hypersecretion and AHR [60].

Therapeutic blocking approaches for this cytokine are represented mainly by the MEDI-528 [61]. This is a humanized IgG1 κ monoclonal antibody which in two phase IIa clinical studies was found to exert a linear pharmacokinetic profile and to improve non-significantly lung function. One of the studies had to be stopped due to the fact that a serious adverse event was found in a patient [62].

2.2.5 Tumor necrosis factor- α

TNF- α is a proinflammatory cytokine with demonstrated pathogenic roles in various chronic diseases, including rheumatoid arthritis, psoriasis or chronic airways diseases. In asthma for example, it was demonstrated that TNF- α was upregulated in the airways mostly in the patients with severe steroid-dependent asthma who demonstrated the largest TNF- α mRNA expression in bronchioloalveolar lavage fluid (BAL) as well as the highest number of TNF- α -producing mast cells in the airways [63].

TNF- α blockade was attempted in asthma with fusion proteins, such as etanercept, or with humanized monoclonal antibodies, such as infliximab or golimumab. Infliximab was evaluated in a clinical study in patients with moderate asthma

and was found to reduce the diurnal lung function variability and the risk of exacerbations, whereas golimumab was assessed in patients with severe asthma but the study was prematurely discontinued due to an unfavorable risk:benefit ratio [64,65].

2.2.6 Other cytokines: IL-17 and IL-25

IL-17 is a cytokine related to autoimmunity contributing to migration and activation of neutrophils. In asthma, IL-17 was recently highlighted as a pathogenic cytokine involved in a subset of severe asthma characterized by heavy neutrophilic inflammation in the airways. Brodalumab is a humanized anti IL-17 antibody which is currently evaluated in other autoimmune diseases, such as psoriasis, demonstrating good efficacy and safety [66]. It is currently tested in asthma.

IL-25 was also found to exert proinflammatory effects in the airways by binding to the IL-17R and activating Th2 lymphocytes, eosinophils and mucus hypersecretion [67]. Similar to IL-17, IL-25 is involved in the pathogenesis of the steroid refractory asthma [68]. Monoclonal IL-25 antibodies are currently evaluated in other autoimmune conditions, such as ulcerative colitis.

2.3 Immunoglobulin E

Immunoglobulin E (IgE) was earlier demonstrated to be involved in the early atopic asthma response as a result of its interaction with FcεR I and II expressed on mast cells, basophils or dendritic cells and drew the attention on them as a potential therapeutic target [69]. Its neutralization with monoclonal antibodies was tested in preclinical models and in many clinical studies in subjects with atopic asthma, and as a result, omalizumab a humanized anti IgE antibody which binds to this antibody and prevents its binding to FcεR I was the first of the kind therapy authorized for this condition. In patients with severe asthma, in particular, omalizumab was found to reduce the exacerbations risk and severity and was associated with steroid dose tapering [70,71].

Subsequently other monoclonal antibodies against other components of the IgE pathway were developed: lumiliximab, for example, was an anti FcεRII antibody which was planned to be developed for asthma was tested in preclinical studies on peripheral mononuclear cells from atopic asthma subjects where it suppressed the allergen-induced activation of Th2 lymphocytes, but subsequently it was developed for chronic leukemia [72]. CGP51901 is another monoclonal anti IgE antibody which binds the free IgE and the IgE bound on the surface of B cells, which after being initially tested in asthma subjects was subsequently discontinued in favor of omalizumab [48]. Other monoclonal antibodies targeting the IgE pathway, such as HAE1 or MEDI-4212, were also planned to be developed for asthma but were subsequently discontinued [48]. The most novel approach is represented by a monoclonal antibody directed against an amino acid fragment expressed only by B lymphocytes-bound IgE and called 'M1' and which has the potential to reduce an allergic

response by depleting the IgE producing cells [73]. MEMP1972A is such an antibody which in Phase I studies performed in patients with allergic rhinitis was found to exert a sustained depletive effect on IgE, whereas in Phase II proof of concept study in asthma, it was found to blunt both early and late asthma responses and reduce the levels of membrane-bound IgE [74,75].

2.4 Chemokine pathways and their targeting monoclonal antibodies

2.4.1 C-C chemokine receptor 4

C-C chemokines are involved in maturation, tissue migration and homing of various populations of lymphocytes, including Th2. C-C chemokine receptor 4 (CCR4) is expressed on the surface of several cell populations, including Th2 lymphocytes or mast cells, and under physiological conditions they maintain the balance among various lymphocyte subsets.

