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Review

"Targeted Therapy in Eosinophilic Chronic Obstructive Pulmonary Disease"

Mathieu Fieldes[1], Chloé Bourguignon[1], Said Assou[1], Amel Nasri[1], Aurélie Fort[2,3], Isabelle Vachier[2], John De Vos[1,4], Engi Ahmed[2*] and Arnaud Bourdin[2,3]*

[1] IRMB, INSERM, Montpellier University Hospital, Montpellier, France (m_fieldes@hotmail.com, chloe.bourguignon@inserm.fr, said.assou@inserm.fr, amel.nasri@inserm.fr, john.devos@inserm.fr)

[2] Department of Respiratory Diseases, Montpellier University Hospital, INSERM, Montpellier, France (isabelle.vachier@medbiomed.fr, e-ahmed@chu-montpellier.fr, a-bourdin@chu-montpellier.fr)

[3] PhyMedExp, University of Montpellier, INSERM U1046, Montpellier, France. (aurelie.fort@inserm.fr)

[4] Department of Cell and Tissue Engineering, Montpellier University Hospital, Montpellier, France

* Correspondence:
e-ahmed@chu-montpellier.fr, a-bourdin@chu-montpellier.fr;
Tel. : EA +33467042020 - AB+33467336126 A
Hopital Arnaud de Villeneuve
371 Av Doyen Gaston Giraud
34295 Montpellier Cx 5

Take Home Message:

Patients with severe COPD and eosinophilic inflammation experience uncontrolled symptoms despite an optimal pharmaceutical treatment. The development of new biomarkers is mandatory for better phenotyping patients to propose innovative targeted therapy.

Abstract:

Chronic obstructive pulmonary disease (COPD) is a common and preventable airway disease causing significant worldwide mortality and morbidity. Lifetime exposure to tobacco smoking and environmental particles are the two major risk factors. Over the last decades, COPD has become a growing public health problem with an increase in incidence. COPD is defined by airflow limitation due to airway inflammation and small airway remodeling coupled to parenchymal lung destruction. Most patients exhibit neutrophil-predominant airway inflammation combined with an increase in macrophages and CD8+ T-cells. Asthma is a heterogeneous chronic inflammatory airway disease. The most studied subtypes is T2 high eosinophilic asthma, for which there are an increasing number of biologic agents developed. However, both asthma and COPD are complex and share common pathophysiologic mechanisms. They are known as overlapping syndromes as approximately 40% of patients with COPD present an eosinophilic airway inflammation. Several studies suggest a putative role of eosinophilia in lung function decline and COPD exacerbation. Recently, pharmacological agents targeting eosinophilic traits in uncontrolled eosinophilic asthma, especially monoclonal antibodies directed against interleukins (IL5, IL4, IL13) or their receptors, have shown promising results. This review examines data on the rationale for such biological agents and assesses efficacy in T2-endotype COPD patients.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a growing cause of morbidity and mortality worldwide [1]. The Global Burden of Disease Study 2015 estimated approximately 174 million prevalent cases in the world. Over the last two decades, specialists in the field have noticed a significant increase in patient numbers mainly due to global population ageing and environmental factors [2]. Several studies report a high prevalence rate ranging from 2.1% to 26.1% of the adult population depending on age, sex, smoking habits, world region, and study inclusion criteria used [2]–[8]. A higher prevalence is reported among men, but recent data indicate a progressive sex-ratio equilibration due to a rise in tobacco smoking in high-income countries and an increase in environmental exposures in low/middle-income countries [4], [9]–[13]. As underlined by the ELISABET study, considerable heterogeneity in the prevalence of COPD is due to an impressive 76.4 % under-diagnosis rate [14]

In 2015, over 3 million people died from COPD in the world [2]. WHO projections are quiet alarming and highlight a possibility of 6 million deaths at the 2050 horizon [15]. Healthcare systems and society face a complex economic problem given that COPD is ranked eighth place in terms of disability-adjusted life years (DALYs), accounting for 2.6% of global DALYs [2]. In Europe, the total cost of respiratory diseases, including healthcare and productivity loss, represents more than €380 billion per year, with €48.4 billion being directly imputable to COPD [16]. Costs are clearly associated with exacerbation frequency, hospital admissions, and disease severity [17]–[21]. Indeed, higher severity of COPD is significantly associated with a higher risk of death [22]. There is no curative treatment currently available and disease management is highly focused on the symptomatic side and limitation of acute exacerbations. New studies based on the triple association of inhaled glucocorticoid (ICS), long-acting β2-agonist (LABA), and long-acting muscarinic antagonist (LAMA) showed a significant 25% reduction in risk of moderate or severe exacerbations compared to 15% for dual therapy (ICS-LABA and LAMA-LABA) [23]. Emerging evidence highlights the complexity of the disease, with the existence of specific COPD patient endotypes and "treatable traits", such as predominant eosinophilic inflammation [24]. A targeted strategy adapted to the different treatable traits/endtoypes appears more appropriate.

