COPD at the borderline between the years 2017 and 2018

BPOC la frontiera dintre anii 2017 și 2018

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Abstract

The burden of chronic obstructive pulmonary disease (COPD) is increasingly felt by researchers and practitioners. At the border between the years, a number of studies were published, which drew my attention through new or older medications, therapeutic strategies, usable biomarkers and fashionable risk factors such as e-cigarettes. There are data that could revive new therapeutic lines or allow a more standardized approach to the practitioner.

Keywords: *COPD, biomarkers, therapeutic strategies, risk factors*

Rezumat

Povara bronhopneumopatiei obstructive cronice (BPOC) este resimțită din ce în ce mai acut de către cercetători și practicieni. La granița dintre ani, a apărut o serie de studii care reținatenția prin medicațiile noi sau vechi, strategiile de abordare, biomarkerii utilizabili și factorii de risc la modă, precum țigara electronică. Acestea sunt date care ar putea să relanseze linii terapeutice noi ori să permită o abordare standardizată mai corectă din partea practicianului.

Cuvinte-cheie: *BPOC, biomarkeri, strategii terapeutice, factori de risc*

Every year, researchers are doing important progresses in discovering new molecules or in the revival of some old drugs and strategies for diminishing the burden of *Chronic Obstructive Pulmonary Disease* (COPD). Between the end of 2017 and the beginning of 2018 some articles drew my attention because they brought some novelties, maybe vital for the next years. COPD is raising many question every time, some of them also coming from these new studies. The authors in the analyzed papers are trying to answer in these recent publications.

The competition between long-lasting anticholinergics is open and newly emerging molecules must be very convincing, before becoming leaders. **Revefenacin®**, a once-daily long-acting muscarinic antagonist (LAMA), used in clinical development for the treatment of patients with COPD, has now the first reported results. In a dose-ranging study, nebulized once-daily revefenacin had a long duration of action in patients, after 7 days of administration in doses up to 700 μg[1]. The drug was administered by a standard jet nebulizer, for 28 days, in 355 COPD patients (mean age: 62 years old, mean forced expiratory volume in 1 second [FEV1] 44% of predicted) randomized in a double-blind, placebo-controlled parallel group study at doses of 44, 88, 175 or 350 μg *vs.* placebo. The primary endpoint was chang from baseline in 28 days of FEV1, and secondary endpoints included weighted mean FEV1 over 0 to 24 hours and rescue medication (albuterol) use. If 44 μg produced a subtherapeutic response, the other tried doses (88, 175 and 350 μg) significantly improved at day 28 FEV1 *vs.* placebo (187.4, 166.6 and 170.6 mL, respectively, $p<0.001$). It seems that at doses ≥88 μg, more than 80% of patients achieved at least a 100 mL increase from baseline FEV1 in the first four hours post dose, compared with 33% of placebo patients, and there is a reducing of the average number of albuterol puffs by more than one puff per day. There are no additional efficacy evidence for the 350 μg dose over that observed with 175 μg revefenacin. Revefenacin was also generally well tolerated, with minimal reports of systemic anti-cholinergic effects. The conclusions of the authors are that this first once-daily LAMA for nebulization has the appropriate dose between 88 and 175 μg. On the other hand, this agent might be considered appropriate only for patients with mild COPD that requires a long-acting agent[1], which isn't a very large patient group. For patients with more than mild symptomatology, a more potent long-acting prescription would call for a combination of bronchodilation therapies, most likely a long-acting beta agonist plus a long-acting antimuscarinic.

