Personalised management of Chronic Obstructive Pulmonary Disease (COPD): Malaysian consensus algorithm for appropriate use of inhaled corticosteroid (ICS) in COPD patients

ABSTRACT
Background: Regarding the long-term safety issues with the use of inhaled corticosteroids (ICS) and the clinical predominance of dual bronchodilators in enhancing treatment outcomes in chronic obstructive pulmonary disease (COPD), ICS is no longer a “preferred therapy” according to the Global Initiative for Chronic Obstructive Lung Disease except on top of a dual bronchodilator. This has necessitated a change in the current therapy for many COPD patients.

Objective: To determine a standardised algorithm to reassess and personalise the treatment COPD patients based on the available evidence.

Methods: A consensus statement was agreed upon by a panel of pulmonologists in from 11 institutes in Malaysia whose members formed this consensus group.

Results: According to the consensus, which was unanimously adopted, all COPD patients who are currently receiving an ICS-based treatment should be reassessed based on the presence of co-existence of asthma or high eosinophil counts and frequency of moderate or severe exacerbations in the previous 12 months. When that the patients meet any of the aforementioned criteria, then the patient can continue taking ICS-based therapy. However, if the patients do not meet the criteria, then the treatment of patients need to be personalised based on whether the patient is currently receiving long-acting beta-agonists (LABA)/ICS or triple therapy.

Conclusion: A flowchart of the consensus providing a guidance to Malaysian clinicians was elucidated based on evidences and international guidelines that identifies the right patients who should receive inhaled corticosteroids and enable to switch non ICS based therapies in patients less likely to benefit from such treatments.

KEYWORDS: COPD, ICS, Malaysian consensus statement, Dual bronchodilator

INTRODUCTION AND CONSENSUS GROUP EVIDENCE REVIEW
According to the recent World Health Organization reports, globally 3.17 million deaths have been attributed to chronic obstructive pulmonary disease (COPD), accounting for a total 5% of all deaths. According to the recent reports, it is estimated that almost half a million Malaysians suffer from COPD. The hospital admission rates for exacerbations due to COPD are quite high in Malaysia and COPD is the 5th leading cause of disease burden, and this figure is projected to rise in the near future. It is important to note that of all the COPD patients in Malaysia, 90% are in Group B and Group D representing the symptomatic burden similar to that prevalent in the UK and Germany. In a hospital setting in Malaysia, most of the COPD patients are exacerbators with 18.5% and 39.7% of them with emphysema and chronic bronchitis, respectively. The non-exacerbator phenotype is observed in 28.6% patients and asthma–COPD overlap is exhibited by 13.2% patients.6 To date, several guidelines are present for the efficient management of COPD, including the
National Institute of Clinical and Healthcare Excellence, International Primary Care Respiratory Group and Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. Historically, the severity of COPD according to GOLD guidelines was evaluated depending on the lung function using forced expiratory volume in 1 second (FEV1) as a parameter. However, taking into consideration the overall health status, COPD patients were graded based both on lung function and symptom burden and exacerbation history as parameters. While in 2014, the guidelines were only slightly modified to define exacerbation frequency as ≥1 exacerbation leading to hospitalisation, the new 2019 and 2020 GOLD guidelines have fundamentally changed the patient gradation by taking into account only symptom burden and exacerbation history into consideration. COPD diagnosis is confirmed based on FEV1/FVC post bronchodilator ratio <0.70 whereas FEV1 alone is now limited only to grade the patient’s airflow limitation. As per 2019 GOLD guidelines, a significant number of patients have been re-categorised – patients previously classified as high-risk groups C and D are now categorised as low-risk groups A and B, respectively. Based on the evidence, new GOLD 2019 guidelines recommend the use of inhaled corticosteroids (ICS) as an add-on therapy to combined bronchodilators only for GOLD D categorised patients, and not for GOLD B patients (with symptoms but infrequent exacerbations). Thus, GOLD endorses the usage of dual bronchodilators as first-line therapy earlier than ICS. Nonetheless, mounting evidence suggests that patient outcomes will not have significant improvement based on the current new GOLD guidelines. For example, in the WISDOM (Withdrawal of Inhaled Steroids during Optimized Bronchodilator Management) trial, a total of 2485 patients who represent the recommended inhaled glucocorticoids groups as per the GOLD guidelines – were assessed for the withdrawal (moderate decreasing over a 12-week period) or proceeded with glucocorticoids, in comparison with those who received triple therapy (long-acting beta-agonist (LABA) + long-acting muscarinic antagonist (LAMA) + glucocorticoids) for 6 weeks. This study demonstrated that although GOLD guidelines recommend the usage of ICS therapy in these patients, there was no significant increase in the rate of COPD exacerbations upon ICS withdrawal. However, ~18% of the patient population with a high blood eosinophil count of ≥300 continued to highly benefit from the usage of ICS therapy.7

