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Early View

Review

Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease: The GOLD Science Committee Report 2019

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Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease: The GOLD Science Committee Report 2019

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Abstract

Precision medicine is a patient specific approach that integrates all relevant clinical, genetic and biological information in order to optimise the therapeutic benefit relative to the possibility of side effects for each individual. Recent clinical trials have shown that higher blood eosinophil counts are associated with a greater efficacy of inhaled corticosteroids (ICS) in COPD patients. Blood eosinophil counts are a biomarker with potential to be used in

clinical practice, to help target ICS treatment with more precision in COPD patients with a history of exacerbations despite appropriate bronchodilator treatment.

The Global initiative for the management of chronic Obstructive Lung Disease (GOLD) 2017 pharmacological treatment algorithms, based on the ABCD assessment, can be applied relatively easily to treatment naïve individuals at initial presentation. However, their use is more problematic during follow up in patients who are already on maintenance treatment. There is a need for a different system to guide COPD pharmacological management during follow up.

Recent large randomized controlled trials have provided important new information concerning the therapeutic effects of ICS and long-acting bronchodilators on exacerbations. The new evidence regarding blood eosinophils and inhaled treatments, and the need to distinguish between initial and follow up pharmacological management, led to changes in the GOLD pharmacological treatment recommendations. This paper explains the evidence and rationale for the GOLD 2019 pharmacological treatment recommendations.

Introduction

Chronic obstructive pulmonary disease (COPD) is a complex condition, with many different components and mechanisms contributing to its pathophysiology and clinical presentation(1). Precision medicine is a patient specific approach that integrates all relevant clinical, genetic and biological information for each individual in order to optimise pharmacological treatment, enabling the therapeutic benefit to be maximized for an individual relative to the possibility of side effects(1, 2). For instance while randomized controlled trials (RCTs) of inhaled corticosteroids (ICS) containing combinations have consistently demonstrated a clinical benefit for the ICS component on a group basis, the presence and magnitude of effect varies greatly between individuals(3). Furthermore, there are concerns about the long-term side effects of ICS use in COPD, in particular pneumonia but also osteoporosis, diabetes, tuberculosis and non-tuberculous mycobacteria infection (1, 3).

Eosinophilic airway inflammation is present in a subset of COPD patients(4, 5). Short term clinical trials have shown that higher sputum eosinophil counts in stable COPD patients predict a greater lung function response to corticosteroids(6, 7). Sputum eosinophil measurements are not widely available in most centers, limiting its use in daily clinical practice and patients cannot always provide adequate samples for analysis. Blood

eosinophil measurements are an alternative biomarker reflecting eosinophilic airway inflammation in COPD patients(4). Recent clinical trials have shown that blood eosinophil counts are associated with the efficacy of ICS in COPD patients(8-13), suggesting the use of this biomarker to identify individuals with a greater probability of treatment benefit with ICS. This provides an opportunity in clinical practice to target ICS treatment with more precision in COPD patients with a history of exacerbations despite appropriate bronchodilator treatment.

The Global initiative for the management of chronic Obstructive Lung Disease (GOLD) 2017 strategy document recommended that an assessment (ABCD grouping) based on symptoms and exacerbation risk should be performed after the initial diagnosis of COPD (14). The ABCD grouping was designed to facilitate a more individualized approach to pharmacological management based on clinical characteristics, with different recommendations for initial treatment and subsequent follow up for each group (14). While these treatment algorithms can be applied relatively easily to treatment naïve individuals at initial presentation, their use is more problematic during follow up in patients who are already on maintenance treatment. One key issue is that the grouping applied to an individual may change over time, which could reflect either a positive response to treatment or worsening of disease (15). A potential solution is to use ABCD **only for initial treatment**, and use a different system to guide pharmacological management in COPD patients who are in follow up and already receiving treatment.

Recent large randomized controlled trials (RCTs) focusing on exacerbation prevention have provided important new information concerning the therapeutic effects of ICS and long-acting bronchodilators(9, 10, 16). This report explains the GOLD science committee`s interpretation of the evidence for blood eosinophils as a biomarker in COPD patients and recent RCT evidence concerning exacerbation prevention. We explain how this information was incorporated into the GOLD 2019 recommendations which set out to provide more clarity regarding initial and follow up pharmacological management.

Initial and follow up pharmacological management; more clarity needed in GOLD

GOLD 2017 pharmacological treatment recommendations were based on the ABCD categorization of patients at diagnosis(14). Using this system to decide on an initial treatment plan is relatively straightforward. Following the relevant algorithm to decide on the next steps after initial treatment requires knowledge of the clinical response to the previous treatment, which guides whether to escalate, switch, de-escalate or maintain the current regimen (15). These important details regarding the response to previous treatment may be lost when the GOLD 2017 treatment algorithms are applied for the first time to a COPD

patient who is already on maintenance inhaled treatment. Furthermore, a beneficial response to the previous treatment may lead to changes in the GOLD ABCD grouping, and the clinician may be confused about whether this change should lead to the subsequent withdrawal of a beneficial pharmacological treatment. COPD patients can change their GOLD group over time(17), and in such situations it is unclear how the ABCD system should be used.