Hence, anti-eosinophilic drugs developed for asthma bring new hope for patients with COPD. This review aims to discuss results from recently published data reporting evidence of efficacy in some patients with COPD.

2. Pathophysiology and Molecular Mechanisms

2.1 General Pathophysiology

COPD is a preventable disease clinically defined by persistent respiratory symptoms and airflow limitation during forced expiration mainly due to airway and/or alveolar abnormalities [12] [25]. Airflow limitation is due to an increased airway resistance combined with mucociliary clearance failure and progressive accumulation of mucus exudate in distal airway lumens [26].

A local chronic inflammatory response is combined with an abnormal and excessive airway remodeling subsequent to damage repair, leading in turn to an alteration of the epithelial barrier and a thickening of the conducting walls of distal airways (< 2mm of diameter) [27], [28]. In addition to lumen narrowing, a substantial decrease in distal airway numbers has been clearly correlated with the COPD severity grade [29]. Lifetime exposure to tobacco smoking and environmental particles (domestic biomass combustion and air pollution) appear to be the two major COPD risk factors in high-income and developing countries respectively [30], [31].

Atsou et al. [3] demonstrate a significant trend between COPD and the amount of tobacco smoking; people consuming over 30 pack-years have a 3.73 [2.62; 5.29] higher risk of developing COPD [4], [5]. Recently, emerging evidence suggests that accelerated FEV1 decline is just one of the possible disease trajectories. Pediatric roots are involved in more than half of COPD cases, where abnormal development and lung growth during childhood leads to an incomplete pulmonary function at the age of 20 [32]–[34]. New genome-wide association studies (GWAS) highlight the genetic background in COPD emergence [35]–[38] with α1 antitrypsin deficiency as one of the most well described genetic disorders [39]. Historically the COPD inflammatory profile is mainly characterized by an increase in macrophages, neutrophils, and CD8+ T-cells in peripheral airways and lung parenchyma due to non-Th2 mechanisms, thus steroid non-responsive [40]–[43]. The percentage of neutrophils in the sputum appears to be higher in COPD patients, with more severe airflow obstruction and development of neutrophilic bronchitis during exacerbations [44] . A

therapeutic strategy targeting this neutrophilic trait (anti-IL-8 and anti-CXCR2) leads to minimal reduction in inflammation with limited reduced blood neutrophil counts or clinical benefit [45]. Sun et al. [46] reported a significant variation in Th1/Th2 cytokines between acute exacerbation and remission of COPD. They demonstrated that the imbalance of cytokines secreted by Th1 and Th2 cells was disrupted in COPD patients. Indeed, acute COPD exacerbation was associated with a decrease in Th1 cells and a dominance by Th2 cells, with a normalization of Th1 cell numbers during the remission step [46].

2.2 COPD and the Eosinophilic Airway Inflammation Trait

Eosinophils are terminally differentiated cells derived from CD34+ eosinophil-basophil progenitors in bone marrow. Progenitors undergo maturation under interleukin 5 (IL5), interleukin 3 (IL3), granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin 33 (IL33), and thymic stromal lymphopoietin (TSLP) stimulation [47]–[50]. Eosinophils play pivotal roles in tissue homeostasis and the inflammatory processes harboring pro-inflammatory genes that appear to be overexpressed in diseases such as asthma [51]. Bafadhel et al. reported from a one-year study a total of 182 exacerbations from 86 COPD cases, of which over one-fourth were associated with sputum eosinophilia [40]. Variations in eosinophil counts according to treatment, exacerbation phase, and sampling time make it difficult to establish clear guidelines on the thresholds for defining eosinophilic inflammation in COPD. Indeed, there is no consensus definition for eosinophilic COPD [41] [49] [52][53]. Currently, the cellular and molecular pathways leading to eosinophilic airway inflammation are well understood in asthma. Eosinophilic inflammation might not be identical in asthma and COPD. Two different pathogenic pathways of the adaptive or innate immune response are involved: i) Allergic eosinophilic inflammation driven by CD4+ Th2 lymphocytes and cytokines such as interleukin 4 (IL4), IL5, and interleukin 13 (IL13). This phenotype is generally well controlled by ICS; ii) Non-allergic eosinophilic inflammation probably imputable to IL5 production by type 2 (T2) innate lymphoid cells (ILC2) [54] [55]. Eosinophilic inflammation is thought to be a main feature of

asthma on a T2-mediated airway inflammation background. COPD is known to be a highly heterogeneous disease with many different clinical features. Some patients present phenotypes differing to those from the general pathophysiology, for instance eosinophilic airway inflammation (eosinophilic endotype) [56]–[58]. Hence, some COPD and asthma patients share similar symptoms. This has been identified as the asthma-COPD overlap (ACO)[49][59]–[61]. However, ACO has provided limited clinical and biological benefits regarding the management of chronic airway diseases given its relatively inaccurate diagnostic criteria (particularly the lack of clear-cut thresholds for quantitative parameters) and the heterogeneity of both inflammatory and structural change patterns [60].