An increased eosinophil count for COPD patients can be associated with an increased risk of disease severity and exacerbations. Typically, patients suffering from acute exacerbations are treated with inhaled or oral glucocorticoids on a long-term basis and have shown a good response to this kind of therapies. This provides evidence that eosinophils play a pivotal role in the pathogenesis of exacerbations in COPD patients. In the last year, we saw an increasing interest on one of the most challenging phenotype of COPD, the eosinophilic phenotype. This eosinophilic phenotype is thought to respond better, perhaps, to inhaled corticosteroids, and is in many ways different from the noneosinophilic patients in the COPD population[2]. **Mepolizumab®**, a cytokine monoclonal antibody focused on eosinophil biology, was studied as a potential player, an alternative therapy in improving the outcomes for patients with the eosinophilic phenotype within COPD. Two studies, METREX and METREO[4], explored this role. Both phase 3 trials were randomized, placebo-controlled, double-blinded, parallel-group and compared mepolizumab (100 mg in METREX, 100 or 300 mg in METREO) with placebo, given as subcutaneous injection every 4 weeks for 52 weeks in patients with COPD who had a history of moderate or severe exacerbations, while taking inhaled glucocorticoid-based maintenance triple therapy. The patients were stratified according to blood eosinophil count (≥ 150 per cubic millimeter at screening or ≥300 per cubic millimeter during the previous year) in the METREX study. In the METREO study, all patients had a blood eosinophil count of at least 150 per cubic millimeter at screening or at least 300 per cubic millimeter during the previous year. The primary endpoint was the annual rate of moderate or severe exacerbations. The results for the METREX group (462 patients with an eosinophilic phenotype) showed the average rate of moderate or severe exacerbations of 1.40 per year for those receiving mepolizumab, compared to patients receiving placebo, who had an average rate of 1.71. The results for the METREO group revealed an average annual rate of moderate-severe exacerbations of 1.19 per year in patients receiving 100 mg of mepolizumab, of 1.27 per year in those

receiving 300 mg of mepolizumab, and of 1.49 in patients who received placebo. A greater effect of mepolizumab, at a dose of 100 mg, compared to placebo, on the annual rate of moderate or severe exacerbations was found among patients with higher blood eosinophil counts at screening. This was another proof that eosinophilic airway inflammation contributes to COPD exacerbations. The safety profile of mepolizumab was similar to placebo. Although the authors found some limitations of the studies, these results suggest that mepolizumab is not only an effective and safe treatment for eosinophilic asthma, but also provide further evidence that inflammation in the lungs, caused by high levels of blood eosinophils, contributes to exacerbations experienced by COPD patients.

Dual bronchodilatation (LABA/LAMA) is already accepted and sustained by GOLD, updated for 2017-2018. It seems that the debate concerning the cardiovascular risk of this long acting bronchodilator isn't at the end. Meng Ting Wang et al.[3] are trying to clear this problem in a study regarding the risk of cardiovascular disease correlated with the new use of inhaled long-acting β_2-agonists (LABAs) or antimuscarinic antagonists (LAMAs) for the treatment of chronic obstructive pulmonary disease (COPD). This nested case-control study included 284220 LABA-LAMA–naïve patients with COPD, at least 40 years old (mean age 71.4 years old; 68.9% men), retrieved from the Taiwan National Health Insurance Research Database for health care claims from 2007 to 2011. The authors found that the new use of **LABAs or LAMAs** is associated with an approximate 1.5-fold increase of severe **cardiovascular risk**, irrespective of prior CVD status and history of exacerbations within 30 days from the therapy initiation. Individual LABA agents, LAMA dosage forms and concomitant COPD regimens did not differ in the CVD risks. It turned out that the cardiovascular risks peaked at around the 30th day after the new initiation of LABA or LAMA therapy waned from 31 to 60 days on and decreased to a level even lower than the baseline risk from 71 to 240 days[4]. A possible recommendation derived from this study is that "the use of inhaled long-acting bronchodilators in COPD needs to be carefully assessed and a thorough cardiovascular physical examination, especially heart rate measurement and electrocardiograms, need to be performed when prescribing LABAs and LAMAs to patients"[4] (particularly in naïve patients) in the first 30 days from the beginning of the treatment.