GOLD 2019 retains the ABCD grouping to decide on appropriate ***initial*** pharmacological treatment (Figure 1). However, GOLD 2019 states that the ABCD grouping ***should not be used*** for patients who are already on maintenance treatment. To make clearer recommendations for such patients, distinct treatment pathways have been constructed for pharmacological management during follow up (Figure 2). Symptoms (dyspnoea and exercise limitation) and exacerbations are still the focus of treatment, and there are separate algorithms for each of these treatable traits(18). The clinician needs to decide the predominant trait that requires further effective treatment at that point in time, and use the relevant algorithm; the exacerbation algorithm should be used for patients suffering with both symptoms and exacerbations. The patient should be placed within the relevant algorithm according to their current treatment, and recommendations for treatment escalation, switching or de-escalation utilised.

Both follow up treatment algorithms include all the currently available inhaled monotherapy and combination treatment classes, in order to encompass all previous treatment possibilities. This explains why ICS/LABA is included in the dyspnoea algorithm; it is not recommended as a treatment for dyspnoea (as no escalation arrow leads towards this treatment), but is included for those patients who are currently being treated with ICS/LABA and now have dyspnoea that needs further treatment. Similarly, LABA or LAMA are stated at the top of each algorithm to cover both of these previous treatment possibilities. The most appropriate treatment algorithm to use should be re-evaluated at each clinic visit, as these pathways have been constructed so that the patient can be switched from one to the other as appropriate.

The dyspnoea algorithm recommends escalation using additional long acting bronchodilator treatment for breathlessness and closely follows the recommendations of the GOLD 2017 report, albeit in a different format. For patients with dyspnoea who are already treated with a dual bronchodilator or triple combination, the option to switch molecules or inhaler device has been added, and there is a reminder to investigate other possible causes of dyspnoea such as heart failure and pulmonary hypertension. Non-pharmacological management approaches including pulmonary rehabilitation should also be considered. The exacerbation pathway recommendations differ from the GOLD 2017 report in both scientific content and

format, due to the incorporation of blood eosinophils as a biomarker and recent evidence from RCTs.

The evidence for blood eosinophils as a biomarker in COPD

Relationship of blood to lung eosinophils

Bronchoscopic and sputum sampling shows the presence of increased eosinophil numbers in some COPD patients(4, 19), promoting the concept of a subgroup of patients with "eosinophilic COPD" due to the increased number of these cells in the airways. There is a statistical correlation between blood and sputum eosinophil numbers in COPD patients, although the relationship remains moderate to weak (5, 20, 21). However, sputum eosinophil counts are prone to considerable inter-sample variability(22, 23), and should not be regarded as the "gold standard" biomarker of eosinophilic lung inflammation. Higher blood eosinophil counts are associated with greater eosinophil counts in lung tissue samples (4, 24), and pathological differences including increased reticular basement membrane thickening (subepithelial fibrosis)(4).

Variability of blood eosinophils

Factors that can influence blood eosinophil counts include sepsis and oral corticosteroids, which reduce counts (5). The intra-class correlation coefficient (ICC) of repeat blood eosinophil counts are reported as 0.64 at 1 year (n=17,724), increasing to 0.70 when excluding patients where oral corticosteroid use and / or concurrent exacerbations may have influenced counts(25), 0.87 at >2 years (n=59) (26) and 0.57 at 3 years (n=1483) (27). ICC values can be interpreted as excellent (>0.75), fair to good (0.40–0.75), or poor (<0.40)(25). These ICC values for repeated blood eosinophil counts in COPD patients, therefore, lie in the fair to good or excellent categories and are similar to reported values for cholesterol (ICC= 0.70–0.72) and glycated haemoglobin (HbA1C; ICC = 0.59) which are commonly used biomarkers in the management of other diseases(25). It should be noted that cholesterol and HBA1C are biomarkers used to monitor the effects of pharmacological interventions, while this paper discusses the use of blood eosinophil counts in COPD to predict pharmacological effects.

Analysis of the number of patients that cross a predetermined threshold over time shows good stability at lower threshold values (5). Using the <150 eosinophils/μL threshold, 87 and 86% of results remained stable at 6 months and >2 years respectively (26). Greater variability has been observed with higher threshold values e.g. using 340 cells /μL, stability was 85% at 6 months and 62% at 2 years (28). The variability observed with multiple testing (at least 3 measurements) (25) remains greater at higher eosinophil counts; 88% with a first blood eosinophil count ≥ 150 cells/μL had a subsequent mean value ≥ 150

cells/µL, while for a first count ≥ 300 cells/µL the proportion with a subsequent mean above this level was 68% (25). For the >300 eosinophils/µL threshold, observational cohorts report that 15.8%, 19% and 20% of values are always above this level after 1 or 2 years follow up, with the proportion at a single measurement being higher (26, 29, 30). The percentage of COPD patients identified above or below given blood eosinophil thresholds may be influenced by geographical variations.