It is noteworthy that a range of 20-40% COPD patients present an exacerbated eosinophilic profile in blood and/or sputum, not only during acute exacerbations but also in stable periods [40] [47] [62]–[65]. It has been demonstrated that blood eosinophil counts in COPD patients are associated with a higher frequency and severity of exacerbations [65]–[69]. Data from two multicenter and longitudinal cohorts (the ECLIPSE and COPDGene studies) reported respective 22% and 32% (p=0.006) increases in risk of exacerbation for COPD patients with a blood eosinophil count threshold of ≥300 cells/μL [52]. A high number of eosinophils is also associated with a better response to ICS and could be a promising response biomarker [66] [67] [70]–[72]. Emerging transcriptomic evidence highlights only a small overlap between genes linked to blood eosinophilic inflammation in asthma and COPD [73]. However, the existence of an overlap is still debated. Considering for example the GLuCOLD cohort; here the presence of a T2 signature in the sputum related to a predicted eosinophilic pattern and steroid sensitivity outcome was not tracked by asthma history [74]. At a glance, it seems that T2 traits and the subsequent eosinophilic patterns carry a significant genetic predisposition [75, p. 5], whereas the clinical taxonomy plays a limited role and the overall story is far from being elucidated.

Over the last decade, emergence of specific anti-eosinophil molecules, such as monoclonal antibodies (mAb) directed against IL5, has led to major improvements in asthma control, improving lung function with diminution of exacerbations [76]–[79]. All these findings suggest that the eosinophilic inflammation pattern is a potential treatable trait in COPD

patients. New evidence on this T2 COPD endotype is rationale for the testing of drugs used for asthma treatment which selectively block eosinophilic and T2 inflammation.

2.2.1 ANTI-IL5 Therapies

IL5 is one of the major cytokines secreted by CD4+ Th2 lymphocytes, eosinophils, ILC2 cells, mastocytes, eosinophils, and basophils, in turn inducing the activation of multiple signaling pathways and the release of cytokines and chemokines [50]. These molecules have a pivotal role in eosinophil recruitment, activation, differentiation, proliferation, and survival [80] [81] and in addition eosinophil degranulation also has a major effect on airway inflammation [82]. Accordingly, IL5 has become an interesting drug target in elevated eosinophil numbers among asthma patients. Targeted treatment, such as antibodies directed against the IL5 cytokine (mepolizumab and reslizumab) or the IL5 receptor (benralizumab), block eosinophil maturation. Note that the mechanism of action of benralizumab is different from that of mepolizumab and reslizumab, both binding exclusively to IL5 and leading to a reduction in eosinophils.

Thus, a strategy based on blood eosinophil depletion could play a role in the management of COPD.

Mepolizumab

Mepolizumab was approved in 2015 by the Food and Drug Administration (FDA) as an add-on therapy for the treatment of severe eosinophilic asthma [83] [84]. It is a fully-humanized mAb (IgG1 κ) directed against IL5, preventing its binding to the α-chain of the IL5 receptor alpha subunit (IL5Rα) present on the surface of eosinophils [85]. Pharmacokinetics is proportional to the dose and time independent. The half-life of mepolizumab is about 20 days, with a maximal concentration at 0.5 to 4.8 hours after the beginning of perfusion [86]. The drug prevents the formation of the IL5-receptor complex and blocks the activation of signaling pathways, leading to a limited eosinophil production, incomplete maturation, and a decreased half-life [87].

Ortega et al. [88] reported from the DREAM and MENSA studies a significant 47% reduction in mean exacerbation rate (rate ratio=0.53, p<0.0001) in severe eosinophilic asthma. The authors also found a significant association between mepolizumab efficacy and high baseline blood eosinophil counts ($\geq$150 cells/µl) [88]. A meta-analysis of eight different studies enrolling 1707 participants with severe asthma and high eosinophil levels concluded an improvement in quality of life and a reduction in asthma attacks without significant benefits on lung function [89].

Dasgupta et al.. [90] performed a single center, double-blind, randomized, placebo-controlled trial for 6 months including 18 patients of 40-80 years old with moderate-to-severe COPD. The authors assessed the effect of monthly injections of mepolizumab 750 mg or placebo in cigarette smoke-related COPD patients with persistent sputum eosinophilia. The primary objective was to determine if mepolizumab induced a significant reduction in sputum eosinophil count. Secondary outcomes were the assessment of the effects on blood eosinophil count, lung function, exacerbation rate, airway remodeling, symptoms and quality of life. Baseline sputum eosinophil counts represented 11% and 7.4% for the mepolizumab-treated arm (n=8) and the placebo group (n=10) respectively. Baseline blood eosinophil counts were 0.7±0.5 cells·mm−3 for the mepolizumab-treated and 0.33±0.29 cells·mm−3 for the placebo groups. After 6 months a significant reduction in sputum (0.50 vs 2.20%, p<0.05) and blood eosinophil counts (0.03 vs 0.26, p<0.05) were reported in the mepolizumab-treated group. However, the additional secondary outcomes showed no significant changes; there was no improvement in lung function or exacerbation rates [90].