CCR4 was found to be overexpressed in T lymphocyte malignancies as well as in asthma. Its blockade with a nonbiological agent was found to be associated with a significant reduction of airways allergy in a preclinical study [76]. Mogamulizumab, a humanized monoclonal antibody against CCR4 was found to exert potent suppressing effects in T cell lymphoma/leukemia and is also planned to be evaluated in asthma [77].

2.4.2 C-C chemokine receptor 3

CCR3 is expressed on the surface of the eosinophil cells and in asthma, along with its ligand, eotaxin is involved in migration in the airways [78]. Furthermore, CCR3 levels were found to correlate with the AHR severity and with asthma severity [79,80]. CAT-213 is a human monoclonal IgG4 antibody against CCR3 which previously was evaluated for its neutralizing affinity *ex vivo* in sputum from asthma patients, but was no longer subsequently developed for this disease [80].

2.5 Other pathogenic pathways and targeting monoclonal antibodies: TSLP, OX40L, kalikrein

Thymic stromal lymphopoietin (TSLP) is also upregulated in atopic asthma as a result of the injury of the airways epithelium by various allergens and it promotes the Th2 inflammation at bronchial level [81,82]. It was also incriminated in asthma development in patients with atopic dermatitis and was also found to be upregulated in a subset of patients with severe asthma characterized by poor steroid sensitivity [83,84]. An experimental study using monoclonal anti-TSLP antibodies found that the inflammation blockade they induced in the airways might be worth being further investigated for its therapeutic potential [85].

OX40 is a member of TNF receptors family expressed on the surface of dendritic cells and along with its ligand OX40L is involved in maturation of Th2 cells [86]. OX40 has been found to be exert a proinflammatory effect

in asthma: in the OX40-/- transgenic mice ovalbumine sensitization is found to induce modest asthmatic traits compared to wild type mice, whereas OX40L blockade with monoclonal antibodies significantly reduces eosinophilic infiltration in the lungs [87].

Tissue kallikrein-1 (KLK1) is a serin protease which was also found to be potent proinflammatory mediators by activating kinins, such as bradykinine, the latter being demonstrated to cause bronchospasm and mucus hypersecretion upon inhalation in subjects with asthma but not in healthy subjects [88]. KLK was also found to be present at high levels in the BAL from asthma subjects, thus further increasing after allergen challenge [89]. DX-2300 is a human monoclonal antibody which is currently in preclinical development as a potential asthma therapy. In a study performed in sheep model of ascaris-induced asthma, DX-2300 given via either inhalatory or intravenous routes was found to block the late asthma response, to reduce the neutrophil influx in the airways and to minimize the amplitude of the kininogen-induced bronchospasm [90].

3. Monoclonal antibodies for COPD

In COPD, the airways inflammation is mainly related to smoking exposure and its pattern is different from that found in asthma. The most prominent feature of this inflammation is represented by the reduced responsiveness to corticosteroids, and this explains why the efficacy of such therapy is limited in COPD compared to asthma. Therefore, there is a significant unmet therapeutic need as far as the anti-inflammatory therapies are concerned. Roflumilast, an oral phosphodiesterase 4 inhibitor was also recently authorized to be used in patients with more advanced disease, but there is still a need for more anti-inflammatory therapies with different mechanisms of action and able to tackle the complex inflammation in COPD.

3.1 Tumor necrosis factor-alpha

TNF- α is a proinflammatory cytokine which was also found to be involved in COPD pathogenesis. Previous studies demonstrated that this mediator is involved in the persistence of the neutrophil inflammation in the airways, and in lung parenchyma also produces weight loss [91]. In fact, in COPD subjects with cachexia, the serum TNF- α levels were found to be significantly higher than in noncachectic homologues [92]. TNF- α expression might also correlate with the disease severity because in one study circulating TNF- α levels were found to correlate directly with dyspnea severity and inversely with pO_2 [93,94].

The first evidence of usefulness of TNF- α blockade in COPD came not as might be expected from the direct efficacy data from a clinical trial but from indirect observation of a significant reduction of hospitalization risks in patients with COPD receiving TNF- α inhibitors for comorbid diseases, such as rheumatoid arthritis [95]. Subsequently, clinical studies

evaluating the effects of TNF- α blockade were evaluated using infliximab. This is a humanized IgG1 anti-TNF- α antibody which is currently authorized for the therapy of rheumatoid arthritis, psoriatic arthritis or other degenerative diseases. The initial short-term small sample study in which sputum neutrophilia was the primary endpoint yielded no robust efficacy results, and a similar modest efficacy was reported in a 24-week randomized study in which, however, a *post-hoc* analysis demonstrated a significant efficacy of infliximab in a COPD subset of cachectic subjects [96,97].

