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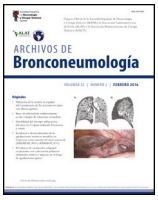

Editorial

COPD Therapy: Beyond Conventional Pharmacology☆

La terapia de la EPOC, más allá de la farmacología clásica

Joaquim Gea

Servicio de Neumología, Hospital del Mar – IMIM. DCEXS, Universitat Pompeu Fabra. CIBERES, ISCIII, Barcelona, Spain

COPD treatment has been traditionally based on drugs aimed at either compensating airflow obstruction or reducing airway inflammation in a non-specific manner. The first group, which act on airflow obstruction, mainly include adrenergic agents (basically β-adrenergic drugs), which modulate the sympathetic response of the airway, and molecules with an anticholinergic effect, which neutralize the parasympathetic system. Recent advances in these drug groups have consisted primarily of prolonging their effect and combining various molecules in a single device. Surprisingly, no drugs have yet appeared that regulate the "non-adrenergic, non-cholinergic" (NANC) airway response system, the mediators of which are different from those of the two conventional autonomous nervous systems mentioned above.[1] The drugs generally associated with a reduction in airway inflammation are inhaled or systemic corticosteroids, and more recently cyclic nucleotide phosphodiesterase (PDE) inhibitors,[2] such as roflumilast and theophylline, initially used as a bronchodilator. These drugs act by inhibiting the PDE4 isoenzyme, although theophylline also inhibits PDE3 and increases histone deacetylase (HDAC) activity. However, in recent years, other prophylactic and therapeutic approaches in COPD have been progressively gaining more importance. Some of these, such as alpha-1 antitrypsin deficiency replacement and respiratory rehabilitation, already have been around for a long time. The latter in particular involves a multidimensional approach, in which both healthier living habits and exercise play a significant role.[3] Healthy lifestyle interventions include stopping smoking and avoiding harmful exposures (coal or wood smoke, environmental pollution). In the specific case of smoking, numerous pharmacological and non-pharmacological options are now available, such as motivational interventions, nicotine replacement therapy, bupropion, varenicline, etc.[4] A healthy diet is also recommended, and nowadays, more emphasis is being given to an appropriate level of physical activity.[5] Indeed, physical activity is no longer thought to depend exclusively on the exercise capacity of the patient but rather on their lifestyle habits and motivation.[5] It is clear nowadays that both dimensions (capacity and lifestyle/motivation) must be taken into account when designing therapeutic interventions. When improving the patient's level of physical activity is ineffective, their program must be adjusted to include rehabilitation and physiotherapy, the mainstays of which are muscle and cardiovascular training.[6,7] Another area that is progressively gaining importance in the treatment of patients with COPD is home non-invasive mechanical ventilation (NIMV). The clear benefit of this therapy in patients with exacerbations has been complemented in recent years with robust evidence in stable, carefully selected patients (mainly with hypercapnia), and even in patients who have recently suffered an exacerbation.[8,9] Nutritional supplements and even anabolic steroids can be useful in selected patients with weight loss or frank cachexia, helping them to restore muscle function and exercise capacity.[10] Nor should we forget the role of lung transplantation, indicated in patients with advanced disease and both endoscopic and surgical lung volume reduction. Finally, the most novel approach witnessed to date is the emergence of biological response modulators (BRM), known more colloquially as "biologics".[11] Of particular interest are antibodies that target certain key molecules in different modalities of the inflamatory response (interleukins and their receptors, immunoglobulins, etc.), kinase-transcription factor inhibitors, and more speculatively, potential microbiome modulators. The most important of the first group are antibodies targeting TNF-α, IL-1 (α and β), IL-4, IL-5, IL-6, IL-8, IL-13, IL-17, IL-23, IL-33, TGF-β, CCL-11, TSLP and IgE, while the new kinase inhibitors (in addition to the old faithfuls, theophylline, corticosteroids, and the macrolides) include IMD-1041 and IMD-0354, losmapimod, PH-797804, RV-568, SB-681323, PF-03715455, and trametinib, solumetinib, and thioredoxin.[12,13] We should also mention probiotics (preparations which contain live microorganisms that are incorporated into the individual's flora) and prebiotics (inorganic compounds that can be used by beneficial microbiota), although these products in particular still lack a firm conceptual basis, since the respiratory microbiome in particular is relatively unknown.[14]

All of these treatments combine to address a relatively new concept of the disease, in which a generic diagnosis of COPD is deemed insufficient. Nowadays a number of individual traits must be taken into consideration, with the aim of offering more precise, and thus more personalized, treatment. Moreover, these individual traits may be common to groups of individuals with the same disease, and may, as such, constitute disease phenotypes. With this approach, COPD would be considered polyphenic (a word that

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E-mail address: jgea@parcdesalutmar.cat

has not yet been generally adopted in the clinical setting, despite being widely recognized in biology), as it encompasses various phenotypes. There is currently great interest in determining if the phenotypes (or at least some of them) correspond to specific endotypes,[15,16] that is to say, if they have common biological mechanisms. This is important for 3 reasons: to improve our knowledge of the different pathophysiological mechanisms of the disease; to determine the most specific biomarkers possible for identifying the above-mentioned endotypes; and to design more personalized treatments.

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