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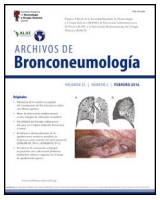

Editorial

Clinical Trials in COPD: Future Challenges

Novel pipeline treatments in Chronic Obstructive Pulmonary Disease (COPD) are inclined toward exacerbation reduction. Although clearly effective in asthma patients, monoclonal antibodies for COPD are one of the main therapeutic target in upcoming clinical trials. There is a clear unmet need in COPD patients at higher risk of poor outcomes despite triple inhaled therapy regarding moderate/severe exacerbations and mortality compared with the general COPD population. First of all, anti-interleukin (IL) 4, anti-IL 4R, anti-IL 5, and anti-IL 13 therapies are currently being studied in eosinophilic COPD patients and frequent exacerbations despite maximal inhaled therapy. Dupilumab, regarding BOREAS trial, is the first treatment that has proven efficacy by reducing adjusted annualized rate of moderate or severe exacerbations on 0.78 compared to 1.10 with placebo in patients with COPD and triple therapy.[1]

Other pipeline treatments include Benralizumab, an anti-IL 4R monoclonal antibody having a primary objective also by reducing annualized rate of exacerbations as part of the RESOLUTE trial in a somewhat similar population of COPD frequent exacerbators.[2] Previous studies (GALATHEA and TERRANOVA) resulted in 17% and 7% reduction over placebo in annual COPD exacerbation rate (both moderate and severe) and severe exacerbation reduction in 43% and 32% was observed in Benralizumab 100 mg group.[3] Another similar clinical trial, in this case MATINEE trial, is ongoing with anti IL-5 Mepolizumab as a treatment for reduction of exacerbation like RESOLUTE and BOREAS. It is important to notice that secondary objectives of all of these trial including change from baseline in pre-dose bronchodilator forced expiratory volume in one second (FEV_1) and quality of life measured by Saint George Respiratory Questionnaire (SGRQ) total and domain scores.[4] Previous evidence demonstrated that Mepolizumab provided a clinically relevant reduction of moderate/severe exacerbations of 18–20% compared with placebo. It's important to notice that such specific COPD population can be a limitation in the external validity of these trials.[5]

Although COPD is generally viewed as a disease driven by neutrophilic inflammation, up to 40% of COPD patients have an inflammatory pattern that includes elevated sputum eosinophils.[6] Approximately 6% of COPD patients with progressive disease uncontrolled with triple therapy, and blood eosinophil levels greater than 300 cells/μL, who could benefit from reduction of eosinophilic inflammation.[7]

Besides biologic therapies regarding eosinophils, new ongoing phase 2 and phase 3 trials are involved in other therapeutic targets, especially IL-33 and its receptor ST2. By playing its role as an alarmin, IL-33 alerts the immunologic system by binding to ST2. This receptor being part of the Toll-like receptor/IL1R superfamily, it is constitutively expressed in different immune cells like regulated T cells, mast cells and ILC2. IL-33 develops a role in the activation of multiple cells including Th2 cells, basophils, macrophages, eosinophils and stimulation of natural killer (NK) cells and neutrophils.[8] In COPD patients, its increased production especially in epithelial and endothelial cells alongside expression of preopheral blood mononuclear cells (PBMC), inducing persistent activation of the immune system favoring COPD progression.[9]

Several clinical trials are being underway regarding IL-33. First of all, we have Itepekimab in the AERIFY and AERIFY-2 trials. Itepekimab is a human IgG4P monoclonal antibody against interleukin-33. It is primary aim involves efficacy compared to placebo with the annualized rate of acute moderate-or-severe COPD exacerbations in former smoker cohort. Secondary objectives include like before, quality of like measured with SGRQ, FEV_1, safety and tolerability during 52 weeks.[10]

Another ongoing trial, but this one with the ST2 receptor and not IL-33 itself, we have Astegolimab, as part of the ALIENTO trial. Astegolimab is a human IgG2 mAb that blocks IL-33 signaling by targeting ST2, the IL-33 receptor. Astegolimab is also a monoclonal antibody administered subcutaneously in COPD patients with primary objective in COPD moderate and severe exacerbation reduction, and secondary objectives including lung function, quality of life, safety and tolerability.[11]

A third molecule involving IL-33 in COPD is currently being studied in the FRONTIER4, OBERON and TITANIA studies named Tozorakimab. Tozorakimab is a high-affinity human immunoglobulin G_1 monoclonal antibody that neutralizes IL-33. FRONTIER 4 trial's primary aim is toward FEV_1 change from baseline to week 12 of treatment compared to placebo.[12]

Novel therapies that are not included in the monoclonal antibody family are also being currently under study like an oral phosphodiesterase inhibitor, named Mitiperstat, as part of the CRESCENDO trial. Mitiperstat is a novel selective myeloperoxidase inhibitor with high potency. Its primary objective is the time to first COPD composite exacerbation (CompEx) event in patients with moderate to severe COPD. Other secondary objectives also include annualized exacerbation rate, lung function, quality of life and breathlessness, cough and Sputum Score (BCSS). This clinical trial design involves 12–24 week evaluation of patients.[13]

Last but not least, we have a 52 week placebo controlled study with an inhaled molecule as an add-on to maintenance triple therapy in subjects with COPD and chronic bronchitis called Tanimilast. Tanimilast is a novel, potent and selective inhaled PDE4 inhibitor of isoforms A-D endowed with anti-inflammatory properties. Two

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similar designed studies, named PILASTER and PILLAR, are currently evaluating this inhaled molecule for reduction in the number of moderate and severe COPD exacerbations. Both trials biggest difference is lung function, having a FEV_1 less than 50% as an inclusion criteria in the PILLAR study, different from PILASTER where patients with FEV_1 less than 80% can be included.[14,15]

Although Th2 and IL-33 signaling looks promising therapies based on mechanism of action and early efficacy signals, it is important to notice that serious hypersensitivity reactions including anaphylaxis are an identified risk regarding use of monoclonal antibodies. Nonetheless, biologics and both phospodiesterase and myeloperoxidase inhibitors are one of the main therapeutic targets in COPD bringing a new paradigm for patients' management. With newer clinical trials results, we can just hope this pipeline therapeutics improve their quality of life of our patients.

Conflict of Interests

The authors state that they have no conflict of interests.

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