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A perspective for chronic obstructive pulmonary disease (COPD) management: six key clinical questions to improve disease treatment

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ABSTRACT

Introduction: In 2011, the GOLD recommendations for the treatment of Chronic Obstructive Pulmonary Disease (COPD) introduced new clinical elements to classify the severity of the disease and to guide pharmacological choice. For the first time in the GOLD documents, treatment decision was no longer guided only by pulmonary function, but by a more complex combination of pulmonary function and clinical aspects. The recent versions of the GOLD recommendations introduce new aspects for the clinicians and pose new question for the management of the disease. In addition, inflammatory biomarkers and blood eosinophil levels, have been considered to guide treatment selection.

Area covered: The evolution of disease management proposed by the GOLD document opens several areas of debate. A series of roundtable discussions among respiratory physicians took place in Italy to address key clinical questions. Particularly, the role of lung function and the use of biomarkers, the adherence to international guidelines and the possibility to personalize the pharmacological approach in COPD patients have been discussed, summarized and analyzed.

Expert opinion: The authors believe that the development of a precision medicine approach tailoring the specific treatment for each patient is the goal of COPD management and may be achieved by considering the phenotypic classification of COPD patients.

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COPD; pulmonary function; biomarker; eosinophil count; exacerbations; ics; de-escalation

1. Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most frequent causes of morbidity and mortality worldwide among chronic conditions [1,2].

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) diagnostic and therapeutic recommendations have been widely used since their first edition in 2001. The GOLD document underwent a significant evolution over the last decade. In the 2001 version of the GOLD document, patients with COPD were divided into four stages that progressively worsened on the basis of forced expiratory volume (FEV)₁ only [3]. Lung function severity was the only clinical element to titrate the inhaled pharmacological regimens. In 2011, the GOLD recommendations introduced new clinical elements to classify the severity of the disease and to guide the pharmacological choice. Compared with previous versions, four groups of COPD patients were identified labelled as: 'A', 'B', 'C' and 'D' based on symptom burden. The latter are appraised by dyspnea (evaluated by the Modified Medical Research Council [mMRC] Dyspnea Scale, which stratifies severity of dyspnea in respiratory diseases, particularly COPD) [4], the COPD Assessment Test (CAT), a questionnaire for patients with COPD used to measure the impact of the disease on the patient's life over time [5], and exacerbation risk (assessed through the history of exacerbation frequency

and the severity of airflow limitation as a surrogate of exacerbation risk) [6]. Therefore, treatment decision for the four segments was no longer guided by only the pulmonary function, but by a more complex combination of pulmonary function and clinical aspects [6]. Later on, starting from the modified 2017 ABCD assessment tool up to a very recent updated version of the document, the FEV₁ evaluation remained central for diagnosis, prognosis and follow-up of COPD, but was removed from the ABCD grading. Indeed, the 'ABCD' patients' classification was exclusively based on symptoms and exacerbation history, regardless of spirometric values [2,7]. The ABCD assessment still guides the initial treatment choice for COPD, while treatment modification in the follow-up (escalation or de-escalation of treatments) are based on the worsening of dyspnea or improvement of exacerbation occurrence. Interestingly, and for the first time, inflammatory biomarkers and, in particular, blood eosinophil levels, have been proposed as an option to guide treatment selection.

From a clinical perspective, the evolution of the disease management proposed by the GOLD document opens several areas of debate. A series of roundtable discussions among respiratory physicians took place in Italy to address and discuss key clinical questions on the management of the disease mainly rising from the evolution of the GOLD document. In particular, the role of lung function and the use of biomarkers,

Article highlights

- The classification of COPD patients on the basis of the severity of the disease and on the best pharmacological treatment has been debated in Italy, following the modifications proposed by the GOLD document, to identify the clinical management and the possibility to personalize the pharmacological approach in specific groups of COPD patients.
- Lung function parameters, such as FEV₁, although central in the diagnosis of COPD, may be inaccurate to predict the prognosis and to define the best treatment for COPD. The evaluation of other indices resulting from a multidisciplinary approach must be considered to address the clinical complexity of a COPD patient.
- There is the need in the daily clinical practice for the identification of easily detectable biomarkers for the assessment of COPD severity, progression and prognosis.
- There is a consistent “gap” between real-life pharmacological treatments, escalation and de-escalation treatment and GOLD recommendations.
- The development of a precision medicine approach tailoring the specific treatment for each patient is the goal of COPD management and may be achieved considering the phenotypic classification of COPD patients.

the adherence to international guidelines and the possibility to personalize the pharmacological approach in specific groups of COPD patients have been discussed and summarized in the present paper. This article provides light and shadows of COPD clinical management.