3.2 Interleukin-1 β

IL-1 β is a proinflammatory cytokine with prominent role in various autoimmune diseases in being released by various cell populations, including macrophages, mast cells or epithelial cells. Canakinumab (ACZ885) is a human anti-IL-1 β antibody, which is currently authorized as an orphan drug for some rare inflammatory syndromes, such as cryopyrin-associated periodic syndrome, and is investigated in a Phase I/II study in COPD [98]. Another similar antibody MEDI-8968 is currently investigated in a clinical study [99].

3.3 Interleukin-8 monoclonal antibody

IL-8 is produced by various cells, such as macrophages, epithelial cells or endothelial cells, and in COPD is found to be upregulated in the airways. ABX-IL8 is a human IgG2 monoclonal antibody which when tested in COPD patients produced an improvement in dyspnea severity [100].

3.4 Interleukin-6

IL-6 plays a major pathogenic role in COPD, in both stable state and during exacerbations and is released as a result of IL-17 action. In COPD, some IL-6 gene polymorphisms were found to be associated with accelerated lung function decline, whereas in healthy smokers these were associated with a higher risk of COPD development [2]. Anti-IL-6 monoclonal antibodies are currently under investigation for their anti-inflammatory efficacy in preclinical models of COPD [101].

3.5 Interleukin-17

IL-17 is another cytokine which was more recently found to contribute to neutrophilic inflammation in COPD and the blocking antibodies which are currently evaluated as experimental therapies were found to reduce this population of inflammatory cells [102].

3.6 Interleukin-18

IL-18 was found to be involved in the inflammation found in COPD: in a study performed on transgenic mice with inducible IL-18, emphysema lesions, mucus cells metaplasia, pulmonary hypertension, airways remodeling as well as airways infiltrates with CD4⁺, CD8⁺ and CD19⁺ were found [103]. MEDI-2338, a humanized monoclonal antibody against IL-18, is currently under investigation as a potential

therapy in COPD. When tested in preclinical studies, it demonstrated a high binding affinity and potent anti-inflammatory effects *in vitro*. MEDI-2338 was also assessed in a Phase I study in subjects with COPD, but the results are not yet available [104].

4. Expert opinion

Asthma and COPD are both chronic inflammatory diseases with different etiologies and pathogenesis. The difference in their inflammation pattern in the airways is also reflected on the therapeutic response to conventional anti-inflammatory therapies, such as corticosteroids. In asthma, disease control can be achieved with inhaled corticosteroids, whereas in COPD such therapies are usually only able to reduce the risk of exacerbations in patients with severe or very severe disease stage.

However, in both diseases, there are patients subsets in which such therapies are not able to reduce the airways inflammation in a sustained and significant manner, and in such patients the disease has clinical features of severity, of rapid progress or is associated with a high lethal risk.

Such patients might benefit by a more aggressive anti-inflammatory therapy regimen, obtained by adding a more specific compound capable of inhibiting the inflammation pathway not adequately tackled by corticosteroids, to the latter.

However, this requires two issues to be addressed. The first one is represented by the detection of inflammatory pathway which is abnormally upregulated and which confer a poor prognosis to the underlying disease. There are a number of studies which were able to document the association between cytokine gene polymorphisms leading to an amplified inflammation, and severe clinical phenotypes in asthma and in COPD. Other studies were able to validate indirect biomarkers of abnormal cytokine expression. Such results might be the basis for the development of a cytokine gene battery test which should become commercially available and could assist the physicians in characterizing the factors of disease severity and further in diagnosing inflammation phenotypes, such as, for example, 'IL-9' phenotype in asthma or 'TNF- α ' phenotype in COPD.

Such specific inflammation pathways can though be upregulated constantly or during disease exacerbation. However, little is known on this aspect and this should be better documented because this dictates the necessity to additionally treat during the stable state or only during exacerbations.

The second one is represented by the availability of therapies that can specifically inhibit the overexpressed cytokine pathway, and one of the most suitable therapeutic blockades is represented by that produced with monoclonal antibodies. In fact, a large range of monoclonal antibodies are currently under investigation for asthma and COPD, and many are currently investigated in clinical studies enrolling patients who do not always belong to the severe subset and this might explain in part, why the clinical efficacy of such therapeutic candidates are lower than expected. A step ahead to detect the disease population in which a certain monoclonal antibody would exert the maximal therapeutic benefit was done recently by two studies investigating two anti-IL-13 monoclonal antibodies. In the clinical study evaluating lebrikizumab, periostin was identified as its biomarker of efficacy, whereas in the study on tralokinumab, the highest sputum eosinophil count was associated with the most beneficial document.

