Chronic Obstructive Pulmonary Diseases:
Journal of the COPD Foundation®

Journal Club

Journal Club: Biologics and Potential for Immune Modulation in Chronic Obstructive Lung Disease

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Abbreviations: chronic obstructive pulmonary disease, **COPD**; thymic stromal lymphoprotein, **TSLP**, interleukin, **IL**; type 2, **T2**; tumor necrosis factor alpha, **TNFα**; inhaled corticosteroid, **ICS**; Food and Drug Administration, **FDA**; T helper type 2 cells, **Th2**; I-2 innate lymphoid, **ILC2**; long-acting beta2-agonist, **LABA**; long-acting muscarinic-agonist, **LAMA**; forced expiratory in 1 second, **FEV_1**

Funding Support: Not applicable
Citation: Mkorombindo T, Balkissoon R. Journal club: biologics and potential for immune modulation in chronic obstructive lung disease. *Chronic Obstr Pulm Dis.* 2022;9(2):285-297. doi: https://doi.org/10.15326/jcopdf.2022.0318

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Keywords:
preserved ratio-impaired spirometry; PRISm; pre-COPD

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Introduction

The debilitating symptoms of chronic obstructive pulmonary disease (COPD) develop due to complex host/environment interactions, including genetic susceptibility, exposure to tobacco smoke, and chronic airway inflammation. Inhaled pollutants, microbial pathogens, and allergens bind with pattern recognition receptors on the bronchial epithelium and promote a cascade of events that trigger both immune and inflammatory changes.[1] The inflammatory response in COPD involves both innate and adaptive immunity, and all major leukocytes have been implicated.[2,3] Cytokines known as alarmins such as thymic stromal lymphopoietin (TSLP), interleukin (IL)-33 and IL-25 are released from the bronchial epithelial cells and can trigger type 2 (T2) and non-T2 immune pathways.[4] The inflammation often persists even after removing the triggering agents due to altered immune responses and alterations to the microbiome.[1-3,5-10]

This chronic inflammatory change and repetitive injury from tobacco smoke and other exposures propagate a cascade of events, including airway remodeling, that results in fixed airflow obstruction and significant respiratory morbidity and mortality. Tobacco smoke is a common, and the best characterized, inflammatory trigger; but microbes[11-18] can contribute to disease development and further cause acute exacerbations as can air pollution.[4,15,18-21] Exacerbations are the major cause of morbidity and mortality for patients with COPD. Typical sputum samples of COPD patients exposed to air pollution contain higher neutrophil and lymphocyte counts but not necessarily higher eosinophil counts.[22] While a lot has been learned in the past few decades about the inflammatory and immune pathways implicated in acute COPD exacerbations and disease progression, the primary anti-inflammatory medications in use have remained oral corticosteroids for treatment of acute exacerbations and inhaled corticosteroids for maintenance therapy in patients that are frequent exacerbators.[23-28] The potential side effects of long-term oral corticosteroids are well known, and corticosteroids are not particularly effective in suppressing neutrophilic inflammation. Other anti-inflammatory agents used for COPD have included phosphodiesterase inhibitors[7,29-31] and macrolide antibiotics, both of which have been shown to reduce neutrophilic inflammation and reduce exacerbation frequency.[5,21,32-36] These drugs are considered immunosuppressive drugs in that they are small molecule therapeutics with effects on several intracellular pathways and raise concerns about

increasing the risk of infection and/or dysbiosis.[37-42] Conversely, immunomodular drugs, such as the biologic therapeutics, target specific immune pathways and have specific effects on a particular pathway or cell type and consequently, they tend to have fewer deleterious side effects. Hence, there has been great interest in looking at whether these agents can reduce exacerbations and perhaps impact pathologic changes such as airway remodeling.[43-46] Immune targeting in asthma and COPD thus far has focused on: (1) targeting and neutralizing cytokines and chemokines, and (2) targeting proteases such as modulating metalloproteinases.[47-50]