2. What is the role of lung function in the clinical assessment of COPD?

Spirometry is a key element in the clinical management of COPD [2]. The concept of persistent airflow obstruction is core to the definition of the disease according to the GOLD document. Thus, the identification of a spirometric airflow obstruction is necessary to the diagnosis of the disease. The percentage predicted FEV₁ has been classically related to the disease severity. The lower the FEV₁, the poorer the overall survival [8,9,10] but also the higher the risk for cardiovascular events [11,12] and for lung malignancy development [13,14,15]. Similarly, spirometric parameters, namely FEV₁, forced vital capacity (FVC) and FEV₁/FVC ratio are important population-level predictors (but not necessarily accurate) of poor COPD outcome. Indeed, FEV₁ weakly correlates with important and one-to-each-other independent clinical aspects with prognostic value of the disease, such as symptoms (mainly dyspnea), patient's health status and exacerbation rate [16,17]. FEV₁ also poorly captures impairment in the small airways, lung hyperinflation and emphysema. Small airway abnormalities represent key pathogenetic sites of the disease. Small airway abnormalities seem to precede the development of airflow obstruction and emphysema [18,19]. The more inflamed, narrowed and thickened the small airways, the more severe is the COPD in a patient in terms of airflow obstruction, quality of life and prognosis [20,21]. Lung hyperinflation is one of the most important functional mechanisms that leads to exercise limitation and dyspnea in COPD patients. The presence of an emphysema-predominant

phenotype, irrespective of the severity of FEV₁ impairment, has been shown to predict poor response to ICS/LABA treatment [22], is independently associated with a rapid annual decline in FEV₁ [23] and is associated with increased mortality in COPD [24]. Thus, FEV₁, despite mandatory for the diagnosis of the disease, fails to accurately depict the actual COPD pathological alterations and the clinical heterogeneity of the disease [25,26,27,28]. Interestingly, a recent study showed that the GOLD 2017 ABCD tool (that omits the FEV₁ impairment for severity grading) cannot fully capture the heterogeneity of COPD patients in term of emphysema presence and lung hyperinflation [29]. Furthermore, the technological advancement of lung imaging techniques has allowed the development of computational algorithms and imaging manipulation, which can detect and reflect peripheral airway abnormalities in COPD patients. Interestingly, it has been shown that these novel imaging parameters are clinically meaningful being related to symptom severity and lung function decline [30,31,32]. Thus, besides FEV₁, symptom assessment and exacerbation frequency evaluation, lung volume measurements and lung imaging must also be considered relevant pieces of information to address the clinical complexity of a COPD patient. Not only, but it has been also shown that patients with symptoms (chronic and exacerbations) and imaging abnormalities of COPD can also present without spirometric obstruction or even normal lung function [33,34]. The recognition that all these clinical elements independently contribute to COPD morbidity and mortality had challenged the definition of the disease [33].

3. What is the role of lung function in the indication and monitoring of therapy in COPD?

FEV₁ and lung function measurements are mandatory to assess the clinical severity of the disease. However, what is the role of lung function in the treatment choice and/or titration? FEV₁ has been used, in the past, to guide the choice of pharmacological therapy of COPD according to the severity of airflow obstruction [3,6,35]. Indeed, FEV₁ is a highly repeatable measurement [36], and improvements in FEV₁ values have been shown to correlate with improvements in health status and exacerbation rate [37,38]. Accordingly, efficacy of most inhaled therapies for COPD is evaluated based on FEV₁ values in several randomized clinical trials.

