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Position paper of the French Society of Respiratory Diseases regarding pharmacological treatment optimization for stable COPD in 2021

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Introduction

The previous French Society of Respiratory Diseases (SPLF, Société de Pneumologie de Langue Française) position paper on

pharmacological treatment optimization in stable COPD was released in 2016 [1]. Many randomized clinical trials assessing new pharmacological treatments/devices have been published since then. The concept of a personalized approach in COPD based on phenotypes, endotypes, and treatable traits generates a growing interest although much uncertainty remains regarding the best way to optimize pharmacological therapy in COPD, and especially regarding the use of

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biomarkers in addition to clinical characteristics. Therefore, existing propositions and guidelines need to be regularly updated, as recently done by several national or international societies or working groups including Global Obstructive Lung Disease, GOLD [2], National Institute for Health and Care Excellence, NICE [3], European respiratory Society, ERS [4] and American Thoracic Society, ATS [5].

In this context, the SPLF decided to update its position on pharmacological treatment optimization in stable COPD in 2021. A working group expert in COPD, representative of pulmonologists, pharmacists, physiologists and general practitioners, reviewed the literature published between 2016 and 2021 [6]. The basis for this position paper is derived from randomized controlled trials, large cohorts, real-world-evidence and expert advices.

Summary of the propositions

The main proposals of SPLF are summarized in Fig. 1. The pre-requisite to their implementation is the confirmation of the diagnosis based on the association of symptoms (dyspnea, chronic cough or regular sputum, and/or a history of recurrent respiratory tract exacerbations), exposure to risk factors (especially tobacco smoking) and spirometry-evidenced persistent airflow limitation (post-bronchodilator $FEV_1/FVC < 0.7$). Any COPD diagnosis should lead to smoking cessation advice, vaccinations (influenza, pneumococcal, COVID), encouragement of regular physical activity, pulmonary rehabilitation if dyspnea during daily activities persists despite optimized pharmacological care, and as-needed short-acting bronchodilators, i.e., short-acting beta-2 agonists (SABA) and/or short-acting muscarinic antagonist (SAMA).

Pharmacological treatment should be individualized and guided by the severity of symptoms, risk of exacerbations, potential adverse effects, and comorbidities. Inhaler technique and adherence should be assessed regularly. Following implementation of therapy, patients should be reassessed for adverse effects and effectiveness, and then maintenance, switching. Escalation or de-escalation of treatments

have to be considered. Step-up should be considered in case of persistent symptoms such as dyspnea or exacerbations. Conversely, step-down should be considered in case of adverse effects (particularly pneumonia for inhaled corticosteroids, [ICS]), lack of effectiveness and/or low levels of eosinophils for ICS ($< 300/mm^3$).

The first line of maintenance treatment that should be considered is monotherapy with a single long-acting bronchodilator. Long-acting beta-2 agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) improve lung function, symptoms (dyspnea) and reduce exacerbations. Clinical trials have shown a better effect on reduction of exacerbations with LAMA (e.g., tiotropium) versus LABA. For this reason, a LAMA should be prioritized in patients with frequent exacerbations (i.e., at least 2 moderate exacerbations in the previous year or at least 1 severe exacerbation/hospitalization in the previous year). ICS monotherapy should never be considered in COPD patients. Long-term ICS with LABAs can be considered in patients with a co-history of asthma or in case of exacerbations despite long-acting bronchodilators. Combination treatment with a LABA and LAMA increases FEV_1 and reduces symptoms and exacerbations compared to monotherapy. The choice between LABA/LAMA and LABA/ICS should consider the predominant symptoms (dyspnea or exacerbations). LABA/LAMA may be preferred in patients with dyspnea ($mMRC \geq 2$) +/- exacerbations. Among patients with at least 2 exacerbations per year, triple inhaled therapy of LABA/LAMA/ICS improves lung function, symptoms and reduces exacerbations compared to LABA/ICS or LABA/LAMA or LAMA alone. Regular treatment with ICS increases the risk of pneumonia especially in patients with more severe disease, lower body mass index, older age and in those with a previous history of pneumonia. Stopping ICS use should be considered after the occurrence of adverse-effects such as pneumonia, especially when blood eosinophils level is under $300/mm^3$. In patients with frequent exacerbations despite triple therapy, macrolides can be considered. Low-dose of long-acting oral opioids may be considered for persistent dyspnea despite appropriate treatments in severe COPD patients. This step-by-step strategy is summarized in Fig. 1.