Blood eosinophils and ICS response

Post-hoc and pre-specified analysis of RCTs have evaluated the relationship between blood eosinophil counts measured before randomization and ICS effects. The evidence from these studies is reviewed according to treatment comparison. Unless stated otherwise, the inclusion criteria of all these studies required patients to have ≥1 moderate or severe exacerbation in the previous year, and the studies were of at least 1 year duration.

ICS/LABA versus LABA

Three post-hoc analyses of RCTs that compared ICS/LABA versus LABA all showed a similar pattern of results (11, 12, 31); there was a continuous relationship between blood eosinophil counts and the effect of ICS on exacerbation prevention, with higher eosinophil counts predicting a greater drug response. The largest analysis (n=4528) used data modelling to demonstrate that no benefit of ICS was observed below 100 eosinophils / µL, with the effect at higher counts being larger (and more likely clinically relevant) (31); the treatment effect at > 300 cells/µL in this and other analyses was approximately a 50% exacerbation rate reduction (11, 12). The data modelling analyses also showed greater ICS effects at higher blood eosinophil counts for FEV_1 and quality of life.

Post-hoc analyses of other studies comparing ICS/LABA versus LABA that have used a single blood eosinophil threshold have been less informative (32). Trying to dichotomize a COPD population using a single eosinophil threshold to define “responders” and “non-responders” is overly simplistic in this situation, as different eosinophil thresholds appear to reflect different magnitudes of ICS response: <100 cells/µL is associated with little or no effect, while relatively large effects are observed at > 300 cells/µL (Figure 3). This is similar to a classical pharmacological dose response curve with drug concentration on the x-axis and drug response on the y-axis, except here the x-axis is the blood eosinophil count.

Triple therapy studies (LABA/LAMA/ICS fixed combination)

In the TRIBUTE study, a pre-specified analysis showed a greater effect of triple therapy (beclomethasone dipropionate / formoterol / glycopyrrolate) versus LAMA/LABA (glycopyrrolate / indacaterol) on exacerbation rate reduction in patients with blood eosinophils ≥2% (20% treatment difference, p=0.029) compared to <2% (6%, p=0.68)(10).

Numerically similar results were obtained using ≥200 cells / µL, although statistically significant benefit was not reached above this threshold (p=0.057).

The IMPACT study enrolled patients with FEV_1 < 50% and ≥ 1 moderate or severe exacerbation in the previous year, or FEV_1 50% - 80% and ≥ 2 moderate or 1 severe exacerbation in the previous year (9). These inclusion criteria enrolled a population with a relatively high exacerbation risk ; 54% had ≥ 2 moderate or severe exacerbations and 26% had ≥ 1 severe exacerbation in the previous year. There was a 25% treatment difference in the annual exacerbation rate in favour of triple therapy (fluticasone furoate / vilanterol/umeclidinium) over LAMA / LABA (umeclidinium / vilanterol). A pre-specified analysis showed a 32% treatment difference (p<0.001) at ≥150 eosinophils / µL, while below this threshold the treatment difference was smaller, but still significantly in favour of triple therapy (12%; p=0.034).

ICS/LABA versus LABA/LAMA

The FLAME study showed that LAMA/LABA (glycopyrrolate/ indacaterol) had a 17% greater effect on exacerbation rate reduction than ICS/LABA (fluticasone propionate / salmeterol)(33). Pre-specified analysis using a 2% eosinophil threshold showed no difference in treatment effect above or below this threshold (33). Subsequent post-hoc analysis using 3 subgroups (<150, 150 to <300 and ≥300 cells / µL) revealed a different pattern of results (34); LABA/LAMA had a much greater effect than ICS/LABA at <150 eosinophils / µL (28% difference; p<0.001), but at 150 to < 300 and ≥300 cells / µL this treatment comparison yielded smaller differences(11% and 7% respectively). Patients with higher eosinophil counts (>600 cells / µL) were excluded, possibly blunting the result in the >300 cells / µL category. This analysis supports the concept of a continuous relationship between blood eosinophils and ICS effects, with reduced ICS effects at lower blood eosinophil counts. In this study, the previous exacerbation history did not influence the treatment differences (34, 35), although the proportion of patients with a history of at least two exacerbations in the previous year was limited (approximately 20%).

