



## Editorial

## Biologics in COPD

## Biológicos en EPOC



Treatments based on precision medicine developed in recent decades have revolutionised the natural course of many diseases. A therapeutic approach directed at the individual characteristics of each patient substantially improves outcomes with fewer side effects. The key to success when prescribing this type of treatment requires identifying therapeutic targets in the different pathologies as well as an appropriate selection of patients, based on the identification of specific phenotypic characteristics (so-called treatable traits) and their biological markers.

In respiratory medicine, there is extensive experience with the use of biologics in asthma and lung cancer, but to date, there are no approved biologics available for the treatment of COPD. The rationale behind their use is based on the inflammatory nature of the disease.<sup>1,2</sup> While the predominant inflammation in most COPD patients is type 1 (T1), with neutrophils as the predominant cell, up to 40% of patients may have overlapping features of type 2 (T2) inflammation, with increased eosinophil counts, orchestrated by Th2 lymphocytes and innate lymphoid cell type 2 (ILC2).<sup>3</sup> In fact, the mechanism of type 1 and type 2 inflammation may overlap in many COPD patients, as demonstrated by the predominant role of IL-13 in the inflammasome of patients with COPD, ACO and asthma.<sup>3</sup> Two clinical phenotypes have currently been distinguished that could allow the identification of molecular targets for new targeted therapies: the eosinophilic exacerbating phenotype, and the non-eosinophilic, predominantly neutrophilic.<sup>4,5</sup>

Until recently, different monoclonal antibodies such as anti-IL-1 receptor,<sup>6</sup> anti-IL-17A<sup>7</sup> or anti-TNF-alpha<sup>8</sup> have been tested for the treatment of COPD with disappointing results or significant adverse effects. More encouraging results have come from studies with monoclonal antibodies approved for the treatment of high T2 asthma that are being investigated in COPD patients, some of which open a new and promising avenue in the therapeutic approach to COPD (Table 1).

The phase III METREX and METREO studies evaluated the efficacy and safety of mepolizumab, an anti-IL-5 monoclonal antibody, versus placebo in 1510 COPD patients with frequent exacerbations. In METREX, patients were stratified according to blood eosinophil count ( $\geq 150$  per  $\text{mm}^3$  at recruitment or  $\geq 300$  per  $\text{mm}^3$  during the previous year or non-eosinophilic) while in METREO, all patients had a blood eosinophil count  $\geq 150$  per  $\text{mm}^3$  at recruitment or  $\geq 300$  per  $\text{mm}^3$  during the previous year.<sup>9</sup> In a pooled analysis the authors report that mepolizumab administered at a dose of 100 mg subcutaneously every 4 weeks reduces the annual rate of moderate/severe

exacerbations by 18% compared to placebo.<sup>10</sup> The Phase III MATINEE study (NCT04133909) is expected to provide further evidence on the use of mepolizumab in patients with eosinophilic COPD.<sup>10</sup>

Benralizumab is a monoclonal antibody that blocks the  $\alpha$ -subunit of the IL5 receptor of eosinophils and basophils, and its efficacy in the treatment of severe asthma with T2 inflammation has been extensively demonstrated in clinical trials and real-life studies. In COPD, a phase II study involving 101 patients with sputum eosinophil counts above 3% assessed the efficacy of benralizumab at a dose of 100 mcg and, although reductions in sputum and peripheral blood eosinophil counts were observed, no significant differences in reduction of exacerbations were evident.<sup>11</sup> Similar results were obtained in the phase III GALATHEA and TERRANOVA studies<sup>12</sup> where treatment with benralizumab at doses of 10, 30 and 100 mg was not shown to be superior to placebo in reducing exacerbations in COPD patients with frequent exacerbations and eosinophil counts  $\geq 220$  per  $\text{mm}^3$ .