Such examples demonstrate the plausibility and feasibility of the approach which should be used in other clinical studies.

Furthermore, an adequate scheduling of such therapies should be established based not only on their pharmacokinetic profile but also on the persistence of the targeted inflammation pathway: in some cases this might be found in the stable disease, whereas in other cases this might be only an event during exacerbations. Some clinical studies performed with TNF- α inhibitor etanercept in COPD exacerbations or with monoclonal antibody benralizumab during acute asthma attacks already support this.

More targeted diagnosis and therapy of inflammation in asthma and COPD open the door for a personalized management in specific disease subsets and this might represent the way forward and the solution for a better disease control.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

Bibliography

Papers of special note have been highlighted as either of interest (●) or of considerable interest (●●) to readers.

1. Makris D, Lazarou S, Alexandrakis M, et al. Tc2 response at the onset of copd exacerbations. *Chest J* 2008;134:483-8
2. He J-Q, Foreman MG, Shumansky K, et al. Associations of il6 polymorphisms with lung function decline and copd. *Thorax* 2009;64:698-704
3. Lotvall J, Akdis CA, Bacharier LB, et al. Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. *J Allergy Clin Immunol* 2011;127:355-60
- **Excellent review on the heterogeneity of asthma phenotypes and endotypes.**
4. Ckless K, Hodgkins SR, Ather JL, et al. Epithelial, dendritic, and CD4+ t cell regulation of and by reactive oxygen and nitrogen species in allergic sensitization. *Biochim Biophys Acta* 2011;1810:1025-34
5. Kon OM, Sihra BS, Loh LC, et al. The effects of an anti-cd4 monoclonal antibody, keliximab, on peripheral blood CD4+ t-cells in asthma. *Eur Respir J* 2001;18:45-52
6. Russell SM, Keegan AD, Harada N, et al. Interleukin-2 receptor gamma chain: a functional component of the interleukin-4 receptor. *Science* 1993;262:1880-3
7. Waldmann TA. The interleukin-2 receptor. *J Biol Chem* 1991;266:2681-4
8. Corrigan CJ, Hartnell A, Kay AB. T lymphocyte activation in acute severe asthma. *Lancet* 1988;1:1129-32
9. Busse WW, Israel E, Nelson HS, et al. Daclizumab improves asthma control in patients with moderate to severe persistent asthma: a randomized, controlled trial. *Am J Respir Crit Care Med* 2008;178:1002-8
10. Allakhverdi Z, Comeau MR, Smith DE, et al. CD34+ hemopoietic progenitor cells are potent effectors of allergic inflammation. *J Allergy Clin Immunol* 2009;123:472-8; e471
11. Kouro T, Takatsu K. Il-5- and eosinophil-mediated inflammation: from discovery to therapy. *Int Immunol* 2009;21:1303-9
12. Bousquet J, Chanez P, Lacoste JY, et al. Eosinophilic inflammation in asthma. *N Engl J Med* 1990;323:1033-9
13. Romagnoli M, Vachier I, Tarodo de la Fuente P, et al. Eosinophilic inflammation in sputum of poorly controlled asthmatics. *Eur Respir J* 2002;20:1370-7
14. Takatsu K, Nakajima H. Il-5 and eosinophilia. *Curr Opin Immunol* 2008;20:288-94
15. Hertz M, Mahalingam S, Dalum I, et al. Active vaccination against il-5 bypasses immunological tolerance and ameliorates experimental asthma. *J Immunol* 2001;167:3792-9
16. Molino NA, Gossage D, Kolbeck R, et al. Molecular and clinical rationale for therapeutic targeting of interleukin-5 and its receptor. *Clini Exp Allergy* 2012;42:712-37
- **Review on the rationale of IL-5 targeting in asthma.**
17. Egan RW, Athwahl D, Chou CC, et al. Inhibition of pulmonary eosinophilia and hyperreactivity by antibodies to interleukin-5. *Int Arch Allergy Immunol* 1995;107:321-2
18. Singh AD, Sanderson CJ. Anti-interleukin 5 strategies as a potential treatment for asthma. *Thorax* 1997;52:483-5
19. Mauser PJ, Pitman A, Witt A, et al. Inhibitory effect of the trfk-5 anti-il-5 antibody in a guinea pig model of asthma. *Am Rev Respir Dis* 1993;148:1623-7
20. Mauser PJ, Pitman AM, Fernandez X, et al. Effects of an antibody to interleukin-5 in a monkey model of asthma. *Am J Respir Crit Care Med* 1995;152:467-72
21. Greenfeder S, Umland S, Cuss F, et al. Th2 cytokines and asthma – the role of interleukin-5 in allergic eosinophilic disease. *Respir Res* 2001;2:71-9
22. Kips JC, O'Connor BJ, Langley SJ, et al. Effect of sch55700, a humanized anti-human interleukin-5 antibody, in severe persistent asthma: a pilot study. *Am J Respir Crit Care Med* 2003;167:1655-9
23. Castro M, Mathur S, Hargreave F, et al. Reslizumab for poorly controlled, eosinophilic asthma. *Am J Respir Crit Care Med* 2011;184:1125-32
24. Hart TK, Cook RM, Zia-Amirhosseini P, et al. Preclinical efficacy and safety of mepolizumab (sb-240563), a humanized monoclonal antibody to il-5, in cynomolgus monkeys. *J Allergy Clin Immunol* 2001;108:250-7
25. Leckie MJ. Anti-interleukin-5 monoclonal antibodies: preclinical and clinical evidence in asthma models. *Am J Respir Med* 2003;2:245-59
26. Flood-Page P, Menzies-Gow A, Phipps S, et al. Anti-il-5 treatment reduces deposition of ecm proteins in the bronchial subepithelial basement membrane of mild atopic asthmatics. *J Clin Invest* 2003;112:1029-36
27. Flood-Page PT, Menzies-Gow AN, Kay AB, Robinson DS. Eosinophil's role remains uncertain as anti-interleukin-5 only partially depletes numbers in asthmatic airway. *Am J Respir Crit Care Med* 2003;167:199-204
28. Flood-Page P, Swenson C, Faiferman I, et al. A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma. *Am J Respir Crit Care Med* 2007;176:1062-71
29. Buttner C, Lun A, Splettssoesser T, et al. Monoclonal anti-interleukin-5 treatment suppresses eosinophil but not t-cell functions. *Eur Respir J* 2003;21:799-803
30. Halder P, Brightling CE, Hargadon B, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med* 2009;360:973-84
- **Paired studies on the efficacy of anti-IL-5 antibodies in two asthma phenotypes.**
31. Nair P, Pizzichini MM, Kjarsgaard M, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med* 2009;360:985-93
- **Paired studies on the efficacy of anti-IL-5 antibodies in two asthma phenotypes.**
32. Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (dream): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012;380:651-9
- **Most recent study on the efficacy of mepolizumab in severe uncontrolled asthma.**