Clustering of disease as either being predominated by neutrophilic or eosinophilic inflammation is a simplification of complex biology; however, these 2 phenotypes have been reproducible with stability over time facilitating the study of the disease.[2] Neutrophilic inflammation is the most common inflammatory phenotype observed in COPD, and the earliest clinical trials of biologic agents in COPD targeted neutrophils and other proinflammatory cytokines.[2,3] Anti-neutrophilic agents that have been investigated include but are not limited to anti IL-1, IL-17, IL-8, anti-CXCR2, and tumor necrosis factor-alpha (TNF-α).[2,51-54] The results from these trials have thus far demonstrated limited clinical benefit.[2,51-54] Treatments targeting IL-1, IL-17, and TNF-α have not been shown to be efficacious in stable COPD. Further, TNF-α inhibition was associated with an increased risk of infection and potential risk of malignancy.[2,51-54] Anti-IL-8 and anti-CXCR2 therapies, however, had some clinical benefit with a small improvement in dyspnea, however, they were associated with an increased risk of infection.[2,51-53]

More recent trials have targeted T2 inflammation, involving cytokines and chemokines promoting eosinophilic inflammation. Eosinophilic inflammation predominates in asthma but is also present in 20%-40% of patients with COPD.[55] The mechanisms of eosinophilic inflammation in COPD remain unclear. While we no longer refer to asthma/COPD overlap but rather refer to patients as having asthma and COPD, Christenson and colleagues found that about 20% of COPD patients enrolled in studies to look at the efficacy of inhaled corticosteroids (ICSs) and previously undiagnosed with asthma, demonstrated a T2 genomic signature of bronchial epithelial cells and that this group of patients demonstrated the best response to inhaled corticosteroids.[56-58] Several T2 targeted biologic agents have proven to be somewhat successful as add-on maintenance therapy for patients with asthma. In 2003, the anti-IgE biologic omalizumab became the first Food and Drug Administration (FDA)-approved biologic therapy for severe allergic asthma. While a substantial number of patients have responded to anti-IgE treatment, a number of asthma patients saw little or no benefit. These results highlighted the heterogeneity of the underlying pathobiology of severe asthma and led to several biologic therapies targeting specific key cytokines, including anti-IL-5 Ligand (mepolizumab)[59-62] and anti-IL-5 receptor benralizumab[63-66] that focus on reducing eosinophilic inflammation. The anti- IL-4 alpha receptor (blocks IL-4 and IL-13) (dupilumab) which has effects on T2 mediated inflammation has been introduced as well and has been found to be efficacious for a subset of severe asthma patients.[67-71]

Studies with biologics in COPD have been relatively few as most of these agents have targeted T2 inflammation, which is less common in the COPD population.[72] Studies with anti-IL-5 agents such as mepolizumab have shown there may be a benefit in individuals with evidence of high blood eosinophils.[62,73] Thus, several investigations into monoclonal agents targeting these cytokines and pathways have been under ongoing investigation.[72] A recent Cochrane review has analyzed how this treatment affected important subgroups.[72] The evaluation of benralizumab also did not meet the pre-specified targets, however, post-hoc analyses showed that the population with severe COPD, with a history of frequent exacerbations and bronchial hyper responsiveness, had a reduction in exacerbations with treatment.[74,75]

Cytokines, referred to as alarmins such as TSLP and IL-33 and IL-25, are released by bronchial epithelial cells in response to exposure to allergens, microbes and air pollutants including cigarette smoke. They are present to a higher degree in COPD and asthma and are important in the recruitment and activation of T helper type 2 (Th2) cells and T2 innate lymphoid (ILC2) cells. Interestingly COPD patients with eosinophilia have been shown to have higher IL-33 concentrations.[3,4,14,76,77]

TSLP triggers T2 inflammation by activating Th2 lymphocytes and innate T2 lymphocytes, leading to a T2/eosinophilic pattern of inflammation. TSLP has also been noted to trigger Th17 and Th1 lymphocytes leading to neutrophil recruitment and maturation. Tezepelumab, an anti-TSLP biologic, has recently been approved for use

in severe asthma patients[20,78-82] (see abstract number 5 below) and has been shown to be effective across a spectrum of asthma patients without any prerequisite biomarker. The fact that it has effects on both Th1 and Th2 pathways and acts higher up in the immune cascade has raised great interest as to whether TSLP may be a potential biologic that can address the neutrophilic or mixed endotype of COPD patients. Studies are planned to examine its efficacy in COPD.