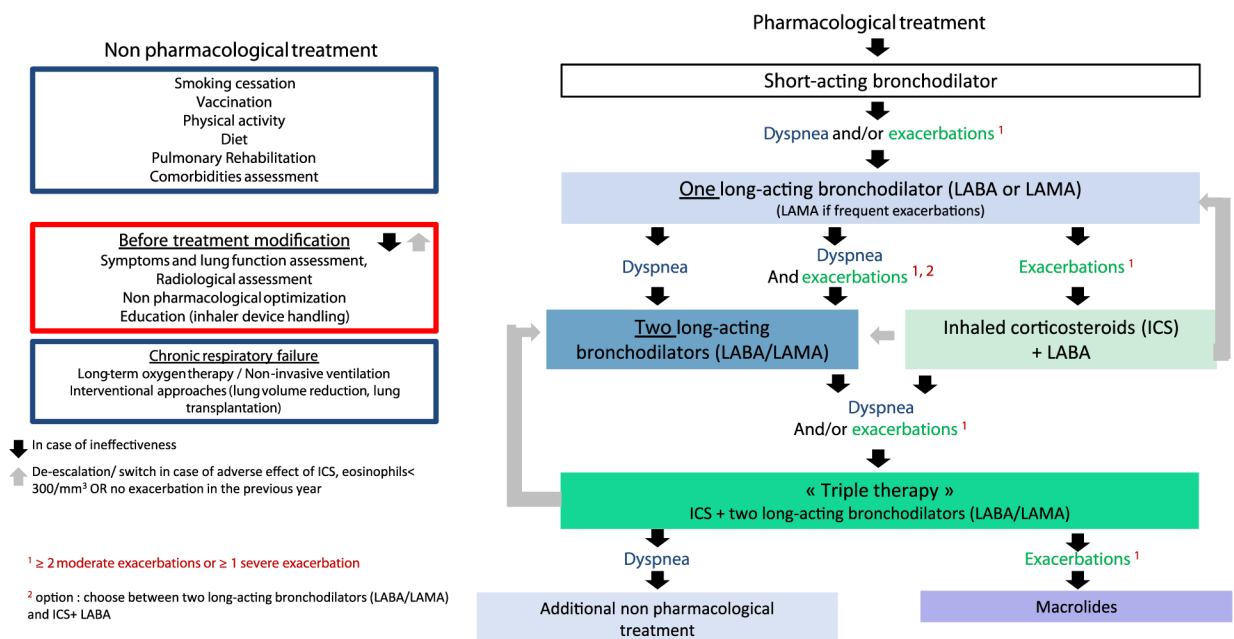


Fig. 1. COPD diagnosis: symptoms and PFT (FEV_1/FVC post-bronchodilation < 0.7).

Table 1

Main similarities/differences between the SPLF position and the other national/international reports. ATS: American Thoracic Society, Eos: eosinophils, ERS: European Respiratory Society, GOLD: Global Obstructive Lung Disease, ICS: inhaled corticosteroids, LABA: Long-Acting Beta-2-Agonist, LAMA: Long Acting Anti Muscarinic, NICE: National Institute for Health and Care Excellence, SCT: Société Canadienne de Thoracologie, SPLF: Société de Pneumologie en Langue Française.