33. Kolbeck R, Kozhich A, Koike M, et al. Medi-563, a humanized anti-il-5 receptor alpha mab with enhanced antibody-dependent cell-mediated cytotoxicity function. *J Allergy Clin Immunol* 2010;125:1344-53; e1342
34. Busse WW, Katial R, Gossage D, et al. Safety profile, pharmacokinetics, and biologic activity of medi-563, an anti-il-5 receptor alpha antibody, in a phase i study of subjects with mild asthma. *J Allergy Clin Immunol* 2010;125:1237-44; e1232
35. Molino NA, Nowak R, Silverman RA, et al. Reduction in the number and severity of exacerbations following acute severe asthma: results of a placebo-controlled, randomized clinical trial with benralizumab. *Am J Respir Crit Care Med* 2012;185:A2753
36. Antoniu SA. Cytokine antagonists for the treatment of asthma: progress to date. *BioDrugs* 2009;23:241-51
37. Andrews AL, Holloway JW, Holgate ST, Davies DE. Il-4 receptor alpha is an important modulator of il-4 and il-13 receptor binding: implications for the development of therapeutic targets. *J Immunol* 2006;176:7456-61
- **Paper describing the role of IL4/IL13 axis in asthma pathogenesis.**
38. Andrews AL, Nasir T, Buchieri F, et al. Il-13 receptor alpha 2: a regulator of il-13 and il-4 signal transduction in primary human fibroblasts. *J Allergy Clin Immunol* 2006;118:858-65
39. Steinke JW, Borish L. Th2 cytokines and asthma. Interleukin-4: its role in the pathogenesis of asthma, and targeting it for asthma treatment with interleukin-4 receptor antagonists. *Respir Res* 2001;2:66-70
- **Excellent review on the IL-4 role in asthma and on the effects of its inhibition.**
40. Sommer M, Eismann U, Gerth J, Stein G. Interleukin 4 co-stimulates the pdgf-bb- and bfgf-mediated proliferation of mesangial cells and myofibroblasts. *Nephron* 2002;92:868-82
41. Ramalingam TR, Pesce JT, Sheikh F, et al. Unique functions of the type ii interleukin 4 receptor identified in mice lacking the interleukin 13 receptor [alpha]1 chain. *Nat Immunol* 2008;9:25-33
42. Leonard C, Tormey V, Burke C, Poulter LW. Allergen-induced cytokine production in atopic disease and its relationship to disease severity. *Am J Respir Cell Mol Biol* 1997;17:368-75
43. Shi HZ, Xiao CQ, Zhong D, et al. Effect of inhaled interleukin-5 on airway hyperreactivity and eosinophilia in asthmatics. *Am J Respir Crit Care Med* 1998;157:204-9
44. Perkins C, Wills-Karp M, Finkelman FD. Il-4 induces il-13-independent allergic airway inflammation. *J Allergy Clin Immunol* 2006;118:410-19
45. Kasaian MT, Miller DK. Il-13 as a therapeutic target for respiratory disease. *Biochem Pharmacol* 2008;76:147-55
46. Batra V, Musani AI, Hastie AT, et al. Bronchoalveolar lavage fluid concentrations of transforming growth factor (tgf)-beta1, tgf-beta2, interleukin (il)-4 and il-13 after segmental allergen challenge and their effects on alpha-smooth muscle actin and collagen iii synthesis by primary human lung fibroblasts. *Clin Exp Allergy* 2004;34:437-44
47. Prieto J, Lensmar C, Roquet A, et al. Increased interleukin-13 mrna expression in bronchoalveolar lavage cells of atopic patients with mild asthma after repeated low-dose allergen provocations. *Respir Med* 2000;94:806-14
48. Catley MC, Coote J, Bari M, Tomlinson KL. Monoclonal antibodies for the treatment of asthma. *Pharmacol Ther* 2011;132:333-51
- **Excellent review on the monoclonal antibodies with therapeutic potential in asthma.**
49. Perkins C, Wills-Karp M, Finkelman FD. Il-4 induces il-13-independent allergic airway inflammation. *J Allergy Clin Immunol* 2006;118:410-19
50. Gavett SH, O'Hearn DJ, Karp CL, et al. Interleukin-4 receptor blockade prevents airway responses induced by antigen challenge in mice. *Am J Physiol* 1997;272:L253-61
51. Ma Y, HayGlass KT, Becker AB, et al. Novel recombinant interleukin-13 peptide-based vaccine reduces airway allergic inflammatory responses in mice. *Am J Respir Crit Care Med* 2007;176:439-45
52. Bree A, Schlerman FJ, Wadanoli M, et al. Il-13 blockade reduces lung inflammation after ascaris suum challenge in cynomolgus monkeys. *J Allergy Clin Immunol* 2007;119:1251-7
53. Kasaian MT, Tan XY, Jin M, et al. Interleukin-13 neutralization by two distinct receptor blocking mechanisms reduces immunoglobulin e responses and lung inflammation in cynomolgus monkeys. *J Pharmacol Exp Ther* 2008;325:882-92
54. Kasaian MT, Raible D, Marquette K, et al. Il-13 antibodies influence il-13 clearance in humans by modulating scavenger activity of il-13alpha2. *J Immunol* 2011;187:561-9
55. Gauvreau GM, Boulet L-P, Cockcroft DW, et al. Effects of interleukin-13 blockade on allergen-induced airway responses in mild atopic asthma. *Am J Respir Crit Care Med* 2011;183:1007-14
56. May RD, Monk PD, Cohen ES, et al. Preclinical development of cat-354, an il-13 neutralizing antibody, for the treatment of severe uncontrolled asthma. *Br J Pharmacol* 2012;166:177-93
57. Piper E, Brightling C, Niven R, et al. A phase 2 placebo-controlled study of tralokinumab in moderate-to-severe asthma. *Eur Respir J* 2012; [Epub ahead of print]
- **Papers evaluating the initial clinical efficacy of anti-IL-13 antibodies in patients with severe uncontrolled asthma.**
58. Corren J, Lemanske RF, Hanania NA, et al. Lebrikizumab treatment in adults with asthma. *N Engl J Med* 2011;365:1088-98
- **Papers evaluating the initial clinical efficacy of anti-IL-13 antibodies in patients with severe uncontrolled asthma.**
59. Corren J, Busse W, Meltzer EO, et al. A randomized, controlled, phase 2 study of amg 317, an il-4alpha antagonist, in patients with asthma. *Am J Respir Crit Care Med* 2010;181:788-96
60. Temann UA, Geba GP, Rankin JA, Flavell RA. Expression of interleukin 9 in the lungs of transgenic mice causes airway inflammation, mast cell hyperplasia, and bronchial hyperresponsiveness. *J Exp Med* 1998;188:1307-20
61. Antoniu SA. Medi-528, an anti-il-9 humanized antibody for the