Another issue which received more evidence at the end of 2017 is **the risk of death or relapsing after hospital discharge**. The big debate concerning the duration of ventilator support and assistance after discharge from the hospital is now a hot topic in many articles published last year. Peter K. Lindenauer et al.[5] analyzed the daily absolute risks of hospital readmission and death at one year after discharge for COPD, stratified by ventilator support, among 2,340,637 hospitalizations. They determined the time required for risks to decline by 50% from maximum daily values after discharge and for daily risks to plateau in the general elderly population. The findings were: among 2,340,637 hospitalizations, the readmission rate at one year was 64.2%, including 63.5%, 66% and 64.1% among those receiving invasive, noninvasive, and no ventilation. Among 1,283,069 hospitalizations, the mortality at 1 year was 26.2%, including 45.7%, 41.8% and 24.4% among the same groups. Daily risk of readmission declined by 50% within 28, 39 and 43 days, and plateaued in 46, 54 and 61 days among those receiving invasive, noninvasive and no ventilation, respectively. The risk of death declined by 50% at 3, 4 and 17 days, and plateaued at 21, 18 and 24 days. Conclusion: the risk of hospitalization and death was significantly higher following discharge for COPD compared to the general Medicare population[5]. There are also important conclusions for practitioners: there is a prolonged risk of readmission and death depending on the need for ventilatory support, and interventions limited to the first month after discharge may be insufficient to improve longitudinal outcomes concerning the future of COPD patients.

E-cigarette it's also a challenging issue in the pneumology world. Evidence concerning the "benefits" and consequences of **e-cigarettes** are presented in an eternal debate. There are now many more articles targeting the effects on different diseases. One of this[6] had a very clear objective: to determine the usage of e-cigarettes in older adults at risk for or with chronic obstructive pulmonary disease (COPD). On a prospective cohort of more than 3500 participants from COPD Gene and 1060 from Spiromics study, which were current or former smokers, aged 45-80 years old, the authors observed whether e-cigarette use was associated with longitudinal changes in COPD progression or smoking habits. From 2010 to 2016, people who had ever used e-cigarettes steadily increased to 12-16%, but from 2014 to 2016 the current use was stable at approximately 5%. E-cigarette users had a heavier conventional cigarette smoking history and worse respiratory health, were less likely to reduce or quit conventional cigarette smoking, had higher nicotine dependence, and were more likely to report chronic bronchitis and exacerbations. Even the e-cigarette users had a more rapid decline in lung function, this trend did not persist after adjustment for persistent conventional cigarette smoking. The final conclusions of the authors demonstrate that e-cigarette use, which is common in adults with or at risk for COPD, was associated with worse pulmonary-related health outcomes, but not with the cessation of smoking conventional cigarettes. Even if this study was an observational one, the authors didn't find any evidence supporting the use of e-cigarettes as a harm reduction strategy among current smokers with or at risk for COPD[6].

A current problem in everyday practice remains the long way between guidelines recommendations and guidelines implementation: from the expert board to the routine of the prescriptions of practitioner in different countries. An example is coming from Netherlands where, despite recommendations in prevailing guidelines to avoid **the use of non-selective (NS)** β-blockers in patients with asthma or COPD, on average, 10 patients per community pharmacy receive NS β-blockers monthly[7]. On 827 asthma/COPD patients with actual use of NS β-blockers and from 153 NS β-blocker prescribers selected and interviewed by authors, 107 prescribers were aware of the drug-disease interaction of the asthma or COPD co-morbidity when initiating the NS β-blocker, and 46 were not. Out of these, 40 prescribers did not consider the contraindication to be relevant. One of the conclusions was that a substantial number of prescribers were unaware of the co-morbidity or did not regard NS β-blockers contraindicated, despite prevailing clinical guidelines. This means that we have to do more for improvement programs, targeting prescribers' awareness and knowledge of NS β-blockers in patients with asthma or COPD.