Two large cohort studies have also been carried out to assess anti-IL5 efficacy on patients with moderate-to-severe exacerbations despite an adequate triple inhaled therapy composed of a combination of LABA, LAMA, and ICS. These two-phase III studies included Mepolizumab versus Placebo as Add-on Treatment for Frequently Exacerbating COPD Patients (METREX study), and Mepolizumab versus Placebo as Add-on Treatment for Frequently Exacerbating COPD Patients Characterized by Eosinophil Level (METREO study). Both the METREX and METREO trials assessed the efficacy and safety of

mepolizumab compared to placebo in patients with COPD and eosinophilic phenotype [91]. The primary outcome for both studies was the annual rate of moderate-to-severe exacerbations. The METREX study included patients with either an eosinophilic phenotype (≥150 eosinophils·mm−3 at screening or ≥300 in the previous year) or a non-eosinophilic phenotype, contrary to the METREO study where patient selection was based on blood eosinophilis count Treated patient groups consisted of mepolizumab 100mg (METREX and METREO) or 300 mg (METREO) that were compared to placebo in addition to ICS/LABA/LAMA tritherapy every 4 weeks for 52 weeks. Subcutaneous injection of mepolizumab 100mg once a month for 52 weeks was associated to a lower annual rate of moderate or severe exacerbations only in COPD patients with eosinophilic phenotype (high stratum group) in the METREX study [92] [93]. In this study, exacerbation rates of 1.40 versus 1.71 per year were observed in the mepolizumab-treated group compared to the placebo group respectively (rate ratio=0.82, p=0.04). No significant improvements in the overall cohort or impact on emergency department visits were noted. On the contrary, the METREO study did not give any insight into the efficacy on exacerbation rate, at either the 100mg (rate ratio= 0.80, p=0.07) or 300mg (rate ratio=0.86, p=0.14) doses [94]. However, both studies reported a well-tolerated mepolizumab treatment with similar incidence of adverse events compared to placebo groups. A dose–response relationship between the increase in eosinophil number and treatment efficacy has already been suggested [56]. Such hopeful results need to be discussed given that further increases in eosinophil count can lead to loss of asthma control after cessation of mepolizumab treatment [95] [96] [97]. Overall, the results of these studies are disappointing and contradictory. Stronger evidence of eosinophilic inflammation is now required for the enrollment of patients in the new phase III study "MATINEE"(https://clinicaltrials.gov/ct2/show/NCT04133909). This means that the proportion of eligible patients will be smaller than expected. Interestingly, a GWAS performed on patients with COPD and blood hypereosinophilia did not demonstrate any robust associations between genetic variants and mepolizumab efficacy (biomarker efficacy) [98].

Reslizumab

Reslizumab is a humanized mAb (IgG4, κ) directed against IL5 and prevents IL5 binding at the eosinophil surface similarly to mepolizumab [99]. Plasma concentrations are dose-proportional with a maximal peak concentration obtained at 6.9 hours after dosing and a reported half-life ranging between 24.5 to 30.1 days [100]. A study with patients aged 18-75 years old with uncontrolled eosinophilic asthma were randomly assigned and received monthly injections of reslizumab at 3 mg/kg (n=53) or placebo (n=53) for 12 weeks. Castro et al. [101] reported the absence of a significant reduction in exacerbations (p=0.0833), but a significant improvement of 0.24 L in FEV1 parameter in the reslizumab group (p=0.0023). A significant diminution in eosinophils in the induced sputum (p= 0.0068) and in blood counts (p <0.0001) was also observed [101]. To our knowledge reslizumab has not yet been evaluated in COPD [41].

Benralizumab

Benralizumab is a humanized mAb directed against IL5Rα with an 18-day terminal half-life [102]. Excision of the fucose sugar residue in the CH2 region of the antibody (afucosylated antibody) results in a 5- to 50-fold higher affinity for the Fcγ receptor (human FcγRIIIa) expressed on natural killer (NK) cells and macrophages. This modification leads to a 1000-fold increase in antibody-dependent cell-mediated cytotoxicity (ADCC) functions [103] and activation of this ADCC mechanism induces rapid eosinophil depletion [104]– [106].

Patients under benralizumab treatment with severe and uncontrolled eosinophilic asthma have shown a significant reduction in annualized exacerbation rate, an improvement in pre-bronchodilator FEV1, and a decrease in oral corticosteroid use [107]–[109]. A phase II, double-blind, randomized, controlled study was performed on an uncontrolled asthma cohort split into two groups: eosinophilic (n=324) and non-eosinophilic (n=285) phenotypes. At week 52, the authors demonstrated a reduction in asthma exacerbations in the patients treated with benralizumab doses at 20 mg (p=0.019) and 100 mg (p=0.010). In particular, these patients had baseline blood eosinophil counts of at least 300 cells/µl [110].

