Combination Inhaled Corticosteroid/Long Acting Beta Agonist Therapy- An Evolving Role in Asthma Care

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There are essentially three main goals of therapy in asthma management; controlling symptoms, preventing exacerbations and preserving lung function. Among the fundamental pharmacotherapies available in asthma management are short acting beta agonists (SABAs), long-acting-beta agonists (LABAs), inhaled corticosteroids (ICS) and leukotriene receptor antagonists. More recently, tiotropium and in selected patients monoclonal therapy have proven useful in severe asthma. Short-acting beta agonists relieve asthma symptoms over a period of 20-30 minutes whereas LABAs provide symptom control over a longer duration (10-24 hours, depending on LABA choice). ICS prevent the onset and severity of symptoms, reduce exacerbations, decrease airway inflammation and remodelling and help preserve lung function in asthmatic patients. Most international guidelines recommend ICS, except in only the mildest asthma and even then consideration of low dose ICS is recommended¹. For safety reasons, LABAs are given in combination with ICS when treating asthma²,³,⁴.

The utilisation of combination ICS/LABA as both regular maintenance therapy and as required reliever therapy in individuals, was reported in 2005⁵. This double-blinded randomised control study, which enrolled asthmatics treated with 400-1000 mcg ICS per day and with a history of at least one exacerbation in the past year, showed that combined inhaled budesonide-formoterol taken by patients as both their maintenance and symptom-relief therapy reduced the relative risk of severe exacerbations by 47% and mild exacerbations by 30% and prolonged the time to first exacerbation when compared to ICS/LABA maintenance + SABA as required. This was an industry sponsored trial (Astra Zeneca), with the sponsor later coining the term ‘SMART’ therapy to describe this therapeutic approach. Advocates of this approach believe that by giving patients who are having increasing symptoms increased doses of both anti-inflammatory (budesonide) and bronchodilator therapy (formoterol), that this will prevent progression of symptoms to an exacerbation of asthma. Currently, Global Initiative for Asthma (GINA) Guidelines 2018 recognise that low-dose combined ICS/LABA (in the form of budesonide-formoterol) can be offered as an alternative to as required SABA, in addition to
maintenance therapy at step 3 and step 4 of the treatment algorithm\(^1\). However, despite these data, there are currently no dual ICS/LABA approved by the FDA for combination use as both a maintenance and reliever therapy in individuals with asthma.

Since this original study, there have been several further prospective studies conducted evaluating the role of budesonide/formoterol combination utilised in this manner\(^6, 7, 8, 9, 10\). Furthermore, no comprehensive systematic review of the literature had been performed evaluating the efficacy of this therapeutic approach with respect to exacerbation reduction and symptom improvement in asthma until a meta-analysis by Sobeiraj et al. was published in the Journal of the American Medical Association (JAMA) in April 2018\(^11\).

The meta-analysis included 16 randomised trials with a total of 22,748 patients included in the analysis. All patients included in the analysis had persistent asthma and were required to have been taking ICS prior to enrolment. 15 of the 16 trials evaluated, utilised a combination budesonide-formoterol dry-powder inhaler. In all studies, the intervention arm used ICS/LABA as both maintenance and reliever therapy. Four trials evaluated this combined approach versus inhaled corticosteroid alone as maintenance therapy. Fourteen trials, incorporating 20,507 patients compared this dual role with ICS/LABA as maintenance. All control arms used a SABA, terbutaline as the reliever agent. The studies that were included assessed at least one of the following outcomes; asthma exacerbations, all-cause or asthma-specific mortality, changes in spirometry, asthma control, asthma-related quality of life or healthcare use.

When ICS/LABA maintenance and reliever was compared to the same dose of ICS alone with SABA as required, there was an absolute reduction in exacerbation frequency by 8.1%. When compared to an increased dose of ICS alone with SABA as required, there was an exacerbation frequency reduction of 11%. Furthermore, ICS/LABA as both maintenance and reliever was associated with improved FEV1 with a mean difference of 0.10 Litres and a reduced need for rescue medication inhalers (mean difference of 0.34 puffs per day). There were very few deaths in either group (3 in total).

Trials comparing ICS/LABA maintenance and reliever to ICS/LABA as maintenance therapy with SABA reliever showed that ICS/LABA maintenance and reliever was associated with a lower risk of asthma exacerbations compared with the same dose of ICS/LABA as maintenance therapy alone (absolute risk reduction 6.4%). Furthermore, there was a lower risk of exacerbation when ICS/LABA maintenance and reliever was compared to higher dose of ICS/LABA as controller only (ARR: 2.8%). However, with respect to FEV1, all-cause mortality, asthma control or asthma-related quality of life, there was no significant difference between ICS/LABA maintenance and reliever and ICS/LABA as maintenance therapy at an equivalent or higher dose.