	Step-up	Step-down
SPLF [6]	<ul style="list-style-type: none"> • LABA or LAMA towards ICS/LABA in case of persisting exacerbations without dyspnea • LABA/LAMA towards LABA/LAMA/ICS in case of persisting exacerbations 	<ul style="list-style-type: none"> • No exacerbation in the previous year • Side-effect of ICS (ex: pneumonia) • Eosinophils < 300/mm³, in the absence of exacerbation
GOLD [2]	<ul style="list-style-type: none"> • LABA or LAMA towards ICS/LABA in case of Eos ≥ 300/mm³ or Eos ≥ 100/mm³ and frequent exacerbations • LABA/LAMA towards LABA/LAMA/ICS in case of persisting exacerbations 	<ul style="list-style-type: none"> • Pneumonia • Inappropriate ICS indication • No ICS benefit
ATS [5]	<ul style="list-style-type: none"> • LABA/LAMA towards LABA/LAMA/ICS in case of ≥ 1 exacerbation in the previous year • LABA/LAMA towards LABA/LAMA/ICS Eos ≥ 150/mm³ or 2% and ≥ 1 exacerbation in the previous year 	<ul style="list-style-type: none"> • No exacerbation in the previous year
ERS [4]	<ul style="list-style-type: none"> • None 	<ul style="list-style-type: none"> • No frequent exacerbation and Eosinophils < 300/mm³
NICE [3]	<ul style="list-style-type: none"> • LABA or LAMA towards LABA/LAMA/ICS in case of daily persisting symptoms or frequent exacerbations 	<ul style="list-style-type: none"> • No symptom after 3 months under LABA/LAMA/ICS
SCT	<ul style="list-style-type: none"> • LABA or LAMA towards ICS/LABA in case of co-existing asthma • LABA/LAMA towards LABA/LAMA/ICS in case of persisting dyspnea 	<ul style="list-style-type: none"> • Inappropriate ICS and no ICS benefit and No exacerbation in the previous year

What are the main principles and evolutions from 2016 to 2021?

A step-by-step approach

As in the previous iteration of the document, a step-by-step approach is proposed to initiate treatment stratified on the risk of exacerbations and the level of symptoms, assessed by mMRC score and/or COPD Assessment Test (CAT) score. The treatment can be stepped-up or stepped-down according to the expression of the disease, i.e., the predominant clinical manifestations (dyspnea/exacerbations) despite an appropriate maintenance therapy. After considering the balance of effectiveness and adverse effects of medications, the working group considers that ICS should be withdrawn in the absence of a history of frequent exacerbations and/or in case of adverse effects (e.g., pneumonia). Withdrawal could be considered if blood eosinophil counts are less than 300/mm³. In such situations, maintenance therapy should consist in one or two long-acting bronchodilators.

The visibility of non-pharmacological components of care has been reinforced

Non-pharmacological components of COPD care are keys and must be systematically proposed to all patients. This point has been emphasized more strongly and fully integrated in the decision tree (Fig. 1).

Eosinophils to guide prescription?

The main changes in COPD treatment strategies relate to the criteria used to guide ICS prescriptions. Clinical trials have shown that ICS combined with a LABA reduce the frequency of COPD exacerbations by an average of 25% [7] and may improve disease prognosis in certain subgroups of patients [8].

In patients with exacerbations, blood eosinophil count could be used to help identifying those with the highest likelihood of benefiting from ICS, but only after evaluating clinical characteristics, such as asthma history, inhaled medication side effects. Withdrawing ICS should be considered in the absence of asthma history and/or no frequent moderate to severe exacerbation since one year and/or in case of ICS side-effect. Blood eosinophil counts < 300 eosinophils/mm³ represent an additional argument to step-down.

How do SPLF positions compare with the most recent international positions and guidelines?

Use of eosinophils [2,4,5]

The main similarities and differences between SPLF position [6] and the other national/international reports regarding the use of blood eosinophil counts are summarized in Table 1.

Dual bronchodilation

In patients with significant dyspnea in their daily activities, ATS guidelines recommend to prescribe dual bronchodilation as first line, whereas SPLF proposes a step-by-step approach starting with monotherapy. The underlying argument is the limited magnitude of difference in both the mean level of dyspnea change and proportion of responders in studies comparing mono and dual long-acting bronchodilation. Of course, we must acknowledge that the definition of a “limited magnitude” is a subjective issue.

What next?

Many questions remain in the area of COPD pharmacological treatment optimization. First, the applicability of guidelines and positions in daily practice remains to be determined, as well as how they are disseminated and used in real-life [9]. Second, despite some advances in the therapeutic management of stable COPD, many patients remain symptomatic, exhibiting symptoms and quality of life impairment and/or exacerbations, justifying intensifying research aiming at developing innovative treatments in COPD. Hopefully, ongoing studies of new devices and drugs including biologics and new strategies to personalized treatment will help to address these current unmet needs.

Conflicts of Interest

None.

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