On the contrary, a phase II, double-blind, randomized, placebo-controlled study assessed the effect of benralizumab in COPD in 101 adults aged 40–85 years old with a moderate-to-severe disease and a sputum eosinophil count of ≥3%. The primary outcome was annual rate of moderate-to-severe exacerbations of COPD at week 56. Patients received a placebo or a benralizumab 100 mg injection, three doses every 4 weeks, followed by five doses every 8 weeks after 48 weeks. The placebo group reported a 0.92 [95% CI 0.67–1.25] and the benralizumab group a 0·95 [95% CI 0.68–1.29] annual rate of acute exacerbations, meaning in all that Brightling et al.. [111] demonstrated a non-significant reduction of 3% [95% CI −58 to +33; p=0·94] in exacerbations. On the other hand, benralizumab treatment was associated with a rapid diminution in blood and sputum eosinophils in patients with COPD and incidence of adverse events was similar to the placebo group. A significant improvement in post-bronchodilator FEV1 in the benralizumab arm was noted as similar to the placebo arm (p=0·014) [111]. Despite this FEV1 increase, no difference was observed in health status [45]. GALATHEA (Benralizumab Efficacy in Moderate-to-Very Severe Chronic Obstructive Pulmonary Disease with Exacerbation History, n= 1044) and TERRANOVA (Efficacy and Safety of Benralizumab in Moderate-to-Very Severe Chronic Obstructive Pulmonary Disease with Exacerbation History, n= 1392) were two phase III, double-blind, randomized, placebo-controlled trials. The primary endpoint was to assess the effect of benralizumab on COPD exacerbation rate. Patients of 40-85 years old were assigned in a 2:1 ratio into an eosinophilic (≥220 cells·mm−3) or non-eosinophilic (<220 cells·mm−3) group. The first three doses were injected every 4 weeks then every 8 weeks, with final assessment at week 56. In both studies patients randomly received placebo, or benralizumab at 30 or 100 mg. In the TERRANOVA study an additional group of patients received benralizumab 10 mg. Results of the GALATHEA study showed no significant improvement in annual rate ratios for exacerbations at any treatment dose: benralizumab 30mg (0.96; p= 0.65) and benralizumab 100mg (0.83; p= 0.05). The same trend was detected in the TERRANOVA study, with corresponding rate ratios of 0.85 (p = 0.06), 1.04 (p = 0.66), and 0.93 (p = 0.40) in the 10 mg, 30 mg, and 100 mg benralizumab groups respectively. No dose effect on benralizumab efficacy was detected and similar adverse

events were observed. Interestingly, in both studies a moderate depletion of blood eosinophils was reported [112]. Criner et al. [113] identified from the TERRANOVA and GALATHEA trails a subtype of patients characterized by a: i) Baseline blood eosinophil count ≥ 220 cells/µL; ii) Three or more exacerbations in the previous year; (iii) Tritherapy as best responder treatment in combination with benralizumab therapy. These patients were associated with a significant reduction in exacerbation rate ratio of 0.70 [95% CI 0.56-0.88] under benralizumab 100 mg treatment every 8 weeks compared to placebo. No improvement was reported for patients treated with benralizumab 30mg [113].

Altogether, these results are more disappointing than those observed with mepolizumab treatment, even more so given there was no relationship found with the level of eosinophilia. A new phase III study (https://clinicaltrials.gov/ct2/show/NCT01914757) will be relevant for the follow-up of the subset of patients who seemingly responded [113]. However, it is highly likely that if outcomes are yet again not achieved, benralizumab treatment will be ruled out for the treatment of COPD and the overall concept of eosinophilic COPD will be challenged. To conclude, the EMA declares that benralizumab is effective in patients with eosinophilic COPD, whereas the FDA claims there is not robust evidence supporting this.

2.2.2 – Anti-IL13 / anti-IL4 Therapy

IL4 and IL13 Th2 cytokines are responsible for many functions and are involved in asthma and COPD development [114]–[118]. IL13 binding to the IL13 receptor alpha 1 (IL13Rα1) induces recruitment of IL4 receptor alpha 1 (IL4Rα1), in turn forming a heterodimeric receptor complex responsible for the activation of signaling pathways [114][119]. IL4 and IL13 share similar biological effects, mainly as they bind the same receptor composed of IL4Rα1 and IL13Rα1, both expressed in airway epithelium[115] [120]–[122] . Indeed, IL4 activates not only through signaling pathways via the IL4Rα and IL13Rα chains, but also via common gamma chain. Likewise, IL13 has also been found to use IL4Rα and IL13Rα chains [123] [124]. IL13 is produced by T cells, mast cells, basophils, and dendritic cells (DCs). It is involved in regulation of inflammatory and immune responses as well as

mucous hypersecretion [125] [126]. Eosinophils have shown secretion of IL13 under GM-CSF and/or IL5 stimulation [127] and ILC2 cells are also able to secrete IL5 and IL13 under stimulation of IL33 and interleukin 25 (IL25) [128]. ILC2s have been found increased in patients with stable COPD or during acute exacerbation [46].