Both asthma and COPD share the common characteristics that their pathogenesis relates to the interactions between various inhalants and the lung innate and adaptive immune responses that are related to a host of predisposing genetic and epigenetic factors. For the subset of severe COPD patients with significant airway inflammation, airflow obstruction, and frequent exacerbations, we have largely used systemic corticosteroids that can have devastating side effects for some of these patients. Several biologics have impacted asthma patients and been considered "life changing" with significant reductions in exacerbations and oral steroid requirements. Given these results, it is not at all unreasonable to ambitiously pursue exploring whether similar targeted therapy may be helpful for our COPD patients. In this issue's Journal Club, we review the most recent literature that examines the potential role of biologics in COPD.

Note: Abstracts are presented in their original, published format and have not been edited to match JCOPDF style.

Abstract 1
Anti-IL-5 Therapies For Chronic Obstructive Pulmonary Disease

Donovan T, Milan SJ,Wang R, Banchoff, Bradley EP, Crossingham I. *Cochrane Database Syst Rev.* 2020;12:CD013432.
doi: https://doi.org/10.1002/14651858.CD013432.pub2

Background: Exacerbations of chronic obstructive pulmonary disease (COPD) are a major cause of hospital admissions, disease-related morbidity and mortality. COPD is a heterogeneous disease with distinct inflammatory phenotypes, including eosinophilia, which may drive acute exacerbations in a subgroup of patients. Monoclonal antibodies targeting interleukin 5 (IL-5) or its receptor (IL-5R) have a role in the care of people with severe eosinophilic asthma and may similarly provide therapeutic benefit for people with COPD of eosinophilic phenotype.

Objectives: To assess the efficacy and safety of monoclonal antibody therapies targeting IL-5 signaling (anti-IL-5 or anti-IL-5Rα) compared with placebo in the treatment of adults with COPD.

Search Methods: We searched the Cochrane Airways Trials Register, CENTRAL, MEDLINE, Embase, clinical trials registries, manufacturers' websites, and reference lists of included studies. Our most recent search was 23 September 2020.

Selection Criteria: We included randomized controlled trials comparing anti-IL-5 therapy with placebo in adults with COPD.

Data Collection and Analysis: Two review authors independently extracted data and analysed outcomes using a random-effects model. The primary outcomes were exacerbations requiring antibiotics or oral steroids, hospitalizations due to exacerbation of COPD, serious adverse events, and quality of life. We used standard methods expected by Cochrane. We used the GRADE approach to assess the certainty of the evidence.

Main Results: Six studies involving a total of 5542 participants met our inclusion criteria. Three studies used mepolizumab (1530 participants), and three used Benralizumab (4012 participants). The studies were on people with COPD, which was similarly