The IMPACT study also compared ICS/LABA (fluticasone furoate / vilanterol) with LAMA/LABA; ICS/LABA had a 10% greater effect on exacerbation prevention in the overall population. The treatment difference was dependent on blood eosinophil counts, with LAMA/LABA having a greater effect at < 150 cells / µL, while ICS/LABA had a greater effect above this threshold. These results differ significantly from FLAME, where ICS/LABA was not superior to LAMA/LABA in any eosinophil threshold or subgroup analysis(34). A key difference between these studies was the exacerbation risk of the enrolled populations, as most of the FLAME population had 1 exacerbation in the previous year (33), in contrast to

the much higher risk of the IMPACT population, indicating that the effects of ICS containing combinations are greater in higher risk populations. Patients with a history of asthma were excluded from FLAME but were allowed to participate in IMPACT, potentially influencing the observed ICS treatment effects. The run-in treatment in the FLAME study was tiotropium, while in the IMPACT study patients continued with their own inhaled treatment. This also may have contributed to the differing results, as some patients requiring ICS would have dropped out during the FLAME run-in period.

ICS step-down studies

The WISDOM study evaluated the stepped withdrawal of ICS from triple therapy. Two post-hoc analyses of WISDOM have shown a significant deleterious effect of ICS withdrawal at higher blood eosinophil counts (≥300 cells / μL)(8, 36). One of these analyses showed a greater deleterious effect in patients with a prior history of ≥2 exacerbations, supporting the concept of greater ICS effects in higher exacerbation risk individuals. The SUNSET study enrolled patients with 0 or 1 exacerbation (66% and 34% respectively) in the previous year who were already on triple therapy for at least 6 months (37). ICS withdrawal appeared to be well tolerated at ≤300 eosinophils / μL, while a clinical deterioration (greater lung function loss) and more exacerbations were observed in those with ≥300 eosinophils / μL.

Other clinical trials

Post-hoc analysis of the INSPIRE study did not shown any significant differences between ICS/LABA versus LAMA using thresholds of 2% and 200 cells / μL, but other thresholds were not investigated(32). A combined analysis of 10 studies showed that pneumonia risk was higher in patients with eosinophils <2% independent of ICS use, although the effect size was small (3.7% versus 3.2%, hazard ratio 1·31; 95% CI 1·06–1·62)(38). A clinical trial reported that blood eosinophil counts may predict which patients receive benefit from oral corticosteroid treatment during exacerbations (39). These data may help direct acute exacerbation management, but do not provide support for the use of blood eosinophils to help direct the use of ICS containing combination inhalers.

Summary; blood eosinophils and ICS response

The clinical evidence reviewed contains subgroup analyses with reduced sample sizes. In such cases, a focus on p values for statistical significance may be less appropriate. However, the magnitude of effect sizes and consistency of data between studies become important considerations. A consistent pattern of results from RCTs conducted in COPD patients at increased risk of exacerbations has emerged, showing that lower eosinophil counts predict a lower or no benefit of ICS in terms of exacerbation prevention, which is particularly evident below approximately 100 eosinophils / μL. The greatest ICS effects were

consistently observed at ≥ 300 eosinophils / µL. These thresholds of <100 and ≥300 eosinophils / µL can therefore be used to help predict the likelihood and magnitude of ICS treatment benefit in clinical practice. These thresholds provide a measure of probability that can be used with other clinical information, notably exacerbation risk, to estimate the likelihood of a treatment benefit from ICS treatment.

The different results observed when comparing the double combination treatments in the FLAME and IMPACT studies highlight that ICS have a greater demonstrable benefit in higher exacerbation risk populations. This can influence the interpretation of blood eosinophil counts and thresholds. In patients with 1 moderate exacerbation in the previous year, the FLAME results indicate that LAMA/LABA is generally a preferred treatment, although ICS/LABA may be a more effective treatment for some patients with eosinophils ≥ 300 cells / µL. In higher risk patients (≥2 moderate exacerbations or 1 severe exacerbation), the IMPACT study demonstrated that the benefits of ICS/LABA over LABA/LAMA were present even at lower blood eosinophil counts, indicating that ICS/LABA use could be considered in high risk patients at > 100 eosinophils / µL, whilst being preferred at higher eosinophil counts.

The number-needed-to-treat (NNT) to prevent one exacerbation (event-based NNT) is dependent on the underlying exacerbation rate and has been approximately derived from the IMPACT results; the NNT to prevent one exacerbation with triple therapy compared to LAMA/LABA (where a 25% reduction in exacerbation rate was observed) has been estimated to lie between 3 and 4(3). These event-based NNTs will vary with blood eosinophil counts, being lower at the higher eosinophil counts where greater ICS effects were observed. The event-based NNT is dependent on the comparator rate of exacerbations, and so will change according to the exacerbation risk of a population. The TRIBUTE study population had a lower exacerbation risk as reflected in the previous 1 year history compared to the IMPACT population, and consequently a lower rate of exacerbations was observed during the study, with a 15% difference between triple therapy and LAMA/LABA for exacerbation rate reduction. The event-based NNT calculation for this study estimates the value to lie between 11–12 (3), with a lower number expected at higher eosinophil counts. The person-based NNT (i.e. to make patient exacerbation free) for IMPACT and TRIBUTE have been estimated to be 25 and 50 respectively for triple therapy versus LAMA/LABA. These NNT estimates emphasize that exacerbation risk influences the magnitude of ICS effects on exacerbation prevention.