Dupilumab

Dupilumab is a human mAb targeting IL4Rα leading to inhibition of IL13 and IL4 signaling [129]. A randomized, placebo-controlled, phase IIb clinical trial showed a significant increase in FEV1 parameter and a reduction in the rate of severe exacerbations in patients with uncontrolled asthma under dupilumab treatment. Improvements were consistent in two different treatment groups; dupilumab 200 or 300 mg every 2 weeks regardless of baseline eosinophil count [130]. These encouraging data must be transposed to COPD patients. A Pivotal Study to Assess the Efficacy, Safety and Tolerability of Dupilumab in Patients With Moderate-to-severe COPD With Type 2 Inflammation (BOREAS study) is underway (NCT03930732) and will give some insights for patients with COPD.

Lebrikizumab

Lebrikizumab is a humanized mAb that binds to soluble IL13 and blocks activation of IL4Rα and IL13Rα1 heterodimers. Two studies related to lebrikizumab are LUTE and VERSE; double-blind, randomized, placebo-controlled studies enrolling 463 patients of 18-75 years old. Hanania et al. [131] found an improvement in asthma exacerbation rate and lung function in patients with moderate-to-severe asthma and a high periostin profile [131]. A phase II, double-blind, randomized, placebo-controlled trial for lebrikizumab (NCT02546700) treatment has been recently carried out in patients with frequent COPD exacerbations despite ICS and at least one long-acting bronchodilator inhaler medication. Data are not yet available.

Tralokinumab

Tralokinumab is also a mAb which specifically targets IL13 [126]. Piper et al. [132] noted no significant improvement in asthma symptoms following treatment based on the Asthma Control Questionnaire score (ACQ-6, p=0.375), but a small effect on FEV1 was shown. Marone et al. [118] concluded a putative efficacy of tralokinumab in a highly selected cohort of asthmatics with an overexpression of IL13. The authors concluded a minor role of IL13 in severe asthma exacerbations [133]. No study or clinical trial data are available in patients with COPD.

2.2.3 – Other targeting strategies: Anti-TSLP, Anti-IL33, Anti-IL25, and anti-IgE drugs

Damage to airway epithelial cells induces the release of several cytokines, such as IL33, IL25, and TSLP, leading to eosinophilic inflammation through ILC2 and Th2 pathways [129]

Tezepelumab

Human TSLP is involved in activation of DCs [134]. Activated DCs then induce conversion of CD4+ T-cells into Th2 cells able to produce the Th2 cytokines IL4, IL-5, and IL13 [135]. Tezepelumab is a human monoclonal antibody directed against TSLP, thus preventing its interaction with the TSLP receptor. Corren et al. [136] reported a significant 62%, 71%, and 66% (p<0.001 for all comparisons with placebo group) diminution of annualized asthma exacerbation rates for tezepelumab treatment at 70 mg every 4 weeks, 210 mg every 4 weeks, or 280 mg every 2 weeks respectively. Pre-bronchodilator FEV1 was also slightly higher in all tezepelumab-treated groups independently of blood eosinophil counts at the beginning of the study [136]. Currently, the Tezepelumab COPD Exacerbation Study (COURSE) is a phase IIa, multicenter, double-blind, randomized trial (NCT04039113) that is recruiting patients to assess the efficacy of tezepelumab on moderate or severe COPD exacerbation rate ratios.

Anti-IGE Therapy

Omalizumab

IgE plays an important role in allergic asthma [137]. Allergen-specific IgE binds to Fc receptors (FCεRI) on the surface of mast cells, basophils, and eosinophils. This binding induces allergic reactions through the release of inflammatory molecules [138]. Omalizumab is a recombinant humanized anti-IgE mAb indicated in patients with moderate-to-severe allergic asthma. Omalizumab binds to the Fc region of the IgE antibody, preventing the binding of IgE to high-affinity IgE receptors, and so blocking the signaling pathways responsible for the release of inflammatory mediators. Omalizumab has been shown to limit asthma exacerbation rates and annual rates of hospital admissions [139] [50]. Maltby et al. [140] reported an improvement in health-related quality of life in individuals with severe allergic asthma and ACO. The Omalizumab in the Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab (PROSPERO study) is a multicenter, single-arm, prospective, 48-week observational study. Study analysis by Hanania et al. [141] showed similar improvements in asthma outcome among patients with and without ACO, but preserved lung function was reported in the ACO group.

