

Editorial

The Future of Biological Therapies in COPD[☆]

Futuro de los tratamientos biológicos en la EPOC

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In recent years new treatments that go further than conventional therapeutical approaches (i.e. bronchodilators and classical antoinflammatory drugs) have been developed for COPD. Bronchodilators are used to try to increase the size of the airway and improve symptoms, while anti-inflammatories, mainly corticosteroids and phosphodiesterase 4 (PDE4) inhibitors, are aimed at reducing inflammation, one of the most significant pathogenic mechanisms in COPD. The new treatments, called “biologics” or “biological response modifiers” (BRM), act by neutralizing or modulating the function of certain molecular targets, and thus have a more specific anti-inflammatory action. To date, they have been developed and used mainly in bronchial asthma and lung cancer, but they are now also appearing on the horizon for the treatment of COPD.

We know that in COPD, the airway develops an inflammatory response to various noxious stimuli (tobacco smoke, particles/gases, microorganisms), which by activating Toll-like receptors (TLRs), cause the recruitment of multiple immune system cells (predominantly neutrophils) and the secretion of inflammatory mediators.¹ The typical immunological response in COPD is thought to be mediated mainly by the helper and cytotoxic T cell subsets (Th1/Tc2).² In the case of asthma-COPD overlap (ACO), other co-activating noxious stimuli, such as allergens, are probably involved, with eosinophils playing an active role in this response. The most important inflammatory mediators include cytokines, chemokines and growth factors, those most probably involved in COPD being tumor necrosis factor (TNF)- α , interleukin (IL)-1 β , IL-4, IL-5, IL-6, IL-8, IL-13, IL-18, IL-23, IL-33, eotaxin (CCL)-1, thymic stromal lymphopoietin (TSLP), and transforming growth factor (TGF)- β .^{1,3,4} Most biological therapies are based on the administration of antibodies against these mediators or their receptors, although inhibitors, mostly of kinases, are also used; and it seems likely that in the near future even modulators of the pulmonary microbiota will be added to the range of available biological treatments.

Antibodies have numerous advantages. They are very specific and show strong affinity for the antigen; they are also metabolically stable, and do not produce toxic metabolites. These compounds are currently either “humanized” or fully human in order to avoid immunogenicity problems. Some can act on two targets simultaneously (bi-specific). They can be used separately or as an adjunct to conventional treatment, and while administration is mainly parenteral, the inhalatory route is being trialed with relative success. The disadvantages of the therapeutic use of antibodies include high costs, that will probably fall in the future, and the possibility of undesirable side effects.

Several antibodies are currently in development or already available on the market, the most important being those directed against TNF α and IL- β , or their respective receptors.⁴ Some have already been tested in COPD and have shown disappointing results and/or significant adverse effects (e.g., etanercept, infliximab, and canakinumab),^{5–8} while the effects of others have not yet been determined in this patient group (e.g., adalimumab, certolizumab, gevokizumab, anakinra o riloncept).^{4,8} The anti-IL-8 antibody, ABX-CXCL8, has been seen to slightly reduce dyspnea, but the effects on pulmonary function and exacerbations were negligible.⁹ No studies in COPD patients have been published to date with antibodies directed against IL-6 (e.g., sirukumab, olokizumab sirukumab, and tocilizumab), TGF- β (e.g., metelimumab and resolimumab), IL-33 (e.g., AMG282), or the IL-4/IL-13 (e.g., pascolizumab) and IL-17/IL-23 (e.g., ustekinumab) signaling axis.^{4,5,8,10} The only exception is the anti-IL-17 antibody, CNTO6785, which however failed to show benefits in this disease.¹¹ It is also interesting to see that some treatments with clear beneficial effects in asthma have also been tested in the ACO phenotype. This includes benralizumab, an anti-IL-5 antibody, that has provided slight functional improvement in this phenotype.¹² In contrast, anti-IgE, anti-CCL-11 and anti-TSLP drugs have shown no clinical improvements in patients with ACO.¹⁰

Inflammatory mediators are regulated by various kinases which act via transcription factors, such as the kappa-light-chain-enhancer of activated B-cells (NF κ -B) and activator protein-1 (AP1). A second therapeutic approach for biologics is inhibition of these molecules. This pathway is being actively investigated, and is already widely used in other diseases. The great disadvantages of this approach are its low specificity, the frequent development of resistance, and the possibility of serious adverse effects.

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Unfortunately, kinase κ B inhibitors (IKK) have so far either produced side effects that are unacceptable to COPD patients (e.g., IMD-1041), or have not yet been tested in this disease (e.g., IMD-0354 and TPCA-1).^{5–7} Inhaled anti-IKK drugs, a route that may reduce adverse effects, are currently under development (e.g., PF104). P38 mitogen-activated protein kinases (MAPK) inhibitors may also be used. Some have already been used with relative success in COPD: for example, SB-681323 (that reduces the release of cytokines in the airway), PH-797804 (that can reduce symptoms and improve lung function), losmapimod (that improves lung function and reduces exacerbations), or inhaled RV-568 (that also seems to improve respiratory function).^{5–7,13,14} Finally, the possibility exists of inhibiting other kinases, such as c-Jun NH2-terminal kinases (JUN NH2) (e.g., SP-600125, already tested in asthma), or extracellular signal-regulated kinases (ERK 1 and 2) (e.g., macrolides, trametinib and genistein), apoptotic signal-regulating kinases (ASK1) (e.g., thioredoxin and GS-4997), TGF- β activated kinase (TAK1) (e.g., 5Z-7-oxozeaenol), and calmodulin-dependent kinase (MK2). The effects of these compounds in COPD patients are still unknown, but promising results have emerged from ex vivo studies,¹⁵ and several clinical studies are already planned.

One possible reason for the lack of more conclusive results with many of the current biologics is that the patients included in many of the trials are inadequately phenotyped or endotyped. It is logical to assume that in such a heterogeneous disease as COPD, the molecular targets will not be the same in all patients. Furthermore, it is important to remember that inflammation is not the only biological process involved in the development and progress of the disease.

Finally, there are other avenues for possible new biological modulation, such as regulation of the pulmonary microbiota or the expression of certain genes involved in the development of COPD, since our knowledge on their function is still very limited, and go beyond the scope of this editorial.

In summary, the typical pulmonary and systemic inflammatory response in COPD may be modulated with the use of biological treatments, which already goes further than corticosteroids and PDE4 inhibitors. These treatments are based primarily on the administration of antibodies against inflammatory mediators or inhibitors of various kinases and/or transcription factors. Most biologics are still in the investigational phase, and some have already shown interesting results, although in some cases these results are offset by significant undesirable effects, that could be reduced if the drug is administered by inhalation.

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Appendix. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.arbr.2018.02.013](https://doi.org/10.1016/j.arbr.2018.02.013).

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