Blood eosinophils are a peripheral biomarker of airway eosinophil numbers and eosinophil associated airway inflammation such as type-2 cytokines and reticular basement membrane thickening (4). The clinical benefits of ICS reported in COPD RCTs do not arise from

suppression of blood eosinophil numbers, but are presumably due to pharmacological effects on a component/ components of airway inflammation that are associated with higher blood eosinophil counts.

Overall, current evidence indicates that the individual assessment of exacerbation risk and blood eosinophil count can be combined to help predict the likelihood of clinical benefit with ICS containing combinations. This should be coupled with an individualized assessment of the risk of side effects, notably pneumonia, mycobacterial infection, osteoporosis, diabetes and cataracts.

Relationship of blood eosinophils to clinical characteristics

Cohort studies have investigated whether blood eosinophil counts are associated with clinical characteristics, such as exacerbation rates. The results have varied, with both negative and positive findings reported for exacerbations (29) (40) (41). A recent publication using both cross-sectional (at baseline) and prospective data from COPDGene and ECLIPSE showed that eosinophils ≥ 300 cells / µl are associated with increased exacerbation risk(27), with the findings being most clearly demonstrated in patients at high exacerbation risk (≥ 2 exacerbations in the previous year). This highlights that exacerbation risk, according to the history of exacerbations, influences the results of these cohort studies. Also, the study showed that increased blood eosinophil counts in COPD was not the same as stating that the patient had asthma COPD overlap (ACO) as the overlap between the two was small. Furthermore, the clinical trials already reviewed of ICS/LABA versus LABA in COPD patients with a history of exacerbations showed that ICS use reduces exacerbation rates in patients with more eosinophils, and the relationship between eosinophil counts and exacerbation rates was only seen without ICS use. Overall, the confounding factors of ICS treatment effect and clinical exacerbation risk are responsible for the heterogeneity between studies. These inconsistent data do not support the use of blood eosinophils as a biomarker to predict exacerbation risk or other clinical outcomes in the general COPD population.

New evidence from clinical trials

The TRIBUTE and IMPACT studies comparing triple therapy versus LAMA/LABA provided, for the first time, evidence of the beneficial effect of the ICS component of triple therapy on exacerbations (15% and 25% exacerbation rate reduction respectively) and quality of life(9, 10). IMPACT also reported a different result to FLAME(33) for the comparison of double combinations, which can be attributed mainly to the different exacerbation risk of the study populations as already discussed. These results from the TRIBUTE and IMPACT studies provide evidence to support the GOLD 2017 recommendation to escalate from LAMA/LABA to triple therapy. In contrast, the situation concerning double combinations has now been

shown to be more complex; as the relative efficacy of double combinations is influenced by both exacerbation risk (and hence study enrichment regarding exacerbation history) and blood eosinophil count.

The DYNAGITO study compared the effect of LAMA/LABA (tiotropium/olodaterol) versus LAMA (tiotropium) on exacerbation prevention in patients with ≥ 1 exacerbation in the previous year (n=7880)(16). A reduction of only 7% (p=0.0498) in the exacerbation rate in favour of LAMA/LABA was observed, which did not meet the a priori level set for significance (0.01). The only similar previous study was SPARK, which showed that LAMA/LABA (glycopyrrolate / indacaterol) reduced moderate to severe exacerbations by 12% (p=0.038) versus glycopyrrolate (the primary outcome) and 10 % (p=0.096) versus open-label tiotropium. Overall, DYNAGITO and SPARK demonstrate a minor additional effect of the LABA component of dual bronchodilator therapy on exacerbation prevention.

Implementing new evidence into GOLD 2019

Initial pharmacological management

The large RCTs in COPD have usually been conducted in populations where the majority of individuals were already taking maintenance treatment before entering the study. Few studies have been specifically designed to evaluate pharmacological interventions in treatment naïve COPD patients. The GOLD recommendations for initial pharmacological treatment are based on existing evidence, but with the limitation that these recommendations have not been directly tested in treatment naïve populations.