The recently published BOREAS study is a 52-week, phase III trial involving 939 individuals diagnosed with COPD with a peripheral blood eosinophil count of at least  $300 \text{mm}^3$  and frequent exacerbations. The efficacy of treatment with dupilumab, a monoclonal antibody that blocks the effects of both interleukin-13 and interleukin-4 by binding to a component of the interleukin-4 receptor  $\alpha$ , which is shared by both cytokines, was assessed. Dupilumab was administered to 468 patients at a dose of 300 mg every 2 weeks subcutaneously in combination with inhaled triple therapy (long-acting  $\beta_2$ -agonist, a long-acting antimuscarinic agent and an inhaled glucocorticoid). The group of patients receiving dupilumab had a lower incidence of exacerbations, better lung function and health status, and fewer severe respiratory symptoms compared to placebo.<sup>13</sup> These results have been reproduced in the NOTUS clinical trial (NCT04456673), which reported a 34% reduction in exacerbations in the same profile of eosinophilic exacerbating COPD patients in a press release, leading the U.S. Food and Drug Administration to authorise its indication in COPD. The European Medicines Agency is currently evaluating the indication. Other biologics are being studied that block other molecules such as epithelial alarmins. (TSLP, IL-33 or IL-25).

One of them is tezepelumab, an anti-TSLP recently approved for severe asthma, which is being studied in COPD patients. The COURSE trial (NCT04039113) is a phase 2a study with tezepelumab or placebo involving patients with moderate to severe COPD with frequent exacerbations despite receiving triple inhaled therapy.

**Table 1**  
Possible therapeutic targets for the biological treatment of COPD and ongoing clinical trials.

Therapeutic target	Biologic	Phase III clinical trials	Ongoing clinical trials	Results
IL-5	Mepolizumab	METREO & METRIX	MATINEE	18–20% reduction of moderate-severe exacerbations compared with placebo (non-significant)
IL-5 receptor	Benralizumab	GALATHEA & TERRANOVA	RESOLUTE	18% and 7% reduction of moderate-severe exacerbations compared with placebo (non-significant)
IL-4 and 13 receptor	Dupilumab	BOREAS	NOTUS	34% reduction of exacerbations, improvement of lung function and state of health (significant)
TSLP	Tezepelumab		COURSE	Unavailable
IL-33	Itepekimab	AERIFY	AERIFY-2	Unavailable
IL-33	Tozorakimab	OBERON & TITANIA	PROSPERO	Unavailable
ST2 (IL-339 receptor)	Astegolimab	ALIENTO	ARNASA	Unavailable

Other biologics that act by blocking IL33 (itepekimab, tozorakimab) or its ST2 receptor (astegolimab) have strong possibilities for the future of COPD treatment with 12 trials currently registered.<sup>14</sup> Itepekimab has published results from a phase 2 trial showing a reduction in exacerbations only in the subgroup of ex-smokers.<sup>15</sup> The AERIFY trial (1 and 2) is a phase 3 trial targeting this population of ex-smokers (NCT04701983), which is under development. No results have yet been reported. Tozorakimab is another anti-IL-33 with promising results from the OBERON and TITANIA trials and is undergoing the PROSPERO extension trial (NCT05742802) to assess efficacy and safety. Astegolimab has not demonstrated a significant reduction in exacerbations in COPD patients, although its effects are being studied in the ongoing phase 3 ARNASA trial (NCT05595642).

Despite the heterogeneity that characterises COPD, one factor that COPD patients have in common is the irreversible effects of the disease even with optimised pharmacological treatment according to guidelines. Despite optimised inhaled therapy and non-pharmacological support, many patients continue to experience exacerbations, which in turn contribute to loss of lung function and impair quality of life. New biologics open a window of hope for these patients. Nevertheless, characterisation based on inflammation biomarkers of patients who are candidates for these treatments is still at a very early stage, which may condition the efficacy of some therapeutic strategies, especially if type 2 inflammation is to be targeted. The numerous drugs that are being evaluated against alarmines (TSLP and IL33) will be decisive in defining the indication for these new therapies in the future.

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