defined with a documented history of COPD for at least one year. We deemed the risk of bias to be generally low, with all studies contributing data of robust methodology. Mepolizumab 100 mg reduces the rate of moderate or severe exacerbations by 19% in those with an eosinophil count of at least 150/μL (rate ratio (RR) 0.81, 95% confidence interval (CI) 0.71 to 0.93; participants=911; studies=2, high-certainty evidence). When participants with lower eosinophils are included, mepolizumab 100 mg probably reduces the exacerbation rate by 8% (RR 0.92, 95% CI 0.82 to 1.03; participants=1285; studies=2, moderate-certainty evidence). Mepolizumab 300 mg probably reduces the rate of exacerbations by 14% in participants all of whom had raised eosinophils (RR 0.86, 95% CI 0.70 to 1.06; participants=451; studies=1, moderate-certainty evidence); the evidence was uncertain for a single small study of mepolizumab 750 mg. In participants with high eosinophils, mepolizumab probably reduces the rate of hospitalization by 10% (100 mg, RR 0.90, 95% CI 0.65 to 1.24; participants=911; studies=2, moderate-certainty evidence) and 17% (300 mg, RR 0.83, 95% CI 0.51 to 1.35; participants=451; studies=1, moderate-certainty evidence). Mepolizumab100 mg increases the time to first moderate or severe exacerbation compared to the placebo group, in people with the eosinophilic phenotype (hazard ratio (HR) 0.78, 95% CI 0.66 to 0.92; participants=981; studies 2, high-certainty evidence). When participants with lower eosinophils were included, this difference was smaller and less certain (HR 0.87, 95% CI 0.75 to 1.0; participants=1285; studies 2, moderate-certainty evidence). Mepolizumab 300 mg probably increases the time to first moderate or severe exacerbation in participants who all had eosinophilic phenotype (HR 0.77, 95% CI 0.60 to 0.99; participants=451; studies=1, moderate-certainty evidence). Benralizumab 100 mg reduces the rate of severe exacerbations requiring hospitalization in those with an eosinophil count of at least 220/μL (RR 0.63, 95% CI 0.49 to 0.81; participants=1512; studies=2, high-certainty evidence). Benralizumab 10 mg probably reduces the rate of severe exacerbations requiring hospitalization in those with an eosinophil count of at least 220/μL (RR 0.68, 95% CI 0.49 to 0.94; participants=765; studies=1, moderate-certainty evidence). There was probably little or no difference between the intervention and placebo for quality-of-life measures. Where there were differences, the mean difference fell below the pre-specified minimum clinically significant difference. Treatment with mepolizumab and Benralizumab appeared to be safe. All pooled analyses showed that there was probably little or no difference in serious adverse events, adverse events, or side effects between the use of a monoclonal antibody therapy compared to placebo.

Authors' Conclusions: We found that mepolizumab and benralizumab probably reduce the rate of moderate and severe exacerbations in the highly selected group of people who have both COPD and higher levels of blood eosinophils. This highlights the importance of disease phenotyping in COPD and may play a role in the personalized treatment strategy in disease management. Further research is needed to elucidate the role of monoclonal antibodies in the management of COPD in clinical practice. It is not clear whether there is a threshold blood eosinophil level above which these drugs may be effective. Studies including cost effectiveness analysis may be beneficial given the high cost of these therapies, to support use if appropriate.

Comments

This is a Cochrane Review of anti-IL-5 (mepolizumab) and anti-IL-5R (benralizumab) in the treatment of COPD, demonstrating some evidence of potential benefits in select subgroups but not broad efficacy. While the body of evidence was not enough to justify approval of IL-5 therapies in COPD, there was a reduction in exacerbation frequency rate in the subgroup with higher baseline blood eosinophils levels, particularly with mepolizumab in the Metrex trial. There were some significant differences in trial design that may partially explain the positive results seen in the mepolizumab trials (particularly METREX [but not METREO]) versus the benralizumab trials. The eosinophil criteria in the benralizumab trials were set at 220 cells/μL at the time of trial entry based on earlier trials showing benefit with a cut-off of 200 cells per microliter and 3 exacerbations in the past 12 months to define their eosinophilic phenotype.[83] The trials with mepolizumab used at least 150 eosinophils/μL at the time of study entry and at least 300 eosinophils/μL in the previous 12 months to define an eosinophilic phenotype. Interestingly, in the mepolizumab trials it was the group that demonstrated baseline eosinophil counts of

less than 150 eosinophils/μL at study entry and greater than 300 eosinophils/μL within past 12 months and who had exacerbations while on maximum ICS-based triple inhaled therapy that showed the greatest reduction in exacerbations in the mepolizumab group suggesting a subgroup more likely to respond. Further, all patients in the mepolizumab trials had to remain on triple inhaler therapy (ICS/ long-acting beta2-agonist [LABA]/long-acting muscarinic-agonist [LAMA]) throughout the entire trial whereas, some participants in the benralizumab trials were on ICS/LABA or LABA/LAMA at the discretion of their study site investigators. This might reflect a significant *clinical trial effect* for the placebo group in the benralizumab studies related to increased adherence to inhaled therapy given that the study investigators were monitoring and adjusting their inhaler therapy. It is instructive that there was less of a response to mepolizumab for those who were treated with antibiotics (and not oral corticosteroids) for their exacerbations, suggesting that there are likely exacerbation subtypes that should be taken into consideration when deciding whether to try an anti-Il-5 agent. Also, the mepolizumab trial had 3% lifelong non- smokers in the trials and this could potentially represent undiagnosed asthma patients. In the benralizumab trials there were no lifelong non-smokers. Given the complexity of COPD pathobiology, a subgroup may benefit from mepolizumab and benralizumab. This is not unlike asthma in so far as the major pivotal studies of mepolizumab and benralizumab demonstrated that using higher eosinophil cutoffs particularly above 300 eos/μL increased the percentage of responders.