However, we already discussed the poor correlation between FEV₁ values and clinical outcomes, such as symptoms, which make FEV₁ inadequate as a tool to guide treatment approaches, which aim at optimal treatment of respiratory symptoms. We also discussed how FEV₁ poorly correlates with exacerbation risk, along with patients with mild airflow obstruction who experience frequent exacerbations [17]. Furthermore, long-acting bronchodilators proved effective through all the spectrum of airflow obstruction in reducing respiratory symptoms. Similarly, a combination of inhaled corticosteroid (ICS), LABA and LAMA have been shown to reduce the exacerbation rate even among patients with milder airflow obstruction [39–41]. These observations suggest that basing it only on the FEV₁ value could prevent

some patients to get the therapy that best suits their clinical needs, which led the GOLD recommendations to progressively abandon lung function assessment in the treatment regimen decision in favor of other relevant treatable traits, such as dyspnea and exacerbation rates, or other composite approaches, such as the Body mass index, airflow Obstruction, Dyspnea and Exercise (BODE) index, which combines body composition with airflow obstruction, dyspnea and exercise capacity. This index can provide a multidisciplinary approach to the patient situation, reflecting the variability of the disease and the different fashion by which the patients could respond to the treatments [42].

However, these approaches open at least two relevant clinical questions: first, what is the generability and applicability of such approaches for inhaled treatments that are clinically indicated mainly based on the lung function impairment? Second, besides FEV₁, could other functional and radiological assessments that better correlate with the underlying pathophysiological abnormalities better drive treatment decision-making in COPD [43–45]? Specifically designed randomized controlled trials are needed to address these questions.

4. Do we have validated biomarkers for COPD management and are we ready to use them?

A biomarker is defined as ‘a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes or pharmacologic responses to a therapeutic intervention’ [46]. Many soluble molecules, cellular receptors, intracellular transcriptor factors or gene expression have been investigated over the last few years as possible biomarkers for COPD expression, progression and prognosis [47,48,49,50,51]. Interestingly, associations have been described between exacerbation risk and mortality, especially with higher CRP and plasma fibrinogen levels [51,52,53]. Leung et al. described a more rapid lung function decline among patients with higher serum pSTPB (pro-surfactant protein B) levels [54]. Interestingly, elevated levels of troponin during COPD exacerbations [55] and elevated NT-proBNP during stable phases have been related to increased risk of all-cause mortality in COPD patients [56]. Thus, these data suggest that some biomarkers can provide clinical meaningful information in the clinical assessment of COPD patients. However, none of these biomarkers have been validated in longitudinal randomized controlled trials as a marker for pharmacological intervention. The identification of a ‘blood-based’ biomarker would be extremely useful in both the clinical practice and the optimization of patients’ enrollment in clinical trials, given the ease of detection and analysis of blood samples.

The role of blood eosinophil levels in the clinical manifestation of the disease has been highly debated. The peripheral blood eosinophil count has been proposed by the 2019 GOLD document, and maintained in the 2020 version, as a parameter to guide or to modify the treatment choice in COPD and in particular to support the use of ICS-based regimens [2]. This indication lies on the observation that in the randomized clinical trials where eosinophil blood counts have been taken into account, the propensity of COPD patients to experience

an exacerbation increases consistently with the increase in blood eosinophil levels for those patients not receiving ICS-containing regimens. On the other hand, patients on ICS-containing regimens do not increase the risk of exacerbation when eosinophil count increases [57–61]. These data support a ‘protective’ effect for ICS-containing treatment to COPD exacerbations in patients with higher blood eosinophil levels. Meta-analyses indicated that 300 cells/ μ L is an effective cutoff value to support the use of ICS-containing therapies, while patients with blood eosinophil count of <100 cells/ μ L are less likely to benefit from treatment with ICS [57,62]. Interestingly, in the FLAME study, which compares the effect of ICS/LABA to LABA/LAMA regimens in COPD patients in terms of exacerbation reduction, a correlation between ICS therapeutic response and blood eosinophil level was not observed. Indeed, LABA/LAMA association was at least as effective as ICS/LABA in exacerbation rate reduction, regardless of baseline blood eosinophil count ($<2\%$ vs $\geq 2\%$) [63]. However, it must be noticed that in the FLAME study, only a small proportion of patients experienced frequent exacerbations (≥ 2), a subgroup of COPD patients that benefit from ICS-containing treatments [64]. This suggests that not only the absolute eosinophil count level should be considered when prescribing ICS, but also the frequency of exacerbations can drive the therapeutic decision-making. Accordingly, the WISDOM and the SUNSET studies, which evaluated safety of ICS withdrawal in COPD patients, demonstrated that non-frequently exacerbating patients with blood eosinophil levels <300 cells/ μ L can undergo a safe and rapid ICS withdrawal, while subjects with ≥ 300 cells/ μ L benefit from continuing ICS-containing regimens [65,66]. Based on these observations, the GOLD 2020 document indicates ICS-containing treatments a primary option for COPD patients with a blood eosinophil count between 100 and 300 cells/ μ L and ≥ 2 moderate exacerbation or at least one severe exacerbation requiring hospitalization in the previous year [2]. The use of biomarkers, mainly eosinophils, in tailoring inhaled treatment and in particular for the use/withdrawal of ICS has been recently reviewed in international recommendations provided by international scientific societies [62,67,68]. Interestingly, while the European Respiratory Society provided conditional recommendation for the withdrawal of ICS in patients with COPD without a history of frequent exacerbations and strong recommendation not to withdraw ICS in patients with blood eosinophil counts ≥ 300 eosinophils/ μ L⁻¹, the American Thoracic Society document provided no recommendation for, or against ICS as an additive therapy to long-acting bronchodilators in patients with COPD and blood eosinophilia, except for those patients with a history of one or more exacerbations (Table 1). The lack of a unique recommendation of this aspect highlights the fact that further evidence is needed on this topic.