The lack of new RCTs in treatment naïve COPD patients means that the GOLD 2019 initial treatment recommendations (Figure 1) are mostly similar to GOLD 2017. The exception is GOLD D, with two key changes. First, eosinophils ≥ 300 cells / µl is suggested as an indicator to consider ICS/LABA treatment, as this threshold identifies patients with a higher likelihood of benefit from ICS treatment. A retrospective analysis of real world clinical practice data supports this recommendation; the effects of ICS/LABA as an initial treatment on exerbation prevention were greater than LAMA treatment in patients with eosinophils ≥ 300 cells / µl, but not below this threshold (42). Second, a box stating that LAMA/LABA is a preferred treatment in GOLD 2017 has been removed due to the new evidence on exacerbation prevention showing that the magnitude of effect of LAMA/LABA over LAMA was smaller than expected (DYNAGITO)(16), and that ICS/LABA is a better treatment than LAMA/LABA in some patients (IMPACT)(9). RCTs have demonstrated the benefits of LAMA/LABA compared to LAMA monotherapy for symptoms and quality of life(43, 44), so there is a practical recommendation to consider LAMA/LABA as first line therapy in more highly symptomatic individuals.

Follow-up pharmacological management

The dyspnoea pathway (Figure 2) closely follows the GOLD 2017 recommendations for groups B and D, using additional long acting bronchodilator treatment to manage symptoms. In contrast, the follow up exacerbation pathway is very different, as the integration of exacerbation risk and blood eosinophil counts influences the recommendations regarding the use of combination inhalers. For escalation from long acting bronchodilator monotherapy to either ICS/LABA or LAMA/LABA, the threshold of ≥300 eosinophils / µl can be used across all COPD patients who require further treatment to prevent exacerbations to favour the choice of ICS/LABA. A lower threshold (> 100 eosinophils / µl) may be used in patients at high exacerbation risk (≥2 moderate exacerbations or 1 severe exacerbation in the previous year) to support ICS/LABA use, as ICS effects appear to be greater in such high risk individuals.

The GOLD 2019 report uses the word “consider” when making treatment recommendations concerning blood eosinophils for two reasons; first, this biomarker provides a degree of probability (not certainty) regarding whether ICS treatment will be beneficial and the magnitude of effect; second, other clinical characteristics including the risk of side effects must also be considered on an individual basis.

For patients already taking LAMA/LABA who are still having exacerbations, we suggest the threshold of > 100 eosinophils / µl to identify individuals with a greater likelihood of achieving clinical benefit when escalating to triple therapy. The continuous nature of the relationship between blood eosinophil counts and ICS benefits means that the magnitude of effect on exacerbations will be greater at higher eosinophil counts, particularly ≥300 eosinophils / µl. For patients with < 100 eosinophils / µl, the escalation to triple therapy is unlikley to have a major influence on exacerbations. Other options include the addition of roflumilast or azithromycin(45, 46).

Advice is provided regarding the discontinuation of ICS, either by the de-escalation from triple therapy to LAMA/LABA or switching from ICS/LABA to LAMA/LABA. The common clinical scenarios when this may be considered are (1) concerns about side effects, such as likelihood and impact of pneumonia (2) inappropriate original indication (e.g. the patient had no history of exacerbations and ICS had been prescribed to manage symptoms) and (3) lack of response to ICS. The withdrawal of ICS should be closely monitored, with evidence indicating that the greatest probability of a deleterious effect is in patients with ≥300 eosinophils / µl.

An important addition to the pharmacological management section is the management cycle (Figure 4), which describes the process of review of symptoms and exacerbations followed

by assessment of inhaler technique and adherence as well as non-pharmacological approaches including pulmonary rehabilitation and self-management education. Assessing, treating and following comorbidities also needs to be considered throughout the management cycle. This provides a wider holistic view of the many factors to be evaluated before deciding whether to adjust pharmacological treatment.

Conclusion

The changes to GOLD 2019 reflect an evolution based on recent evidence, rather than change of direction, towards a more personalized approach to COPD management advocated in previous GOLD reports. The focus on managing symptoms and reducing exacerbation risk remains the same. Blood eosinophils have been added in order to help clinicians better manage decisions regarding the benefits versus risks of using ICS. Blood eosinophils provide information regarding probability of benefit, and the interpretation of this information is clearer in patients with high exacerbation risk. Clinical decisions regarding the use of ICS containing combination treatments must focus on exacerbation risk, supported by eosinophil biomarker information, and evaluate side effect risk for each individual.

GOLD 2019 pharmacological treatment recommendations often provide more than one choice, as evidence has shown these to be effective options. This creates complexity in decision making, in contrast to the simplicity of recommending only one treatment option in each situation. However, the heterogeneity of COPD patients means that treatment recommendations and algorithms should allow flexibility for the individual clinical characteristics and needs of each patient to be taken into account, as well as differences between health care systems. GOLD 2019 attempts to provide flexibility in this context, allowing different treatment choices and also providing a framework to help clinicians choose. The area of most debate and complexity is the use of combination inhalers to prevent exacerbations. Recent clinical evidence shows that each of these combination inhalers can be regarded as optimum treatments in some patients, who can be identified using clinical characteristics and a blood biomarker (9, 10). Individualization of COPD pharmacological treatment has progressed significantly since the days of FEV_1 guided pharmacological management(47).