- treatment of asthma. *Curr Opin Mol Ther* 2010;12:233-9
62. Parker J, Oh C, LaForce C, Group tM-CT. Safety profile and clinical activity of multiple subcutaneous doses of medi-528, a humanized anti-interleukin-9 monoclonal antibody, in two randomized phase 2a studies in subjects with asthma. *BMC Pulm Med* 2011;11:14
63. Howarth PH, Babu KS, Arshad HS, et al. Tumour necrosis factor (tnfalpa) as a novel therapeutic target in symptomatic corticosteroid dependent asthma. *Thorax* 2005;60:1012-18
- **Paper discussing the role of TNF- α in asthma pathogenesis and the effects of its inhibition.**
64. Erin EM, Leaker BR, Nicholson GC, et al. The effects of a monoclonal antibody directed against tumor necrosis factor-alpha in asthma. *Am J Respir Crit Care Med* 2006;174:753-62
65. Wenzel SE, Barnes PJ, Bleecker ER, Investigators oborTA. A randomized, double-blind, placebo-controlled study of tumor necrosis factor-alpha blockade in severe persistent asthma. *Am J Respir Crit Care Med* 2009;179:549-58
66. Papp KA, Leonardi C, Menter A, et al. Brodalumab, an anti-interleukin-17-receptor antibody for psoriasis. *N Engl J Med* 2012;366:1181-9
67. Suzukawa M, Morita H, Nambu A, et al. Epithelial cell-derived il-25, but not th17 cell-derived il-17 or il-17f, is crucial for murine asthma. *J Immunol* 2012;189:3641-52
68. Petersen BC, Lukacs NW. Il-17a and il-25: Therapeutic targets for allergic and exacerbated asthmatic disease. *Future Med Chem* 2012;4:833-6
69. Holgate S, Smith N, Massanari M, Jimenez P. Effects of omalizumab on markers of inflammation in patients with allergic asthma. *Allergy* 2009;64:1728-36
70. Holgate ST, Chuchalin AG, Hebert J, Omalizumab 011 International Study G. Efficacy and safety of a recombinant anti-immunoglobulin e antibody (omalizumab) in severe allergic asthma. *Clin Exp Allergy* 2004;34:632-8
- **One of the landmark studies evaluating omalizumab in patients with asthma.**
71. Holgate S, Buhl R, Bousquet J, et al. The use of omalizumab in the treatment of severe allergic asthma: a clinical experience update. *Respir Med* 2009;103:1098-113
72. Poole JA, Meng J, Reff M, et al. Anti-cd23 monoclonal antibody, lumiliximab, inhibited allergen-induced responses in antigen-presenting cells and t cells from atopic subjects. *J Allergy Clin Immunol* 2005;116:780-8
73. Brightbill HD, Jeet S, Lin Z, et al. Antibodies specific for a segment of human membrane ige deplete ige-producing b cells in humanized mice. *J Clin Invest* 2010;120:2218-29
74. Scheerens H PW, Zheng Y, Wang Y, et al. Treatment with mep1972a, an anti-m1 prime monoclonal antibody, reduced serum ige in healthy volunteers and patients with allergic rhinitis. *Am J Respir Crit Care Med* 2012;185:A6791
75. Gauvreau G BL, Cockcroft DW, Davis B, et al. Effect of an anti-m1 prime monoclonal antibody, mep1972a, in a phase ii proof-of-activity allergen challenge study in patients with mild asthma. *Am J Respir Crit Care Med* 2012;185:A6793