The use of ICS in COPD patients rises the clinical problem of ICS-related side effects mainly increased risk of infections/pneumonia [59,69–71]. On these regards, Contoli et al. showed that in ICS-naïve COPD patients the use of ICS-containing treatments was associated with increased bacterial load after 1 year of treatment, thus confirming the hypothesis of a pro-infective effect of ICS in COPD. Interestingly, the increased bacterial load was limited to COPD patients with blood

Table 1. Comparison of the guidelines for the use/withdrawal of ICS according to the adoption of eosinophils as a biomarker, released by American Thoracic Society (ATS), European Respiratory Society (ERS) and the GOLD document.

ICS Use or Withdrawal	ATS Document [67]	ERS Document [68]	GOLD Document [62]
Use	<ul style="list-style-type: none"> Patients with blood eosinophilia and a history of ≥ 1 exacerbation in the past year requiring antibiotics or oral steroids or hospitalization 	<ul style="list-style-type: none"> Eosinophil count ≥ 300 cells/μL: strong recommendation for ICS continuation (irrespective of exacerbations and/or hospitalizations) 	<ul style="list-style-type: none"> History of hospitalization(s) for exacerbations ≥ 2 moderate exacerbations per year Blood eosinophils > 300 cells/μL History of, or concomitant asthma
Withdrawal	<ul style="list-style-type: none"> Patients on triple therapy (ICS/LABA/LAMA) and no exacerbations in the past year 	<ul style="list-style-type: none"> Eosinophil count < 300 cells/μL and exacerbations < 2 per year and no hospitalization: conditional recommendation for ICS withdrawal 	<ul style="list-style-type: none"> Repeated pneumonia events Blood eosinophils < 100 cells/μL History of mycobacterial infection
Case consideration	<ul style="list-style-type: none"> No recommendation either for use or withdrawal of ICS as an additive therapy to long-acting bronchodilators in patients with COPD and blood eosinophilia 	<ul style="list-style-type: none"> Eosinophil count < 300 cells/μL and exacerbations ≥ 2 per year or 1 hospitalization: limited evidence available. Discuss risks and benefits with the individual patient 	<ul style="list-style-type: none"> 1 moderate exacerbation per year Blood eosinophils 100–300 cells/μL

eosinophil levels below $\leq 2\%$ [72]. Similarly, Singh et al. showed that sputum eosinophil counts were lower in COPD patients with airway bacterial detection at stable state and during exacerbations compared to those patients without bacterial infection [73]. These findings indicate an inverse relationship between bacterial infection/colonization and eosinophil counts. Thus, in the presence of low levels of blood eosinophils, not only there is no evidence to support the favorable effects of ICS, but there is also evidence of potential side effects. Blood eosinophil levels can represent a meaningful piece of information in the clinical assessment of a COPD patient. However, several concerns increased, which related to the usefulness and applicability of blood eosinophil count in the daily clinical practice. First, the cutoff levels used to predict therapeutic response to treatment do not identify patients with abnormal values of eosinophil counts but the values range within the range of normality. Second, blood eosinophil count fluctuates and is unstable over time in a single COPD patient and poorly correlate with disease status [74], which hampers the predictive value of a single measurement.