3. Discussion

Eosinophilic airway inflammation is a common trait in patients with asthma and COPD. Some patients with COPD and uncontrolled asthma, despite maximal adequate treatment (ICS, LABA, and LAMA), are eligible for treatment with molecules targeting specific components of eosinophilic inflammation in asthma. Mepolizumab has shown encouraging results in the asthma trajectory and has become one of the most studied anti-IL5 therapies in COPD [142]. Regarding results from the METREX/METREO studies, mepolizumab therapy is thought to reduce the rate of exacerbations in COPD patients with an elevated blood eosinophil level. This trend was only confirmed in the METREX cohort, where patients with hypereosinophilia (high stratum) demonstrated a significant reduction in moderate-to-severe exacerbations. No significant trend was found in the METREO cohort regardless of the injection dose (100 or 300 mg). Patients with ≥300 eosinophils·mm−3 benefit more from mepolizumab 100mg therapy, with a 23% lower mean annual rate of moderate or severe exacerbations (rate ratio=0.77 [95% CI 0.63-0.94]). It is noteworthy that the DREAM/MENSA trial in asthma reported a significant reduction in the mean exacerbation rate of patients under mepolizumab treatment (rate ratio=0.53 [95% CI 0.44-0.62]) [88]. These differences could be explained by higher exacerbation rates in COPD and a weaker impact of IL5 in the pathophysiology of COPD compared to asthma. Moreover, a decrease in sputum and blood eosinophil counts did not lead to significant improvements in lung function parameters or remodeling patterns, thus questioning the importance of eosinophil involvement in the disease [90]. Regarding the limited proof of efficacy and the cost-effectiveness balance, in 2018 the FDA decided not to approve mepolizumab as an add-on therapy for COPD [56]. No other anti-IL5 therapies, such as reslizumab use, have been reported in COPD.

Direct targeting of IL5Rα with benralizumab in the GALATHEA and TERRANOVA trials has reported no significant improvement in annualized COPD exacerbation rate combined with limited diminution of blood eosinophil counts. The authors explain the difference due to different cut-off values for the eosinophil counts, limited patient asthma history characteristics, and variation in previous medications [112]. A subtype of patients in the

GALATHEA and TERRANOVA trials with moderate-to-very severe COPD showed elevated peripheral blood eosinophils ($\geq 300/\mu l$) and experienced more than three exacerbations. This was despite patient triple therapy being associated to a significant reduction in exacerbations. Heterogeneous results along with no reduction in acute COPD exacerbations, contrary to results with mepolizumab treatment, were possibly due to small sample sizes. In addition, no attenuation of symptoms nor impact on quality of life was reported, but surprisingly a significant lung function improvement based on FEV1 parameter was noted with long-lasting effects [111]. The RESOLUTE trial (NCT04053634) designed to assess the efficacy and safety of benralizumab in highly exacerbated patients with moderate-to-severe COPD will bring new insights on highly selected populations. The limited benefits of anti-IL-5/IL-5R treatment in COPD may relate to different factors: a) patient heterogeneity in clinical trials; currently applied cut-off values for blood eosinophil counts in COPD are less consensual than in asthma, meaning that the population may not be sufficiently enriched, b) mechanisms of airway eosinophilia in COPD might be different from asthma, driven in an IL-5-independent manner. For instance, eotaxin, GM-CSF, IL-13, impaired macrophage efferocytosis [143], CCL5, alarmins etc., have been shown to be potentially relevant candidates, c) ambiguous clinical evidence that eosinophilia is differentially linked to COPD exacerbation, steroid sensitivity, or lung function compared to asthma.

It is not clear whether patients with sputum or blood eosinophilia represent a stable COPD phenotype over time. Little is known about the other clinical characteristics of T2 phenotype in COPD patients [144]. Whether eosinophilic airway inflammation arises due to increased bone marrow production and/or increased eosinophil recruitment into the airway is less well-documented than in asthma [145].

In a recent study [73], the authors aimed to identify the transcriptomic signatures in bronchial brushing samples from both patients with asthma and COPD in the U-BIOPRED and EvA cohorts, respectively. Using a blood eosinophil count cut-off of 200/mL, no genes were found differentially expressed between the COPD and asthma cohorts. The authors found that only 12 genes were associated with blood eosinophil count in the COPD cohort,

versus more than 1000 among patients with asthma. These genes were in majority related to T2- mediated immunity. The only common gene to both eosinophilic asthma and COPD was Cystatin-SN (CST1). However, in the validation cohorts CST1 and blood eosinophil count were weakly correlated. Cystatin is a cysteine protease inhibitor expressed by the airway and nasal epithelium and implicated in T2 immunity, such as eosinophilic nasal polyps [146]. Epithelial CST1 expression is upregulated by the epithelial alarmins TSLP and IL- 33, and it also stimulates alarmin release itself. Cystatin can also promote eosinophilic inflammation via fibroblast activation and subsequent release of pro-eosinophilic chemokines [146]. This study highlighted very few shared biological mechanisms between eosinophilic COPD and eosinophilic asthma. Unbiased bronchial epithelial gene expression studies have shown that CCL26 is also associated with blood eosinophil counts in COPD patients [74].

Studies based on the IL4R receptor targeting strategy with dupilumab have shown significant improvement in asthmatic patient lung function combined with a diminution of annualized exacerbation rate [130], [147]–[149]. These encouraging results have led to the assessment of the use of dupilumab in COPD and a trial is ongoing (NCT03930732). Given the disappointing and disruptive results that have been reported from studies on the anti-IL13 targeted strategy in uncontrolled and severe asthma, some authors have concluded a minor role of IL13 in asthma [133]. In COPD, there may be eosinophil-driven mechanisms that may involve non-IL-5 T2 cytokines such as IL-13, and therefore anti-IL-5 biologics do not show impressive clinical results. Eosinophil-derived IL-13 was shown to promote alveolar macrophage MMP-12 production and lead to airspace enlargement, indicating IL-13 involvement in the emphysematous progression of COPD [150].