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FIGURE LEGENDS

Figure 1. GOLD 2019 recommendations for initial pharmacological management. Abbreviations: eos = blood eosinophil count (cells / µL), mMRC = modified medical research council dyspnoea questionnaire, CAT = COPD assessment test

Figure 2. GOLD 2019 recommendations for follow up pharmacological management

Figure 3. The relationship between blood eosinophil counts and the effects of inhaled corticosteroids (ICS) on exacerbation prevention in COPD patients

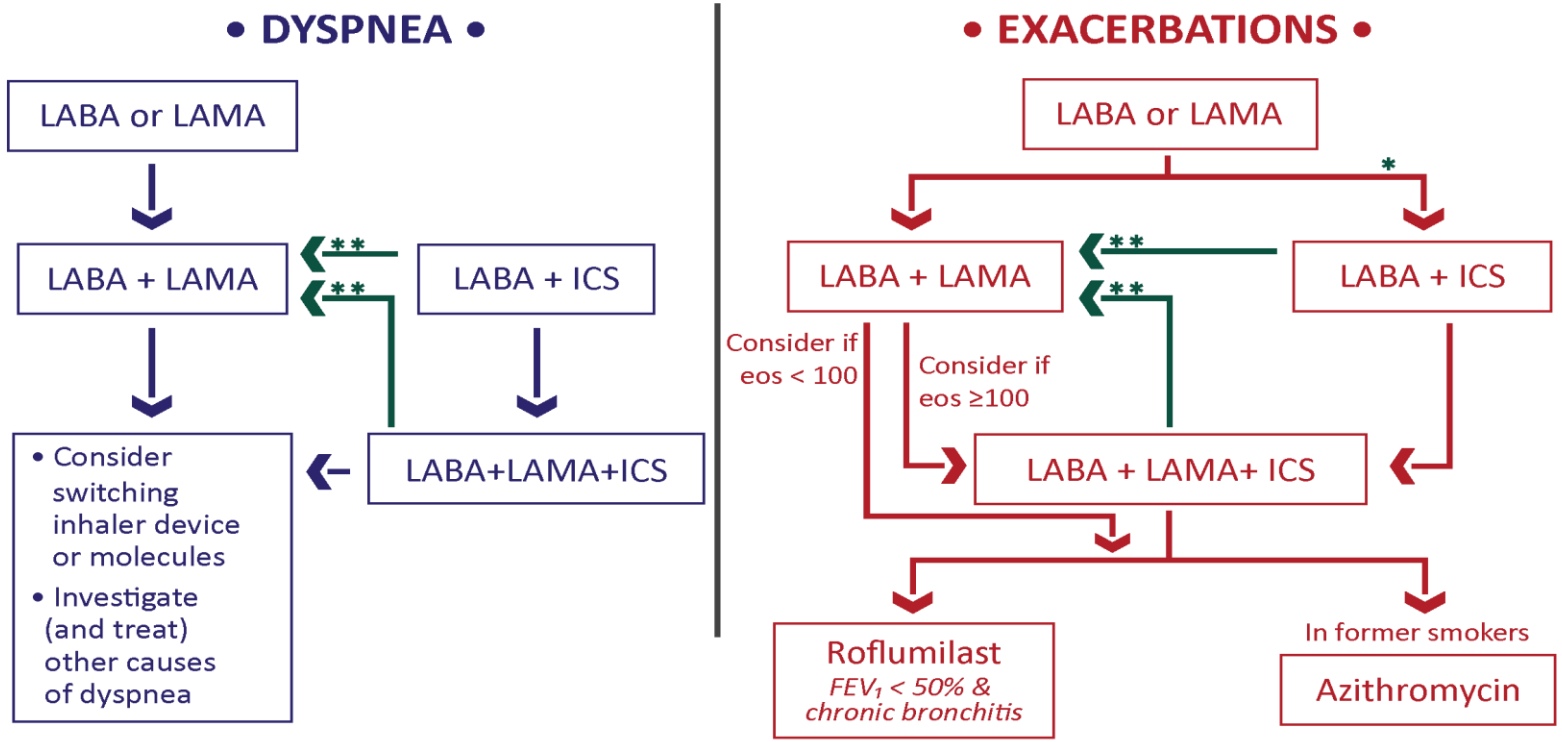
Figure 4. GOLD 2019 management cycle recommendation

INITIAL PHARMACOLOGICAL TREATMENT

≥ 2 moderate exacerbations or ≥ 1 leading to hospitalization	**Group C** LAMA	**Group D** LAMA or LAMA + LABA* or ICS + LABA** *Consider if highly symptomatic (e.g. CAT > 20) **Consider if eos ≥ 300
0 or 1 moderate exacerbations (not leading to hospital admission)	**Group A** A Bronchodilator	**Group B** A Long Acting Bronchodilator (LABA or LAMA)
	mMRC 0-1 CAT < 10	mMRC ≥ 2 CAT ≥ 10