Concerning the possible bacterial infection and the related antibiotic use in COPD acute exacerbation, several possible biomarkers have been tested to guide the use of antibiotic therapy in these patients. Several studies investigated the role of procalcitonin as a biomarker for diagnosis, prognosis and possible treatments of the patients developing acute exacerbation requiring hospitalization, leading promising but not conclusive results [75,76]. Interestingly, also serum C-reactive protein has been tested in primary care to drive antibiotic prescriptions in patients presenting with COPD exacerbation. The study showed that CRP-guided prescribing of antibiotics resulted in a lower percentage of patients who reported antibiotic use and who received antibiotic prescriptions from clinicians, with no evidence of harm in patients with COPD exacerbation [76].

The possibility to identify the most effective treatment using a serum biomarker will disclose potential benefits both for the outcome of the patients and for the overall healthcare system.

5. Does the real-life use of inhaled pharmacological regimens reflect GOLD indication?

Numerous evidences demonstrated the existence of a huge gap between indications in International Guidelines, recommendations or scientific literature and 'real-life' pharmacological approaches in COPD patients. Both undertreatment and overtreatment have been recognized in the daily practice. In an Italian observational study, a clear missed correspondence between the 2008 GOLD recommendations and the clinical COPD management was observed, with 62% of evaluated patients receiving inappropriate pharmacological treatment: in particular, no regular pharmacological treatment for COPD was shown in 7.4% of patients, either in stages I–II and in stages III–IV of airflow obstruction [77]. Another more recent cross-sectional observation in 17 centers from southern Italy demonstrated that a high percentage of patients were not treated with any drug across the 2015 GOLD staging, ranging from 10.56% in Group A to 11.03% in Group D [78].

At the same time, ICS-containing treatments are the most frequently prescribed treatment irrespective of the clinical assessment of the patients, with evidence of a frequent and precocious use of ICS even in early stages of the disease [77–80]. A significant proportion of patients classified as Groups A or B (according to the 2011 GOLD assessment tool) are treated with ICS (38.8% and 51.8%, respectively) in a survey performed in Europe [80]. In Italy, ICS/LABA/FDC was the most frequently prescribed drug regardless of COPD stage [77], particularly in early disease phase (patients inappropriately prescribed with triple therapy despite being in Group A) (Figure 1) [78].

Real-life studies also showed a tendency to overprescribing triple inhalational therapy (LABA/LAMA/ICS) among COPD patients. A very recent multicenter, longitudinal, observational study explored patients' satisfaction to COPD treatment showed that despite the vast majority of patients who belonged to GOLD group B, the triple LABA+LAMA+ICS combination was the most frequently prescribed treatment (38%) [81]. It has been shown that a significant proportion of newly diagnosed COPD patients step up to triple therapy within the first 2 years from

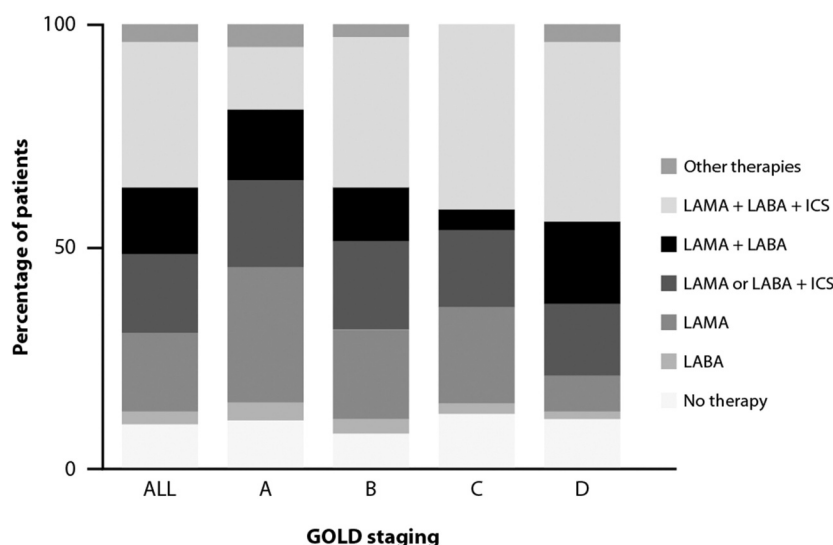


Figure 1. Ongoing treatment at the first visit (Reproduced from [78], with permission from Dove Press).

the diagnosis [82,83]. Di Marco et al. identified factors associated with escalation to triple therapy, in particular previous prescription of ICS/LABA FDC, and persistence of respiratory symptoms, older age, functional and clinical assessment by a pulmonology in the follow-up [83].