76. Nakagami Y, Kawase Y, Yonekubo K, et al. Rs-1748, a novel cc chemokine receptor 4 antagonist, inhibits ovalbumin-induced airway inflammation in guinea pigs. *Biol Pharm Bull* 2010;33:1067-9
77. Antoniu SA. Mogamulizumab, a humanized mab against c-c chemokine receptor 4 for the potential treatment of t-cell lymphomas and asthma. *Curr Opin Mol Ther* 2010;12:770-9
78. Willems LI, Ijzerman AP. Small molecule antagonists for chemokine ccr3 receptors. *Med Res Rev* 2010;30:778-817
79. Taha RA, Laberge S, Hamid Q, Olivenstein R. Increased expression of the chemoattractant cytokines eotaxin, monocyte chemoattractant protein-4, and interleukin-16 in induced sputum in asthmatic patients. *Chest* 2001;120:595-601
80. Dent G, Hadjicharalambous C, Yoshikawa T, et al. Contribution of eotaxin-1 to eosinophil chemotactic activity of moderate and severe asthmatic sputum. *Am J Respir Crit Care Med* 2004;169:1110-17
81. Bosnjak B, Stelzmueller B, Erb K, Epstein M. Treatment of allergic asthma: modulation of th2 cells and their responses. *Respir Res* 2011;12:114
82. Bartemes KR, Kita H. Dynamic role of epithelium-derived cytokines in asthma. *Clin Immunol* 2012;143:222-35
83. Han H, Xu W, Headley MB, et al. Thymic stromal lymphopoietin (tslp)-mediated dermal inflammation aggravates experimental asthma. *Mucosal Immunol* 2012;5:342-51
84. Shikotra A, Choy DF, Ohri CM, et al. Increased expression of immunoreactive thymic stromal lymphopoietin in patients with severe asthma. *J Allergy Clin Immunol* 2012;129:104-11; e109
85. Shi L, Leu S-W, Xu F, et al. Local blockade of tslp receptor alleviated allergic disease by regulating airway dendritic cells. *Clin Immunol* 2008;129:202-10
86. Kaur D, Brightling C. Ox40/ox40 ligand interactions in t-cell regulation and asthma. *Chest J* 2012;141:494-9
- **Paper highlighting the potential role of OX40 as a therapeutic target.**
87. Hoshino A, Tanaka Y, Akiba H, et al. Critical role for ox40 ligand in the development of pathogenic th2 cells in a murine model of asthma. *Eur J Immunol* 2003;33:861-9
88. Barnes PJ. Bradykinin and asthma. *Thorax* 1992;47:979-83
89. Christiansen SC, Proud D, Sarnoff RB, et al. Elevation of tissue kallikrein and kinin in the airways of asthmatic subjects after endobronchial allergen challenge. *Am Rev Respir Dis* 1992;145:900-5
90. Sexton DJ, Chen T, Martik D, et al. Specific inhibition of tissue kallikrein 1 with a human monoclonal antibody reveals a potential role in airway diseases. *Biochem J* 2009;422:383-92
91. Di Francia M, Barbier D, Mege JL, Orehek J. Tumour necrosis factor-alpha levels and weight loss in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1994;150:1453-5
92. de Godoy I, Donahoe M, Calhoun WJ, et al. Elevated tnfr-alpha production by peripheral blood monocytes of weight-losing copd patients. *Am J Respir Crit Care Med* 1996;153:633-7
93. Takabatake N, Nakamura H, Abe S, et al. The relationship between chronic