Overall, this meta-analysis supports the use of ICS/LABA as both maintenance and reliever therapy in
persistent asthma given the significant reduction in exacerbation risk compared to conventional therapeutic strategies. Persistent asthma severity was not further defined in most trials except for the pre-requisite that enrolled patients needed to be using ICS prior to study. Most patients in individual trials were using high dose ICS or ICS/LABA indicating severity worse than mild persistent asthma, generally moderate to severe. Patients commencing ICS/LABA as maintenance and reliever should be counselled that although there is a reduced frequency of exacerbations, there is no evidence to support improved asthma control or quality of life with this strategy. Most of the high-quality, randomised control trials assessing efficacy of this approach were performed using a dry-powder inhaler containing a combination of budesonide and formoterol. It should be noted that benefit may be specific to the inhaler device and particular drugs used.

Despite the multiple trials performed there remained a deficit in our knowledge base. The question as to whether or not ICS/LABA could be utilised as required as a reliever only and without also taking regular maintenance therapy had not been addressed. This has recently been rectified.

Shortly following publication of the JAMA meta-analysis, 2 large, multi-centre, double-blind, randomised trials have provided evidence for the use of combination ICS/LABA as reliever therapy in mild asthma\textsuperscript{12,13}. Previous studies had largely studied the effect of reliever ICS/LABA in addition to maintenance ICS/LABA in higher severity asthma. No previous study had included only mild asthmatics taking ICS/LABA as needed without a maintenance regimen containing ICS therapy. Both were industry sponsored (Astra Zeneca). These trials were designed and run in parallel but were powered for different primary outcomes.

The first trial, Symbicort Given as Needed in Mild Asthma (SYGMA) 1, enrolled 3849 patients with mild asthma requiring GINA step 2 treatment, meaning patients with mild but sub-optimally controlled asthma taking terbutaline as required or well-controlled asthmatics on low-dose maintenance ICS. Participants were randomly assigned to one of three treatment groups for 52 weeks duration: placebo twice daily and budesonide-formoterol (200/6 mcg) as needed, placebo twice daily and terbutaline as needed or budesonide (200 mcg) twice daily and terbutaline as needed. The primary outcome was to assess asthma control in the budesonide-formoterol as needed group versus the terbutaline group. Asthma control was measured using an electronic record kept by the patient incorporating several factors; inhaler use, daily asthma symptoms, night-time awakenings, morning and evening peak flows and additional inhaled or systemic steroid use. The study showed that budesonide-formoterol combination used as needed was superior to terbutaline as needed for improving asthma control (34.4 versus 31.1, mean % weeks with well controlled asthma). However, budesonide-formoterol as required was inferior to budesonide maintenance therapy with respect to asthma control (34.4 versus 44, mean % of weeks with well controlled asthma).
The SYGMA 2 trial enrolled 4215 patients with mild asthma (GINA Stage 2) to budesonide-formoterol as needed or budesonide maintenance and terbutaline as needed. This study was designed in parallel with SYGMA 1 to examine whether budesonide-formoterol as required was non-inferior to regular budesonide maintenance therapy for preventing severe exacerbations. In this way, both SYGMA trials address the main goals of asthma management as defined by GINA guidelines, which are to achieve good symptom control and to minimise risk of future exacerbations. SYGMA 2 trial utilised a more “real-world” design, omitting daily reminders to use medications which were used in SYGMA 1. In terms of the primary outcome, budesonide-formoterol as needed was found to be non-inferior to budesonide maintenance therapy for annual exacerbation risk (0.11 versus 0.11, total number of exacerbations per patient-year).

In summary, the SYGMA Trials highlight that there is no significant difference in exacerbation risk for mild asthmatics treated with budesonide-formoterol as needed versus maintenance twice daily ICS therapy at the same dose. However, mild asthmatics treated solely with as needed budesonide-formoterol can expect a higher symptom burden than patients with maintenance ICS. Of note, in the SYGMA 1 trial, the median daily steroid dose in the budesonide/formoterol group was 17% of that in the budesonide maintenance group-an important consideration for many parents. These trials will help to individualise treatment approaches for mild asthmatics depending on a patient’s own concerns regarding exacerbation risk, symptom control and steroid use. Patients with a history of poor compliance to treatment are probably more likely to adhere to ICS/LABA therapy as needed as only one inhaler is required and there is no set timetable for using the inhaler. Furthermore, patients with mild asthma may accept a higher symptom burden with as needed ICS/LABA therapy given there is a simplified regime, reduced steroid use and a similar risk of severe exacerbation. These trials suggest that these are acceptable management strategies.

Conflict of Interest
Dr Joseph Walsh has no conflict of interest to declare. Dr Desmond Murphy has received consultancy fees for his role on advisory boards for Nycomed, Mundipharm, Boehringer-Ingelheim, Teva, Rowex, Menarini, Astra-Zeneca, GSK, Bayer, Gilead, Pharmaxis and Novartis. He has received speaker’s fees from GSK, MSD, Menarini, Astra-Zeneca, Teva, Bayer, Boehringer-Ingelheim and Novartis. He has travelled to international conferences as a guest of Astra-Zeneca, Novartis and Menarini.

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