A similar conclusion can be drawn by studies reporting experiences other than the Italian situation. The SPIROMICS, a multicenter study recruiting patients from 12 clinical centers in the USA, concluded that almost 50% of the prescribed inhaler regimens did not align with GOLD document. The non-alignment was equally divided between overuse and underuse of inhalators and did not change over time, underlying the necessity to keep on checking on the patients over time to assure a tailored therapy [84].

ICS overuse might have several explanations: i) evidence coming from specific randomized controlled trials that are generalized to the whole population of COPD [69,70,85,86,88]; ii) the concept that COPD is still considered an inflammatory disease in which the airway inflammation can be effectively modulated by an anti-inflammatory drug; iii) the additive/synergistic pharmacological effect to long-acting bronchodilators, especially LABAs [89,90]; iv) a sort of 'copy and paste' to COPD of the positive ICS effects observed in asthma [91]; and v) the inappropriate differential diagnosis between the two obstructive pulmonary diseases [77].

Nevertheless bronchodilators, mainly LAMA (in particular, tiotropium), and associations of LABA/LAMA [40,63,92] have been shown to provide reduction of moderate/severe exacerbations and improvement of lung function in a wide spectrum of COPD patients across disease severity [93].

Another important point to consider is that the ICS overuse observed in real-world evidence can expose COPD patients to a higher risk of ICS side effects. A clear association has been demonstrated between ICS use and several side effects, such as pneumonia [70,71,94,95], upper respiratory tract infections [96], osteoporosis and bone fractures, diabetes, cataracts, mycobacterial infection, which could be linked to the higher dosages used in COPD compared with asthma, but also linked

to the COPD population characteristics (older age, frequent and multiple comorbidities, concomitant medications) [97].

Accordingly, 2020 GOLD recommendations suggest limitation to the use of ICS in specific COPD subgroups only, especially frequent exacerbators (despite adequate bronchodilators treatment) and subjects with history of asthma [2]. A careful evaluation of pneumonia risk and the presence of an increased peripheral blood eosinophil level, which could predict ICS response, are also recommended before the addition of ICS to inhalational treatment [2].

6. Treatment escalation and de-escalation: what are we doing and what should we be doing based on clinical evidence?

The heterogeneous clinical spectrum of COPD requires appropriate adjustment of therapy over time. The 2020 GOLD recommendations suggest treatment escalation or descalation according to the worsening or improvement of symptom and exacerbation persistence, respectively [2]. However, the evidence for such an interesting approach is limited. Indeed, few studies specifically evaluated the effectiveness of step up and the safety of step down of pharmacological treatments in COPD. Data in support derive from studies where patients were switched to step-up treatment after a run-in period; however, no study to our knowledge formerly tested treatment step up during the course of the study [70,87,88,94,98,99,100].

Data from real-life observation studies showed a gap between clinical practice and international recommendations in terms of treatment escalation and de-escalation. Undertreatment, requiring escalation, can occur in a significant proportion of mild but also severe COPD patients [77]. On the other hand, a large retrospective observational study showed a clear tendency toward progressive treatment escalation (to triple therapy), irrespective of baseline disease severity, not followed by descalation [79]. Considering the widespread ICS prescription, it could be argued that there is