- hypoxemia and activation of the tumor necrosis factor- α system in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000;161:1179-84
94. Garrod R, Marshall J, Barley E, et al. The relationship between inflammatory markers and disability in chronic obstructive pulmonary disease (copd). *Prim Care Respir J* 2007;16:236-40
 95. Suissa S, Ernst P, Hudson M. Tnf- α antagonists and the prevention of hospitalisation for chronic obstructive pulmonary disease. *Pulm Pharmacol Ther* 2008;21:234-8
 - **Seminal paper demonstrating the improvement in COPD morbidity in patients undergoing anti-TNF- α therapy.**
 96. Rennard SI, Fogarty C, Kelsen S, et al. The safety and efficacy of infliximab in moderate to severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007;175:926-34
 97. van der Vaart H, Koeter GH, Postma DS, et al. First study of infliximab treatment in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005;172:465-9
 98. Dhimolea E. Canakinumab. *mAbs* 2010;2:3-13
 99. A study to evaluate the efficacy of medi8968 in chronic obstructive pulmonary disease (spring). NCT01448850. Available from: www.clinicaltrials.gov [Accessed on October 2012]
 100. Mahler DA, Huang S, Tabrizi M, Bell GM. Efficacy and safety of a monoclonal antibody recognizing interleukin-8 in copd*a pilot study. *Chest J* 2004;126:926-34
 101. Kubera J HK, Williams C, Hubeau C. Interleukin-6 neutralization abrogates acute exacerbation-like disease in a model of cigarette smoke-induced pulmonary inflammation. *Am J Respir Crit Care Med* 2012;185:A3876
 102. Shen N, Wang J, Zhao M, et al. Anti-interleukin-17 antibodies attenuate airway inflammation in tobacco-smoke-exposed mice. *Inhal Toxicol* 2011;23:212-18
 - **Paper evaluating the inhibitory effects of mAbs against IL-17 in an animal model of smoking-induced airways inflammation.**
 103. Kang M-J, Choi J-M, Kim BH, et al. IL-18 induces emphysema and airway and vascular remodeling via ifn- γ , il-17a, and il-13. *Am J Respir Crit Care Med* 2012;185:1205-17
 104. Medi-2338. Available from: <http://www.ncats.nih.gov/files/MEDI2338.pdf>

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