FOLLOW-UP PHARMACOLOGICAL TREATMENT

1. **IF RESPONSE TO INITIAL TREATMENT IS APPROPRIATE, MAINTAIN IT.**
2. **IF NOT:**
   - ✓ Consider the predominant treatable trait to target (dyspnea or exacerbations)
     - Use exacerbation pathway if both exacerbations and dyspnea need to be targeted
   - ✓ Place patient in box corresponding to current treatment & follow indications
   - ✓ Assess response, adjust and review
   - ✓ These recommendations do not depend on the ABCD assessment at diagnosis

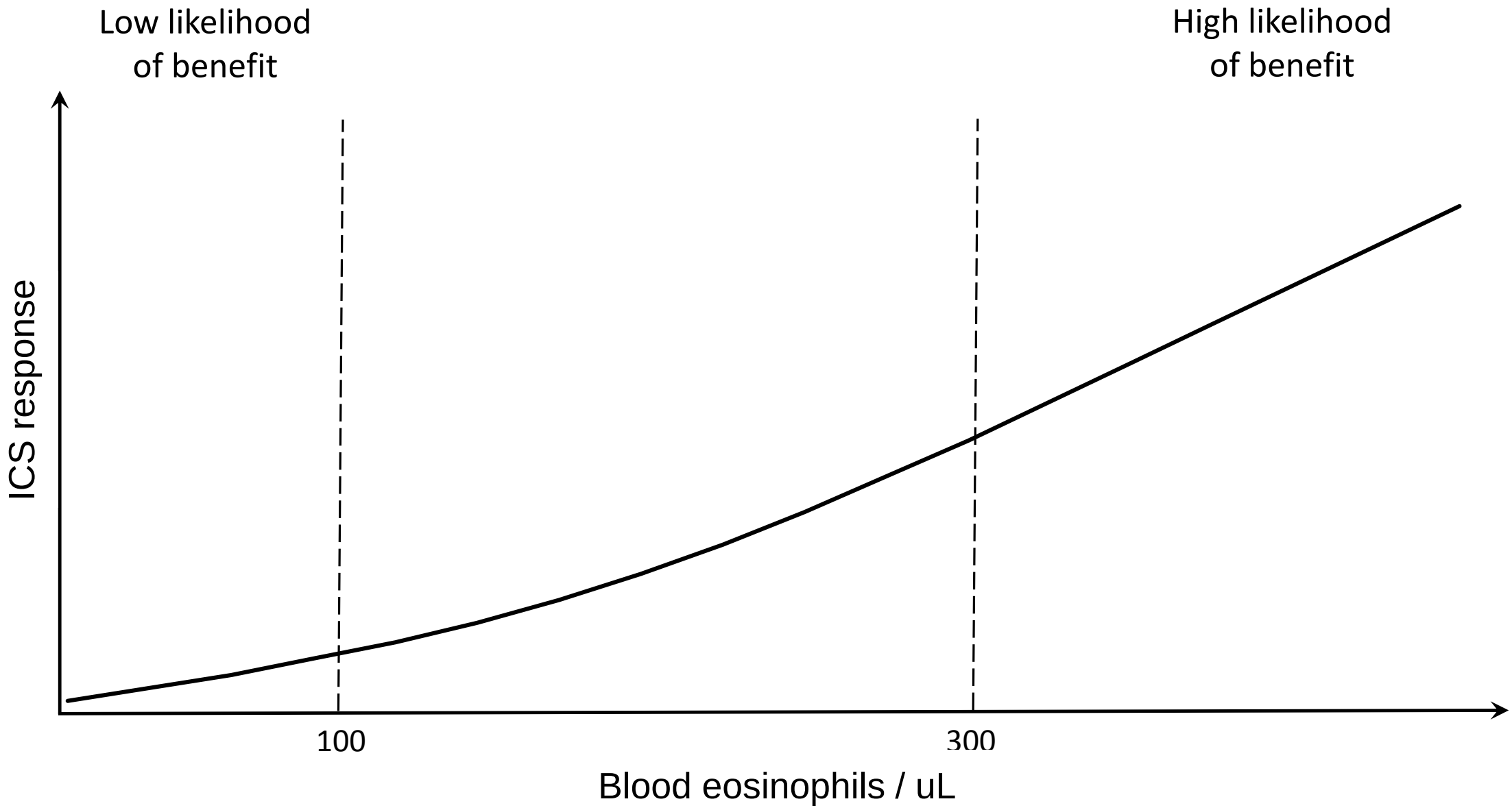


eos = blood eosinophil count (cells/µL)

** Consider if eos ≥ 300 or eos ≥ 100 AND ≥2 moderate exacerbations / 1 hospitalization*

*** Consider de-escalation of ICS or switch if pneumonia, inappropriate original indication or lack of response to ICS*

Figure 3


Low likelihood
of benefit
High likelihood
of benefit
ICS response
100
300
Blood eosinophils / uL

MANAGEMENT CYCLE