Abstract 2
Astegolimab, An Anti-ST2, in Chronic Obstructive Pulmonary Disease (COPD-ST2OP): A Phase 2a, Placebo-Controlled Trial

Yousuf AJ, Mohammed S, Carr L, et al. *Lancet Respir Med.* 2022; In press.
doi: https://10.1016/S2213-2600(21)00556-7

Background: Chronic obstructive pulmonary disease (COPD) is a heterogeneous inflammatory airway disease. The epithelial-derived IL-33 and its receptor ST2 have been implicated in airway inflammation and infection. We aimed to determine whether Astegolimab, a selective ST2 IgG2 monoclonal antibody, reduces exacerbations in COPD.

Methods: COPD-ST2OP was a single-center, randomized, double-blinded, placebo-controlled phase 2a trial in moderate-to-very severe COPD. Participants were randomly assigned (1:1) with a web-based system to received 490 mg subcutaneous Astegolimab or subcutaneous placebo, every 4 weeks for 44 weeks. The primary endpoint was exacerbation rate assessed for 48 weeks assessed with a negative binomial count model in the intention-to-treat population, with pre-specified subgroup analysis by baseline blood eosinophil count. The model was the number of exacerbations over the 48-week treatment period, with treatment group as a covariate. Safety was assessed in the whole study population until week 60. Secondary endpoints included Saint George's Respiratory Questionnaire for COPD (SGRQ-C), FEV1, and blood and sputum cell counts. The trial was registered with ClinicalTrials.gov, NCT03615040.

Findings: The exacerbation rate at 48 weeks in the intention-to-treat analysis was not significantly different between the Astegolimab group (2.18 [95% CI 1.59 to 2.78]) and the placebo group (2·81 [2·05 to 3·58]; rate ratio 0·78 [95% CI 0·53 to 1·14]; p=0·19]). In the pre-specified analysis stratifying patients by blood eosinophil count, patients with 170 or fewer cells per μL had 0·69 exacerbations (0·39 to 1·21), whereas those with more than 170 cells per μL had 0·83 exacerbations (0·49 to 1·40). For the secondary outcomes, the mean difference between the SGRQ-C in the Astegolimab group versus placebo group was –3·3 (95% CI –6·4 to –0·2; p=0·039), and mean difference in FEV1 between the two groups was 40 mL (–10 to 90; p=0·094). The difference in geometric mean ratios between the two groups for blood eosinophil counts was 0·59 (95% CI 0·51 to 0·69; p<0·001) and 0·25 (0·19 to 0·33; p<0·001) for sputum eosinophil counts. Incidence of treatment-emergent adverse events was similar between groups.

Interpretation: In patients with moderate-to-very severe COPD, Astegolimab did not significantly reduce exacerbation rate, but did improve health status compared with placebo.

Comments

IL-33 is another alarmin cytokine released from bronchial epithelial cells in response to allergen, microbes, and air pollutants. It shares similar features to tezepelumab, acting at a higher point in the immune/inflammatory cascade. This small single-center study (N=81) of astegolimab

is the first study of a monoclonal antibody to the IL-33 receptor (ST2). The study population had to have at least a 10-year pack history and be in Global Initiative for Chronic Obstructive Lung Disease[84] stage 2–4. There was no pre-specified eosinophil criteria cut-off, but they had to have had at least 2 moderate to severe exacerbations in the previous 12 months. Treatment resulted in a non-significant reduction in exacerbation frequency with a reduction in eosinophils and mild improvement in lung function. Interestingly, in a subgroup analysis, those with elevated blood eosinophil levels had slightly more robust improvements in forced expiratory volume in 1 second (FEV_1). A larger study that uses the information from this trial to determine an appropriate eosinophil cut-off and other entry criteria will help to evaluate whether this therapy may be useful for COPD patients.