a high percentage of COPD patients taking ICS therapy, without a clear clinical need and, even more importantly, with an unjustified exposure to increased risk of treatment-related side effects [2,91,101]. In these subjects, an ICS de-escalation should be carefully evaluated [91]. However, removal of ICS from treatment can be challenging in COPD patients. Patients with moderate COPD and no exacerbations in the previous year can be switched from salmeterol/fluticasone to LABA without any loss of efficacy [102]. The WISDOM study, which is specifically designed to evaluate the effect of an ICS step down in COPD patients, showed non-inferiority in moderate/severe exacerbation risk between ICS withdrawal and ICS maintenance arms. However, it must be recognized that ICS-withdrawal patients had a greater reduction in mean FEV₁ [103]. Similarly, previous studies showed that ICS withdrawal can lead to worsening in symptom and quality of life [104,105]. Interestingly, a post-hoc analysis of the WISDOM study showed that ICS withdrawal in patients with blood eosinophils level above 300 cells/ μ l is associated with an increased risk of exacerbation [65]. These data suggest to carefully evaluate indication for initiation of ICS rather than opportunity to withdrawal because, despite ICS withdrawal can be clinically feasible in several patients, but it can lead to patients' reported outcomes worsening. There is also no clear indication on how to descalate ICS-containing treatments. In the WISDOM trial, a progressive de-escalation was performed in three steps over 12 weeks; however, it is not feasible in clinical practice because of the absence of clinical indication of low dose ICS in COPD and even because of the frequent clinical assessments of the patients during withdrawal (every 6 weeks) [103]. The use/withdrawal of ICS in COPD is a highly debated hot topic in COPD. Interestingly, the American Thoracic Society and The European Respiratory Society have very recently provided detailed and clinically useful recommendations on this topic [67,68].

7. How far are we on the roadmap to tailored management of COPD?

COPD is a complex and heterogeneous syndrome, characterized by multiple components, by different phenotypes (clinical, diagnostic, functional aspects) and different endotypes (the biologic mechanisms involved in the disease pathogenesis) [106]. Not all of them are present in all suffering patients and a variability could also be recognized in the same patient from time to time [106]. This is the reason why the scientific community is extensively discussing about the opportunity to use a 'precision medicine' approach for COPD management and treatment, based on the identification, in every single patient, of 'treatable traits' [106,107]. The final aim should be to implement a chronic airways disease multidimensional management [107].

Despite that, a huge discrepancy exists between scientific literature, international recommendations (mainly provided by the GOLD, with its periodic report) and the clinical practice approach [78,79,108,109]. Furthermore, precision medicine and personalized therapy are not easy tasks to comply with in the daily disease management, and more evidence is

required to allow its application [107]. Finally, the evolution in international recommendations generated several areas of debate, especially related to the role of pulmonary function and biomarkers.

According to the evidence presented in previous sections of this work, it clearly appears that pulmonary function evaluation is still a critical part of proper COPD assessment and a valuable tool for early recognition of small airway alterations and treatment adjustment in the course of the disease: in line with the above described personalized approach, it could require second- and third-level tests to better assess the COPD phenotype [43,44,110,111].

An important step towards precision medicine is the increasing importance of biomarkers, namely the peripheral blood eosinophil count, in predicting inhaled corticosteroids therapeutic response and identifying COPD patients who could benefit the most from ICS treatment [58–61]. Nevertheless, its use as a biomarker is not supported by specifically designed randomized trials and mainly derives from *post-hoc* analysis of randomized controlled trials. Variability in individual blood eosinophil levels should also be considered when considering the use of such a biomarker in treatment decisions.

The use of ICS-containing treatments is another crucial issue in COPD management, with a clear gap between what is recommended and what really happens in the daily practice [60,77,78,80,82,83]. A careful evaluation of ICS risk/benefit ratio is always needed before starting or in the course of ICS therapy. In addition to that, physicians' education is required on the need/opportunity for ICS de-escalation, mainly indicated in case of symptoms resolution, pneumonia, severe ICS side effects, absence of a clear indication and lack of clinical benefit [2,91,101].

It is worth mentioning that, regarding the possibility of a tailored treatment, the COPD phenotypic approach is an option. This approach aims to identify the different phenotypes of COPD to classify patients in groups that share specific characteristics, with the goal of unify the prognostic methods, treatments, possible outcome or adverse events within the same group [112]. Despite the great potential, the classification into different phenotypes is not always univocal, as the criteria proposed to define the phenotypes are variable and each patient may be included in more than one group [113,114].

In conclusion, in the last few years, we have come a long way in tailoring the management of the COPD patient; however, the aim to find a common, reasonable, integrated and evidence-based approach still requires further steps towards the application of a precision medicine and a multidimensional management of COPD.

8. Expert opinion

The six questions tackled here pointed out some considerations that need to be evaluated to improve the management of COPD in the clinical practice. To guide the professionals in the most efficient patients' assessment we highlighted some crucial points that summarize the future perspective of COPD practice.