The latest ERS congress in 2017 announced new evidence on triple therapy in COPD with all the drugs in a single device. This triple combination therapy of inhaled corticosteroids (ICSs), long-acting beta2 agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) has become an option for the maintenance treatment of COPD and as a "step-up" therapy from single or double combination treatments with many benefits on improving lung function, symptoms, health status and reducing exacerbations. If in the past the practicioners could do this by using different inhalers, now **a new triple fixed-dose combination** of extrafine beclomethasone dipropionate (100 µg/puff)/formoterol fumarate (6 µg/puff)/glycopyrronium bromide (12.5 µg/puff) has been developed as a hydrofluoroalkane pressurized metered dose inhaler. Two large pivotal studies of 52 weeks – Trilogy and Trinity[8] – showed that extrafine fixed ICS/LABA/LAMA triple combination is superior to fixed ICS/LABA combined therapy and also superior to the LAMA tiotropium, in terms of lung function and exacerbation prevention in COPD patients at risk for exacerbation. GOLD recommends the triple therapy as a step-up option for group D patients. Both studies support this recommendation, but also the actions in reducing exacerbations in patients from subgroup GOLD B (while on maintenance treatment including ICS/LABA, LABA/LAMA or LAMA) and for the subset who continue to exacerbate, despite maintenance treatment.

There are two other important battles to win in the future, concerning early treatment of COPD and preventing high mortality: to treat with more positive results the stages 1 and 2 of the disease, and the second one, to find the magic marker for predicting mortality to this kind of patients. It seems that the quest of using **tiotropium in patients with early-stage chronic** obstructive pulmonary disease received an answer[9,10]. In a 2-year multicenter, randomized double-blind placebo-controlled Chinese trial on the use of tiotropium for 841 patients staged 1 and 2, tiotropium improved forced expiratory volume in one second throughout the trial duration, reduced the rate of decline in forced expiratory volume in one second after the bronchodilator use over 24 months, decreased the frequency of exacerbations and improved the quality of life (*versus* placebo). Although there are no guidelines suggestions for a screening in general population because of the lack of benefit of **early detection and treatment,** now this study underlines the importance of identifying patients with early stage COPD, because the initiation of therapy with tiotropium in this population may be beneficial.

Biomarkers are easily accessible and might reflect chronic obstructive pulmonary disease (COPD) activity. In the last years, the researchers are looking for a panel of blood biomarkers (C-reactive protein [CRP], neutrophils, eosinophils, albumin, and vitamin D), useful for predicting the **mortality in COPD**. Analyzing the mortality in a sample of 431 patients for 36 months, Mendy A et al.[11] found that participants with high CRP, eosinophil count <2%, hypoalbuminemia and hypovitaminosis D had worse baseline FEV1 and subsequently higher mortality compared to controls. The addition of **CRP with eosinophil and/or neutrophil count** significantly improved a base model for the prediction of mortality which included age, gender, race/ethnicity, body mass index, smoking, poverty income ratio, asthma, diabetes, hypertension and history of stroke or myocardial infarction. High CRP and neutrophils, as well as low eosinophils, are predictive of poor COPD prognosis.

At the beginning of 2018, there is also a progress in identifying how polymorphisms of cytokine genes can modulate the individual's susceptibility to environmental stimuli in COPD development. It is known that C-X-C motif chemokine 10 (CXCL10) mediates recruitment inflammatory cells such as monocytes. Yan Wang et al.[12] evaluated the association between CXCL10 tag-SNPs and COPD risk. They found that the "T" allele of rs56061981 was significantly associated with reducing the risk of COPD, while the "G" allele of rs56316945 was significantly associated with increasing the risk of COPD. SNP rs56316945 was significantly associated with increasing the risk of COPD under different models, except recessive model after adjusting for gender, age, pack year and biomass. This study suggests that rs56061981 and rs56216945 in **CXCL10 gene promoter contribute to COPD susceptibility.**

Conclusions

There are more and more progresses in many fields of research for COPD patients. This could lead to a change of actual guidelines in the near future. Probably, the most important areas to cover in the next years are: finding a good biomarker for predicting exacerbation and mortality, more tools for the early detection of this disease, new therapeutic algorithms and preventive educational activities. ■

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