Abstract 3
Safety And Efficacy of Itepekimab in Patients With Moderate-To-Severe COPD: A Genetic Association Study and Randomised, Double-Blind, Phase 2a Trial

Rabe KF, Celli BR, Wechsler ME, et al. *Lancet Resp Med.* 2021;9(11):1288-1298.
doi: https://doi.org/10.1016/S2213-2600(21)00167-3

Background: Genetic data implicate IL-33 in asthma susceptibility. Itepekimab, a monoclonal antibody targeting IL-33, demonstrated clinical activity in asthma, with potential in chronic obstructive pulmonary disease (COPD). In this study we first aimed to test the hypothesis that genetic variants in the IL-33 pathway were also associated with COPD. Based on the strong association of IL-33 pathway genes with pulmonary diseases like asthma and COPD, we conducted this phase 2a trial to assess the safety and efficacy of itepekimab in patients with moderate-to-severe COPD on a stable regimen of triple-inhaled or double-inhaled background maintenance therapy.

Methods: In this two-part study, genetic analyses of loss-of-function and gain-of-function variants in the IL-33 pathway, previously associated with asthma risk, were initially characterized for COPD. We then did a double-blind, phase 2a trial comparing itepekimab with placebo in patients with moderate-to-severe COPD despite standard therapy, at 83 study sites in ten countries. Patients aged 40–75 years who were current or former smokers, had been diagnosed with COPD for at least 1 year, and were on a stable regimen of triple-inhaled or double-inhaled background maintenance therapy, were randomly assigned (1:1) to receive itepekimab 300 mg or placebo, administered as two subcutaneous injections every 2 weeks for 24–52 weeks. The primary endpoint of the phase 2a trial was annualized rate of moderate-to-severe acute exacerbations of COPD during the treatment period. The key secondary outcome was change in prebronchodilator FEV1 from baseline to weeks 16–24. Pre-specified subgroup analyses were done for each of the endpoints, including by smoking status. Efficacy and safety analyses were done in all participants who received at least one dose of assigned treatment (modified intention-to-treat population). This trial is registered at ClinicalTrials.gov (NCT03546907).

Findings: Genetic analyses demonstrated association of loss of function in IL33 with reduced COPD risk and gain of function in IL33 and IL1RL1 variants with increased risk. Subsequent to this, in the phase 2 trial, 343 patients were randomly assigned to placebo (n=171) or itepekimab (n=172) from July 16, 2018, to Feb 19, 2020. Annualised rates of acute exacerbations of COPD were 1·61 (95% CI 1·32–1·97) in the placebo group and 1·30 (1·05–1·61) in the itepekimab group (relative risk [RR] 0·81 [95% CI 0·61–1·07], p=0·13), and least squares mean prebronchodilator FEV1 change from baseline to weeks 16–24 was 0·0 L (SD 0·02) and 0·06 L (0·02; difference 0·06 L [95% CI 0·01–0·10], p=0·024). When analysis was restricted to former smokers, treatment with itepekimab was associated with nominally significant reductions in acute exacerbations of COPD (RR 0·58 [95% CI 0·39–0·85], p=0·0061) and FEV1 improvement (least squares mean difference 0·09 L [0·02–0·15], p=0·0076) compared with placebo. Current smokers treated with itepekimab showed no treatment benefit versus placebo for exacerbations (RR 1·09 [0·74–1·61], p=0·65) or FEV1 (least squares mean difference 0·02 [−0·05 to 0·09], p=0·54). Treatment-emergent adverse events (TEAEs) occurred in 135 (78%) patients in the itepekimab group and 136 (80%) in the placebo group. The most common TEAEs were nasopharyngitis (28 [16%] in the itepekimab group vs 29 [17%] in the placebo group), bronchitis (18 [10%] vs 14 [8%]), headache (14 [8%] vs 23 [13%]), and upper respiratory tract infection (13 [8%] vs 15 [9%]).