The 26-week, randomised, double-blind, SUNSET trial, which assessed the impact of direct de-escalation of long-term triple therapy to indacaterol/glycopyrronium in 527 non-frequently exacerbating COPD patients, revealed that there was no difference in exacerbations upon de-escalation of ICS and only displayed a small decrease in lung functionality. However, patients with a high eosinophil count of ≥300 cells/µL were at a greater risk of exacerbation (rate ratio: 1.86; 95% CI: 1.06–3.29) upon ICS withdrawal. Therefore, it is of utmost importance to characterise when ICS therapy has to be recommended and how ICS treatment can be withdrawn safely. Given that several adverse events outweigh the benefits of ICS therapy, if any; the new GOLD guidelines have rightfully limited the role of ICS therapy to severely impaired COPD patients. Furthermore, based on the clinical evidence that ICS-containing regimens have little or no effect in patients with a blood eosinophil count of <100 cells/µL, while patients with >300 cells/µL demonstrate enhanced benefit of ICS therapy, the recent 2019 GOLD guidelines recommended the use of absolute blood eosinophil count as a guide for the escalation and de-escalation of ICS treatments.8 Thus, the recent real-life studies mimicking clinical scenarios including OPTIMO, CRYSTAL and FLASH have demonstrated the managed adequacy of direct switch of ICS-regimens to non-ICS regimen in non-frequently exacerbating moderate-severe COPD patients.9 11

OVERWHELMING EVIDENCE OF THE ICS SIDE EFFECTS IN COPD PATIENTS

Even though ICS treatment is much appreciated in asthma, its usage in the administration of COPD is to a great extent misrepresented. Furthermore, its usage in COPD patients is ridden with several safety concerns. ICS usage has been accounted earlier to cause a collection of serious adverse events. While certain symptoms are minor, some of the other side effects are sufficiently vast to cause significant morbidity, including pneumonia, deleterious impact on bone health, candidiasis, increased risk of diabetes onset and progression, cataract and osteoporosis.12-14 A recent Cochrane review that assessed the efficacy of LABA/ICS therapy with LABA alone monotherapy from over 14 studies demonstrated that patients on LABA/ICS therapies showed a moderate increase in the risk of pneumonia in comparison to non-ICS therapy.15 In the 26-week LANTERN study, the lung functionality and rate of exacerbations were comparatively better in the once-daily indacaterol/glycopyrronium (LABA/LAMA and dual bronchodilator) group compared to those on 500/50 μg twice-daily fluticasone/salmeterol (LABA/ICS) group. The rate of occurrence of pneumonia (2.7% versus 0.8%) and upper respiratory infection (7% versus 3.5%) was significantly higher with ICS therapy.16 In the ILLUMINATE study, pneumonia was reported only in the patient group receiving fluticasone/salmeterol (LABA/ICS) group (4 patients; 1.5%).17 The FLAME study which compared the LABA/LAMA versus the LABA/ICS therapies over a longer duration of 1 year also showed similar increased incidence of pneumonia (4.8% versus 3.2%) in patients receiving ICS therapy, in comparison to those on dual bronchodilators.18 The SUNSET study also reveals no significant differences in terms of COPD exacerbation in long-term triple-therapy after the withdrawal of ICS treatment.19 The incidence of pneumonia was reported to be 50% higher (hazard ratio: 1.53) in triple therapy or ICS-containing treatment regimens as compared to the LABA/LAMA therapies.

The TORCH study has earlier recorded that upon ICS therapy, 1 COPD exacerbation prevention has resulted in the incidence of 3 new cases of pneumonia, thus flagging the necessity of reiating ICS therapy.20 Thus, a recent study by Suissa, et al. has reported a rapid reduction of pneumonia (RR: 0.58; 95% CI: 0.54–0.61) after 4 months of ICS discontinuation highlighting the benefits of ICS withdrawal. In the light of reduced rate of exacerbation and the incidence of pneumonia per annum, these results emphasise a
compelling need to switch to non-ICS therapies like dual bronchodilators from LABA/ICS or LAMA/ICS or triple therapies.