Increased expression of CST1 and IL-13 genes have been recently shown in eosinophilic COPD airways [151].

These promising sub-studies deduce the hypothesis that a small proportion of patients with COPD may benefit from anti-IL5 therapy. Indeed, at this point most clinical trial evidence does not support the use of anti-IL5 treatment in COPD [94], [112]. To our knowledge, no results on patients with COPD have been published for anti-IL13 and anti-IL4 treatment.

Omalizumab, an anti-IgE treatment, has shown an improvement in health-related quality of life in individuals with severe allergic asthma and ACO. Anti-TSLP strategies are ongoing, with assessment in patients with COPD in a phase IIa, multicenter, double-blind randomized trial (NCT04039113) (COURSE study).

5. Conclusions

A significant proportion of patients with severe COPD and eosinophilic inflammation experience uncontrolled symptoms despite an optimal pharmaceutical treatment. Recently, targeted strategies directed specifically against cytokines or receptors involved in eosinophilic inflammation have provided significant improvement in asthma. Biological agents used in asthma have limited therapeutic effects on patients with COPD. These disappointing results are thought to be due to the existence of multiple disease origins and a highly complex role of eosinophils. Indeed, several studies have shown the global effects of eosinophilic patterns on exacerbations, but no impacts on the trajectory of the disease, such as lung function decline, were mentioned. A better understanding of such complex cellular mechanisms and a clear consensus on peripheral blood eosinophils are needed to improve patient gradations in routine clinical practice. Not only biomarkers but also elucidation of the role of eosinophilic and T2 inflammation in COPD is warranted. In conclusion, the development of new biomarkers is mandatory for a better patient selection in order to propose these innovative therapies to the best responder patient profile. This step forward to personalized medical treatments for patients with COPD will match the right targeted treatment to the right patient.

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Figure Legend:

Figure 1 - Simplified representation of the eosinophilic inflammation pattern in asthma and COPD. Allergens, cigarette tobacco, and other pollutants attack airway epithelial cells and contribute to a local injury. Release of epithelial-derived innate cytokines IL25, IL33, and thymic stromal lymphopoietin (TSLP) in response to environmental factors play key roles in: (i) The maturation of Th2 cells through dendritic cell activation; (ii) The activation of innate immune cells including type 2 innate lymphoid cells.

Release of Th2 cytokines (IL4, IL5, and IL13) promotes the activation of resident macrophages and recruitment of innate cells such as basophils and eosinophils. Finally, activation of these several pathways participates in airway remodeling, mucus overexpression, and eosinophilic inflammation maintenance.

Therapeutic strategy to control eosinophilic inflammation in asthma and COPD (monoclonal antibodies). Benralizumab acts in an ADCC way resulting in eosinophilic depletion. Mepolizumab and reslizumab target the soluble IL5 form to limit recruitment and activation of eosinophils. Omalizumab limits mastocyte activation through IgE depletion. Dupilumab inhibits eosinophil activation via IL4Rα, contrary to lebrikizumab and tralokinumab which target soluble IL13 cytokine. Tezepelumab blocks ILC2 activation by preventing TSLP binding.

ADCC (antibody-dependent cell-mediated cytotoxicity), Baso (Basophil), B cell (B lymphocytes), COPD (chronic obstructive pulmonary disease), DC (dendritic cell), Eos (eosinophil), IgE (Immunoglobulin E), ILC2 (type 2 innate lymphoid cell), IL5 (interleukin 5), IL5Rα (interleukin 5 receptor α), IL25 (interleukin 25), IL25R (interleukin 25 receptor), IL33 (interleukin 33), IL33R (interleukin 33 receptor), Mac (macrophage), MHCII (major histocompatibility complex class II), NK (natural killer cell), TCR (T-cell receptor), Th (T-helper cell), TSLP (thymic stromal lymphopoietin).

(Illustrations from Smart Servier medical website)

Airway epithelium

Allergens

IL13-induced mucus hypersecretion

Pollutants
Tobacco smoke

AIRWAY INFLAMMATION/DESTRUCTION

TSLP IL33 IL25

TSLP IL33 IL25

TSLP IL33 IL25

Mac

NK

Mac

NK

Anti-IgE
Omalizumab

Naive T cell

DC

B cell

IgE

Mastocyte

IL4, IL13, IL9

DC

MHC II

TCR

TH2

IL4/IL13

↑ Goblet cell proliferation

Anti-IL4Rα
Dupilumab

Anti-IL4/13
Lebrikizumab
Tralokinumab

↑ Goblet cell proliferation

IL13

IL4R

Eos

IL5Rα

IL5Rα

Eos granules

ADCC

NK
Mac

Anti-IL5Rα
Benralizumab

IL5

Anti-IL5
Mepolizumab
Reslizumab

ILC2

TSLPR

IL33R

IL25R

Anti-TSLP
Tezepelumab

ADCC

NK
Mac

Baso