Interpretation: The primary endpoint in the overall population was not met, subgroup analysis showed that

itepekimab reduced exacerbation rate and improved lung function in former smokers with COPD. Two phase 3 clinical studies are ongoing to confirm the efficacy and safety profile of itepekimab in former smokers with COPD.

Comments

This study highlights the heterogeneity of COPD. In this phase 2 study of itepekimab, a monoclonal antibody directed against IL-33, there was a reduction in exacerbation frequency in reformed smokers who were frequent exacerbators. Given the broad biologic effects of IL-33, the observed differences in treatment responses, as observed in former smokers and those with high eosinophil counts, highlight the complex pathobiology of exacerbations and the involvement of multiple pathways.

Abstract 4
Activation of Immune Cell Proteasomes in Peripheral Blood of Smokers and COPD Patients: Implications for Therapy

Kammerl IE, Hardy S, Flexeder C, et al. *Eur Resp J.* 2022;59(3): 2101798.
doi: https://doi.org/10.1183/13993003.01798-2021

Background: Immune cells contain a specialized type of proteasome, i.e. the immunoproteasome, which is required for intracellular protein degradation. Immunoproteasomes are key regulators of immune cell differentiation, inflammatory activation, and autoimmunity. Immunoproteasome function in peripheral immune cells might be altered by smoking and in chronic obstructive pulmonary disease (COPD), thereby affecting immune cell responses.

Methods: We analyzed the expression and activity of proteasome complexes in peripheral blood mononuclear cells (PBMCs) isolated from healthy male young smokers as well as from patients with severe COPD and compared them with matching controls.

Results: Proteasome expression was upregulated in COPD patients as assessed by quantitative reverse transcriptase-PCR and mass spectrometry-based proteomic analysis. Proteasome activity was quantified using activity-based probes and native gel analysis. We observed distinct activation of immunoproteasomes in the peripheral blood cells of young male smokers and severely ill COPD patients. Native gel analysis and linear regression modelling confirmed robust activation and elevated assembly of 20S proteasomes, which correlated significantly with reduced lung function parameters in COPD patients. The immunoproteasome was distinctly activated in COPD patients upon inflammatory cytokine stimulation of PBMCs in vitro. Inhibition of the immunoproteasome reduced proinflammatory cytokine expression in COPD-derived blood immune cells.

Conclusions: Given the crucial role of chronic inflammatory signaling and the emerging involvement of autoimmune responses in COPD, therapeutic targeting of the immunoproteasome might represent a novel therapeutic concept for COPD.

Comments

Patients with COPD, particularly smokers, have greater susceptibility to respiratory tract infections that contribute to acute exacerbations of the disease. Immunoproteasomes are key regulators of immune cell differentiation, inflammatory activation, and autoimmunity. They are found in immune cells and are critical in intracellular protein degradation. Degradation products, including amino acids, act as major histocompatibility complex class I antigens that enable immune surveillance by CD-8 positive T cells. Cigarette smoke causes oxidative stress leading to damage of both DNA and proteins, resulting in degradation and remodeling of lung tissue. This injury may also impair clearance of pathogens such as viruses and bacteria. These immunoproteases play a major role in inflammatory signaling by regulating activation of inflammatory transcription factors such as NF Kappa B. They also play a key role in initiating innate and adaptive immune dysfunction that drives the development of COPD. The immunoproteasome activity is crucial for the differentiation and function of T helper cells, namely Th1 and Th17 differentiation. There are immunoproteasome selective inhibitors being developed at the current time and being touted as potentially helpful for certain hematologic malignancies and autoimmune diseases such as Lupus. Given the prominent role of T regulatory cell Th1/Th17 function in COPD and the potential involvement of autoimmune responses, immunoproteasome selective inhibitors may represent a novel potential therapeutic target for patients with COPD.

Abstract 5
Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma

Menzies-Gow A, Corren J, Bourdin A, et al. New Eng J Med. 2021;384:1800-1809. doi: https://doi.org/10.1056/NEJMoa2034975

Background: Tezepelumab is a human monoclonal antibody that blocks thymic stromal lymphopoietin, an epithelial-cell–derived cytokine implicated in the pathogenesis of asthma. The efficacy and safety of Tezepelumab in patients with severe, uncontrolled asthma require further assessment.