(1) The role of lung function in the clinical assessment of COPD:

Although the study of pulmonary function is key in the diagnosis of COPD and of severity and prognostic assessment in clinical management, the FEV₁ alone does not capture COPD complexity. Therefore, extensive lung function measurements should be used to provide valuable and clinical meaningful information.

FEV₁ is not a surrogate measure of symptoms/quality of life and exacerbation risk, and clinical evaluation of symptoms through appropriate methods (ie questionnaires) should be implemented in clinical practice and integrate information obobtained through spirometry.

(2) The role of lung function in the indication and monitoring of therapy in COPD:

Given the poor correlation between FEV₁ values and patients' reported outcomes, FEV₁ is considered inadequate to guide treatment options that aim at optimal treatment of respiratory symptoms. However, FEV₁ poorly reflects underlying pathophysiological abnormalities that correlate with relevant clinical outcomes.

Specifically designed randomized controlled trials are needed to address whether deeper lung function of imaging assessment can improve our decision-making in the management of the disease.

(3) The need for validated biomarkers for COPD management in the daily clinical practice:

Several biomarkers have been proposed over the last few years as possible biomarkers for COPD expression, progression, and prognosis but none of them have been validated in specific randomize controlled trial.

Among those, blood eosinophils represent a potential valuable biomarker to drive therapeutic options. In COPD subjects with low blood eosinophil count (<100 cells/ μ l) not only the favorable effect of ICS-containing regimens is limited but there is also evidence from increased risk of ICS-related side effects. The use of blood eosinophil count in guiding treatment decision, however, has some limitations: validation of cut off, the lack of prospective randomised controlled trials and the poor stability of the measurement.

(4) The relationship between the real-life use of inhaled pharmacological regimens and GOLD indication:

There is a huge gap between GOLD recommendations, international scientific literature, and real-life clinical practice. Infact undertreatment, as well as overtreatment, is common, with a highly reported ICS overuse, and a wide number of COPD patients already initiated to ICS in the primary care setting and in the early disease state.

Possible reasons behind ICS overuse could be linked to the positive clinical experience in asthma (that has been inferred to COPD), to an inappropriate differential diagnosis between asthma and COPD, and to the perception of high

efficacy of the ICS class with lower perception of possible adverse effects.

Efforts have been made to better define the COPD patient candidate to ICS therapy, identifying history of asthma and frequent exacerbators (despite adequate bronchodilators treatment), as factors to consider in which ICS is more likely to obtain a favorable risk/benefit ratio. Peripheral blood eosinophil count, although with some limitations, could also be of value in identifying the ICS 'highly responders' subgroups.

(5) What we can do and what should we do, based on clinical evidence concerning treatment escalation and de-escalation:

A gap between international recommendations and clinical practice has been demonstrated for both treatment escalation and de-escalation. The appropriate use of ICS means the need/opportunity for a treatment step down in every condition where there is a high risk for side effects, a lack of efficacy or an inappropriate prescription.

Based on recent scientific evidences, in patients with low incidence of exacerbations and low levels of blood eosinophils ICS can be safely withdrawn in terms of exacerbation risk but can experience worsening in symptoms and quality of life.

In addition, ICS initiation should be carefully evaluated because, once initiated, the withdrawal can be a clinical challenge.

9. The road to tailored treatment

The phenotypic approach aims to identify the different phenotypes of COPD patients to unify the approach within the same group, but the different criteria do not guarantee a univocal classification yet.

HIGHLIGHTS BOX

- The classification of COPD patients on the basis of the severity of the disease and on the best pharmacological treatment has been debated in Italy, following the modifications proposed by the GOLD document, to identify the clinical management and the possibility to personalize the pharmacological approach in specific groups of COPD patients.
- Lung function parameters, such as FEV₁, although central in the diagnosis of COPD, may be inaccurate to predict the prognosis and to define the best treatment for COPD. The evaluation of other indices resulting from a multidisciplinary approach must be considered to address the clinical complexity of a COPD patient.
- There is the need in the daily clinical practice for the identification of easily detectable biomarkers for the assessment of COPD severity, progression and prognosis.
- There is a consistent 'gap' between real-life pharmacological treatments, escalation and de-escalation treatment and GOLD recommendations.
- The development of a precision medicine approach tailoring the specific treatment for each patient is the goal

of COPD management and may be achieved considering the phenotypic classification of COPD patients.

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