**PROPOSED ALTERNATIVE APPROACH OVER THE ICS-BASED THERAPY IN COPD PATIENTS**

Several studies highlight the beneficial role of dual bronchodilator (LABA/LAMA) therapies instead of ICS combination therapies. In a more extended span treatment of LAMA/LABA versus fluticasone/salmeterol, the FLAME study showed favourable results with indacaterol/glycopyrronium with a significantly reduced percentage of exacerbations (11%; p=0.003) and significant improvement in St. George’s Respiratory Questionnaire (SGRQ) score as compared to fluticasone/salmeterol treatment. In the LAMA/LABA group, the average time to the first exacerbation was also significantly longer (71 versus 51 days; p<0.001). In the large (N = 1499), long-term (2 year) INSPIRE study, which evaluated the rate of moderate and/or severe exacerbations in LABA/ICS group versus the long-acting bronchodilator – tiotropium bromide, LABA/ICS treatment arm did not demonstrate any difference in exacerbation rate compared to that of tiotropium arm. While 62% of fluticasone/salmeterol group patients had at least one exacerbation (rate of exacerbation = 1.28/year) compared to 59% in the tiotropium group (rate of exacerbation = 1.32/year). Additionally, there was no significant difference between the incidence of rate of exacerbations per year (1.28 versus 1.32; p=0.656) and the
hospitalisations due to exacerbations (16% versus 13%). LABA/ICS therapy was considerably less safe, with the incidence of pneumonia in 8% of patients and a hazard ratio of 1.94 (95% CI: 1.19–3.17, p=0.008) for the time to reported pneumonia.20 The IMPACT study showed that triple therapy with inhaled glucocorticoid, LABA and LAMA results in lower rate of exacerbations and hospitalization due to COPD compared to dual therapies of either inhaled glucocorticoid + LABA or LAMA/LABA. The INSTEAD study has also affirmed a safe switch from ICS regimen to a non-ICS regimen without any loss of efficacy with respect to breathlessness or SGRQ scores.21

The DACCORD and WISDOM studies, wherein ICS withdrawal followed by LABA/LAMA initiation did not result in an increased risk of exacerbations, endorse the safe mortality. A recent CLAIM study that evaluated the effect of LABA/LAMA combination therapy on cardiac function in 62 COPD patients showed improved cardiac function, thus emphasising the beneficial role of early usage of bronchodilators in COPD patients.22

CONSENSUS GROUP RESULTS:
The present Malaysian consensus group reviewed the latest available information in the field and arrived at an ideal algorithm which enables efficient management of COPD, clearly discerning the use of ICS and/or de-escalating or stepping up from LABA/LAMA as per the personalised requirement of the individual patient. Thus, the overall objective of the current Malaysian consensus group is to strategise the guideline for COPD in directing to a more personalised treatment to benefit both general practitioners and also the patient treatment outcomes.

The Malaysian consensus group advisory board meeting included chest physicians from government sectors in Malaysia. The participants (chest physicians) included are as stated in the author list as above.

A comprehensive discussion of several studies in the recent past, which re-emphasised the necessity for withdrawal of ICS and endorsed the safety of withdrawal of ICS, was undertaken.

Based on the evidence from recent studies, a consensus statement for appropriate use of ICS and LABA/LAMA has been proposed by the Malaysian consensus group. A stepwise methodology relying upon the response of the individual patient was proposed to make clinical judgements for efficient and safe management of COPD. In Malaysia, FUKKM restricts the use of ICS/LABA in COPD only to Respiratory specialists and we recommend the use of mono ICS for escalation only in selected patients to avoid initiation of ICS/LABA in majority of the patients. Figure 1a and 1b represents the algorithm that shows how the clinician should make a decision as to continue or withdraw/switch ICS treatment depending on the incidence of asthma before the age of 40 years, blood eosinophil count and the history of exacerbations.

CONCLUSION
The Consensus flowchart provides a guide to clinicians in Malaysia based on evidences and international guidelines to identify the right patients who should receive inhaled corticosteroids and enable switch to non ICS based therapies in patients less likely to benefit from such treatments.

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ABBREVIATIONS
ICS, inhaled corticosteroids; COPD, chronic obstructive pulmonary disease; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; GOLD, global initiative for chronic obstructive lung disease; FEV1, forced expiratory volume in 1 second; WISDOM, withdrawal of inhaled steroids during optimized bronchodilator management; SUNSET, long-term triple therapy de-exalation to indacaterol/glycopyrronium in COPD patients; OPTIMO, appropriateness of treatment in moderate COPD patients; CRYSTAL, effect of glyCpyrronium or indocateRol maleate and glcyopyrronium bromide fixed-dose combination (FDC) on SympToms and heAlth status in patients with moderate COPD; FLASH, assessment of switching salmeterol/fluticasone to indacaterol/glycopyrronium in A symptomatic COPD patient cohort; LANTERN, a randomized study of QVA149 versus salmeterol/fluticasone combination in patients with COPD; ILLUMINATE, efficacy and safety of once-daily QVA149 compared with twice-daily salmeterol-fluticasone in patients with chronic obstructive pulmonary disease; FLAME, once-daily QVA149 and twice-daily salmeterol/fluticasone on the reduction of COPD; TORCH, towards a Revolution in COPD Health; INSPIRE, investigating new standards for prophylaxis in reducing exacerbations; IMPACT, Informing the pathway of COPD treatment; INSTEAD, the Indacaterol Switching Non-exacerbating Patients with Moderate COPD From Salmeterol/Fluticasone to Indacaterol; DACCORD, Die ambulante Versorgung mit langwirksamen Bronchodilatatoren: COPD-Register in Deutschland (Outpatient Care With Long-Acting Bronchodilators: COPD Registry in Germany); CLAIM, effect of lung deflation with indacaterol plus glycopyrronium on ventricular filling in patients with hyperinflation and COPD.

REFERENCES