Methods: We conducted a phase 3, multicenter, randomized, double-blind, placebo-controlled trial. Patients (12 to 80 years of age) were randomly assigned to receive Tezepelumab (210 mg) or placebo subcutaneously every 4 weeks for 52 weeks. The primary end point was the annualized rate of asthma exacerbations over a period of 52 weeks. This end point was also assessed in patients with baseline blood eosinophil counts of less than 300 cells per microliter. Secondary end points included the forced expiratory volume in 1 second (FEV1) and scores on the Asthma Control Questionnaire–6 (ACQ-6; range, 0 [no impairment] to 6 [maximum impairment]), Asthma Quality of Life Questionnaire (AQLQ; range, 1 [maximum impairment] to 7 [no impairment]), and Asthma Symptom Diary (ASD; range, 0 [no symptoms] to 4 [worst possible symptoms]).

Results: Overall, 1061 patients underwent randomization (529 were assigned to receive Tezepelumab and 532 to receive placebo). The annualized rate of asthma exacerbations was 0.93 (95% confidence interval [CI], 0.80 to 1.07) with Tezepelumab and 2.10 (95% CI, 1.84 to 2.39) with placebo (rate ratio, 0.44; 95% CI, 0.37 to 0.53; P<0.001). In patients with a blood eosinophil count of less than 300 cells per microliter, the annualized rate was 1.02 (95% CI, 0.84 to 1.23) with Tezepelumab and 1.73 (95% CI, 1.46 to 2.05) with placebo (rate ratio, 0.59; 95% CI, 0.46 to 0.75; P<0.001). At week 52, improvements were greater with Tezepelumab than with placebo with respect to the prebronchodilator FEV1 (0.23 vs. 0.09 liters; difference, 0.13 liters; 95% CI, 0.08 to 0.18; P<0.001) and scores on the ACQ-6 (−1.55 vs. −1.22; difference, −0.33; 95% CI, −0.46 to −0.20; P<0.001), AQLQ (1.49 vs. 1.15; difference, 0.34; 95% CI, 0.20 to 0.47; P<0.001), and ASD (−0.71 vs. −0.59; difference, −0.12; 95% CI, −0.19 to −0.04; P=0.002). The frequencies and types of adverse events did not differ meaningfully between the two groups.

Conclusions: Patients with severe, uncontrolled asthma who received Tezepelumab had fewer exacerbations and better lung function, asthma control, and health-related quality of life than those who received placebo. (Funded by AstraZeneca and Amgen; NAVIGATOR ClinicalTrials.gov number, NCT03347279)

Comments

This large, well-designed clinical trial of tezepelumab for severe asthma showed that treatment resulted in significant therapeutic benefit. FDA approval made this the first biologic agent approved for use in asthma without limitations based on phenotype or biomarkers. As stated above, the fact that it blocks both Th2 and Th1 pathways and acts higher up in the immune/inflammatory cascade may provide a broader scope of action to suppress the inflammatory changes that lead to exacerbations, and airway remodeling. A clinical trial evaluating this therapy in moderate to severe COPD is currently underway. (NCT04039113).

Bottom Line

Chronic airway inflammation is central to the pathogenesis of COPD and there is a shortage of targeted treatments that successfully modulate the key inflammatory pathways. Advances in understanding the pathophysiology of asthma have led to several novel biologic and small molecule therapies that have attempted to address the immune/inflammatory response. Biologics targeting T2 inflammation have successfully changed asthma management for a subset of patients, but it is clear there are still asthma patients who are not responders to biologics currently available. This points to the heterogeneity of the severe asthma population in terms of their underlying pathobiology and likely to comorbidities that are not optimally managed. The same issues apply to use of biologics in the COPD population. While no biologics are FDA-approved for treating COPD, studies targeting T-2 inflammation and neutrophilic inflammation will help in defining appropriate patient selection for these different agents. Studies already suggest that at least a subgroup of patients may benefit not only

in terms of reducing exacerbations but, hopefully, also in reducing their dependance on oral corticosteroids and their attendant significant side effects. There are several ongoing investigations for numerous treatment targets upon which we patiently await.

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