



## EDITORIAL

## Monoclonal antibodies for chronic obstructive pulmonary disease



Recently, monoclonal antibodies have been used for the treatment of various severe diseases, such as rheumatoid arthritis, ankylosing spondylitis, multiple sclerosis, cancer infections among others. They have immunomodulatory effects, are prepared against specific cytokines, inhibit specific enzymes or signaling molecules. Today, more than 60 monoclonal antibodies have been approved for clinical therapeutic use.<sup>1</sup> Monoclonal antibodies are generally well tolerated, but those that suppress the immune system may reactivate latent infections, such as tuberculosis or hepatitis B.<sup>1</sup>

In pulmonary diseases, monoclonal antibodies have been tested primarily in asthma with significant results.<sup>2</sup> The anti-IgE and the anti-interleukin-5 (IL-5) antibodies are now part of the regular treatment of severe asthma.<sup>3</sup> The anti-IL-5 antibodies had been shown to be very effective in severe eosinophilic asthma.<sup>2</sup>

These findings led to the hypothesis that these antibodies could be also effective in the sub-group of COPD patients with high eosinophilic counts in the blood. Thereafter, two monoclonal antibodies (Mepolizumab, Benralizumab), both against IL-5 have been tested in eosinophilic COPD patients.

In 2017 Pavord et al. performed two randomized, placebo-controlled, double-blind, parallel-group trials of Mepolizumab (METREY and METREO).<sup>4</sup> One hundred mg in METREX and 100 or 300mg in METREO of Mepolizumab were given to an eosinophilic phenotype of COPD patients (>150 per cubic millimeter). The primary end point in both trials was the annual rate of moderate or severe exacerbations. It was concluded that Mepolizumab at a dose of 100 mg was associated with lower annual rate of exacerbations than placebo. In addition it was shown that the greatest effect was found among patients with higher blood eosinophilic counts.<sup>4</sup>

In 2019 Fernandez Romero et al.<sup>5</sup> reviewed the literature of the clinical efficacy, safety and side effects of Mepolizumab in the management of eosinophilic COPD patients and concluded that out of the three trials only one study showed significant effect on the annual rate of exacerbations.<sup>5</sup> In addition, Condreay et al.<sup>6</sup> analysed

in more detail the results of the METREX and METREO studies in order to identify genetic variants associated with the efficacy of Mepolizumab. This post-hoc analysis failed to identify genetic effects on Mepolizumab-treatment response.<sup>6</sup>

More recently, the results of another monoclonal antibody, Benralizumab, for the prevention of COPD exacerbations were published.<sup>7</sup> Benralizumab, an IL-5 receptor alpha-directed monoclonal antibody was tested in two trials (GALATHEA and TERRANOVA) in patients with eosinophilic COPD (>220 per cubic millimeter). Various doses of benralizumab were used vs placebo with primary end point the annual exacerbations. The study showed that at 56 weeks, none of the COPD exacerbation rate for any dose reached significance vs placebo.<sup>7</sup>

Basing the treatment on the number of eosinophils in the blood could be the wrong hypothesis, since there is no strong evidence that they reflect the number and the function of the eosinophils in the lung tissue. Tumor necrosis factor (TNF) inhibitors were shown to be effective in a small subgroup of severe asthma patients but were ineffective in COPD, although they showed same effect among patients with COPD and rheumatoid arthritis.<sup>8</sup>

It is obvious that there are very few studies of monoclonal antibodies in COPD with controversial results for anti IL-5 or TNF-alpha and this may be because the pathogenesis of COPD at the cellular and molecular level is extremely complex.<sup>9</sup> A large number of phenotypic pathways, involving the immune system, with even larger number of endotypes have been identified as playing a role in COPD. Thus, a single monoclonal antibody cannot be effective on all pathways and this may reflect that there is no dominant role for any single cytokine or chemokine in COPD.<sup>10</sup> Better understanding of the pathogenesis of COPD at the cellular, molecular, genetic and immune levels may lead to more targeted use of monoclonal antibodies in restricted groups of patients with COPD with specific endotypes. Although, monoclonal antibodies could be the future of personalized treatment in COPD, there is a long way to go before they became part of everyday practice in COPD.

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## Conflicts of interest

No conflict of interest to declare

## References

1. Maris JD. Overview of therapeutic monoclonal antibodies. [www.uptodate.com](http://www.uptodate.com). Accessed Oct 3rd, 2019.
2. Bel EH, Ten Brinke A. New Anti-Eosinophil drugs for asthma and COPD: targeting the trait. *Chest*. 2017;152(6):1276–82.
3. Tzortzaki EG, Georgiou A, Kampas D, Lemessios M, Markatos M, Adamidi T, et al. Long-term omalizumab treatment in severe allergic asthma: the South-Eastern mediterrenian “real life” experience. *Pulm Pharmacol Ther*. 2012;25(1):77–82.
4. Pavord ID, Chanez P, Criner GJ, Kerstjens HAM, Korn S, Lugogo N, et al. Mepolizumab for eosinophilic chronic obstructive pulmonary disease. *N Engl J Med*. 2017;377(17):1613–29.
5. Fernandez Romero GA, Beros J, Criner G. Mepolizumab for the prevention of COPD exacerbations. *Expert Rev Respir Med*. 2019;13(2):125–32.
6. Condreay LD, Gao C, Bradford E, Yancey SW, Ghosh S. No genetic associations with mepolizumab efficacy in COPD exacerbations with peripheral blood eosinophilia. *Resp Med*. 2019;155:26–8.
7. Criner GJ, Celli BR, Brightling CE, Agusti A, Papi A, Singh D, et al. GALATHEA Study Investigators; TERRANOVA Study Investigators. Benralizumab for the prevention of COPD exacerbations. *N Engl J Med*. 2019;381(11):1023–34.
8. Matera MG, Calzetta L, Cazzola M. TNF-alpha inhibitors in asthma and COPD: we must not throw the baby out with the bath water. *Pulm Pharmacol Ther*. 2010;23(2):121–8.
9. Tzortzaki EG, Papi A, Neofytou E, Soultziz N, Siafakas N. Immune and genetic mechanisms in COPD: possible targets for therapeutic interventions. *Curr Drug Targets*. 2013;14(2):141–8.
10. Matera MG, Page C, Rogliani P, Calzetta L, Cazzola M. Therapeutic monoclonal antibodies for the treatment of COPD. *Drugs*. 2016;76(13):1257–70.

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