

## **Global Initiative for Asthma 2019 Guidelines: New Changes to the Treatment of Mild Asthmatics 12 Years and Older**

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The 2019 edition of the Global Initiative for Asthma (GINA) report<sup>1</sup> is an evidence-based strategy focusing on translation into clinical practice. Its newest recommendations for adults and adolescents ( $\geq 12$  years) with mild asthma are to initiate as needed inhaled corticosteroid (ICS) containing controller treatment as first line management. This mild asthma (Step 1) group is defined by GINA as symptoms less than twice per month and no exacerbation risk factors.

High short acting beta agonist (SABA) (e.g. Salbutamol, Terbutaline) usage is associated with adverse clinical outcomes. Dispensing  $\geq 3$  canisters per year is associated with higher risk of emergency department presentations and dispensing  $>12$  canisters per year with higher risk of death<sup>2</sup>. One of the key findings of the 2014 UK National Report for Asthma Deaths<sup>2</sup> was overprescribing of SABAs and insufficient provision of ICS. The current edition of GINA is a population level risk reduction strategy based on evidence that SABA-only treatment increases risk of severe exacerbation and asthma-related death, and that adding an ICS significantly reduces this risk. Proposed mechanisms for increased adverse clinical outcomes due to SABA use include  $\beta$ -receptor downregulation, decreased bronchoprotection, rebound hyperresponsiveness and decreased bronchodilator response. It is also likely that adverse associations with SABAs are not due to direct medication effects but are due to their preferential use by patients over ICS preparations, masking worsening asthma symptoms.

Inhaled SABA has been first line management for 50 years for patients with asthma. The current GINA recommendations represent a major change in management. The new ICS-formoterol strategy gives high importance to reducing exacerbations in patients with mild asthma. Poor adherence in this patient group is a common modifiable risk factor. When a patient's reliever is SABA-only, poor adherence with maintenance ICS exposes the patient to risks of SABA only treatment. The new ICS-formoterol strategy makes use of normal patient behaviour (seeking symptom relief) to deliver the controller.

The new GINA recommendations are supported by indirect evidence from SYGMA 1<sup>3</sup> and SYGMA 2<sup>4</sup> (Symbicort given "as needed" in mild Asthma). Both studies were double-blinded, multisite, parallel-group randomised controlled trials conducted in mostly adult populations with 3,849 patients (average age  $39.6 \pm 16.6$  years) and 4,215 patients (average age  $41.0 \pm 17.0$  years) respectively. Inclusion criteria for both studies included age  $\geq 12$  years, a diagnosis of asthma for over 6 months and suitable pulmonary function tests. Patients were enrolled if they were uncontrolled on as needed SABA or controlled on mono-maintenance therapy with leukotriene receptor antagonist or low dose ICS ( $\leq 400$   $\mu\text{g}$  budesonide/equivalent per day) with use of as needed SABA for the last 30 days. These studies found a reduction in severe exacerbation rate of approximately two-thirds when an as needed budesonide-formoterol strategy was used compared with SABA-only therapy, achieved with  $<20\%$  of the average ICS dose as compared with daily ICS. While results for asthma symptom control were slightly better in the SYGMA trials for maintenance low dose budesonide compared with as needed ICS-formoterol, the risk of severe exacerbations was non-inferior. Further evidence for as needed ICS-formoterol, comes from the START<sup>5</sup> trial, another randomized, open-label, parallel-group, controlled trial involving 675 patients aged 18 to 75 years with mild asthma. This study showed that exacerbation rates among patients treated with as-needed budesonide-formoterol was significantly lower compared with as needed SABA and did not differ significantly from patients who received maintenance budesonide. However in START maintenance treatment with budesonide was again superior to as needed budesonide-formoterol in asthma symptom control as measured by the Asthma Control Questionnaire-5.

SYGMA 1 and 2 were conducted with formoterol, a fast and long acting full B2 agonist. It is important to note that there is insufficient evidence to extrapolate to other long acting beta agonists such as salmeterol which has a slower onset of action but similar bronchodilator capacity. “Other controller options” for adolescents  $\geq 12$  years and adults with mild asthma recommended by GINA 2019 include low dose ICS taken whenever SABA is taken. Evidence for this strategy comes from studies in patients eligible for GINA Step 2 treatment including BEST<sup>6</sup>, BASALT<sup>7</sup> and TREXA<sup>8</sup> trials. Both BEST and BASALT were conducted in patients  $> 18$  years however TREXA was conducted in patients 6-18 years with mild asthma. This randomised double blinded placebo controlled trial of 843 patients showed that daily ICS was the most effective treatment in preventing exacerbations however as-needed ICS with SABA was more effective at reducing exacerbations compared with SABA alone.

Importantly the ICS-formoterol strategy recommended for patients with mild asthma by GINA 2019 does not apply to patients  $\leq 11$  years of age. In the 6-11 years the recommended reliever remains SABA only. ICS-formoterol is only introduced at step 3 as controller therapy when these patients are uncontrolled at low dose ICS after inhaler technique, adherence and risk factors are addressed. Meta-analysis of ICS-formoterol as a maintenance and reliever therapy for children aged 4-11 years has shown an absolute risk difference of -12.0% for exacerbations compared with a higher dose of inhaled corticosteroid and LABA as controller therapy<sup>9</sup>. This regimen is not recommended for children  $< 12$  years in current guidelines and importantly ICS-formoterol is not recommended in Ireland for children under 6 years of age.

Patients with mild asthma remain a difficult group to separate discretely in practice. Central to their care remains correct inhaler device/technique, good medication adherence, good patient knowledge, use of an asthma action plan and addressing modifiable risk factors. The British Thoracic Society (BTS) 2019 asthma guideline<sup>10</sup> in contrast to GINA recommends considering the option of combined maintenance and reliever therapy in adult patients who have a history of asthma attacks on medium dose ICS or ICS/LABA. This difference of opinion between GINA and BTS has provided increased options for patients and clinicians but has potential to cause disarrangement in patient management. The introduction of the ICS/formoterol strategy may constitute a step in the journey towards personalized medicine in asthma however further research is needed to clarify optimal management strategies.

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