Reply: About the recommendation of the GINA strategy report on asthma step 1

Reply to S. Ferretti and co-workers:

The changes to treatment recommendations for mild asthma published by the Global Initiative for Asthma (GINA) in 2019 [1], and further updated in 2020 [2], have prompted extensive discussion. The letter by S. Ferretti and co-workers provides the opportunity to correct some misunderstandings, and to respond to questions about why as-needed short-acting β_2-agonist (SABA) alone is no longer recommended in step 1 of the GINA treatment figure for adults and adolescents. The term "step 1" refers to a particular level of treatment and not to a type of patient or a phenotype of asthma.

S. Ferretti and colleagues are correct in describing the recommendation for SABA alone (without inhaled corticosteroid (ICS)) at step 1 in guidelines for many years as "traditional", as there is *no evidence* to support SABA-only treatment of asthma. Its inclusion in the first asthma guidelines 30 years ago and its ongoing inclusion in many current guidelines appear to have been based on an untested assumption that patients with asthma symptoms on fewer than 2–3 days a week would not benefit from ICS, and should therefore be treated with SABA alone.

The risks of SABA-only treatment have been described by GINA for many years (not only since 2019, as claimed). However, for recommendations to change, evidence was required for a feasible therapy that was safer than SABA alone. From 2007, given the risk reduction with maintenance and reliever therapy (MART) with as-needed ICS–formoterol *versus* as-needed SABA reliever [3], GINA members submitted protocols for studies of as-needed ICS–formoterol in mild asthma, but obtaining agreement from industry took several years [1]. In the meantime, by 2014, GINA had found that there was no evidence to support the traditional threshold of symptoms on more than 2–3 days per week for initiating ICS; that patients with less frequent symptoms could still have severe or sometimes even fatal exacerbations [4]; and that in the START study, in which almost half of patients had symptoms less than twice per week (so-called "intermittent asthma"), low dose ICS almost halved the risk of serious asthma-related events (emergency department visits, hospitalisation or death) [5]. Therefore, in 2014, GINA recommended ICS if symptoms occurred more often than twice a month, corresponding to the lowest frequency of baseline symptoms in the START study [5]. As explained in the *European Respiratory Journal* at the time, this was "not necessarily to reduce the (likely low) burden of symptoms, but to reduce the risk of severe exacerbations" [6]. This recommendation was subsequently supported by further analyses of the START study, which found that the risk reduction with ICS was independent of baseline symptom frequency [7].

In 2018, the two large SYGMA randomised controlled trials (RCTs) [8, 9] provided strong evidence for the GINA 2019 recommendation for as-needed low dose ICS–formoterol as a step 2 option, and the clinical relevance of this approach was enhanced by publication in 2019 of further two RCTs [10, 11] that were open-label so the as-needed inhaler was used as in real life. Together, these studies totalling almost 10 000 patients who were symptomatic on SABA alone [8–10], or whose asthma was well (or partly [11]) controlled on low [8, 9, 11] or medium dose ICS [11], showed that as-needed low dose ICS–formoterol reduced the risk of severe exacerbations by two-thirds compared with as-needed SABA alone, and to a similar or greater extent than maintenance ICS, with clinically similar symptom control, extremely low ICS exposure and without the need for daily treatment [12]. The benefit of as-needed ICS–formoterol for both severe exacerbations and symptom control was seen in patients with either type 2 low or type 2 high inflammatory profile [10, 11, 13]. A recent meta-analysis found that as-needed budesonide–formoterol

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The recommendation by GINA against SABA-only treatment of asthma for adults and adolescents is supported by evidence of harm from even modest SABA over-use, and strong evidence for as-needed ICS–formoterol as a safe and effective way to reduce asthma risk https://bit.ly/3oy0tK2

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reduced the risk of emergency department presentation in patients with mild asthma by 35% (OR 0.65, 95% CI 0.43 to 0.98) compared with maintenance ICS [14].

These four studies included patients who were eligible for step 2 treatment with ICS by GINA 2012 [8, 9] or GINA 2014 [10, 11] criteria; as above, GINA step 2 from 2014 onwards applies to patients with symptoms twice a month or more, or any risk factors for asthma exacerbations. What then is the evidence to support extension of this recommendation to step 1 for adults and adolescents with even milder asthma, *e.g.* symptoms less than twice a month? The rationale can be summarised as follows:

1) There is no evidence for the safety or efficacy of SABA-only treatment of asthma.
2) Taking SABA four times a day for even 1 week significantly increases exercise-induced bronchoconstriction, airway hyperresponsiveness, allergic responses and airway inflammation, and decreases bronchodilator response [15]. This would not necessarily be noticed by patients because they still obtain some symptom relief. However, decreased bronchodilator response prompts patients to take more doses, increasing the potential for SABA over-use. In turn, SABA over-use is clearly associated with harm, including increased risk of asthma mortality with even modest usage (average ⩾1.6 puffs per day) [16].
3) Maintenance ICS reduces the risk of severe exacerbations by half to two-thirds, even when baseline symptoms are very infrequent (0–1 days in 2 weeks, or twice a month). Evidence for this includes the START reanalysis (above) [7], and a recent *post hoc* analysis of the Novel START study that found that the reduction in exacerbations with as-needed budesonide-formoterol compared with SABA alone was independent of whether patients had SABA use more often than twice per week, or twice a week or less, at baseline [17]. The latter patients (approximately half of the Novel START study population) would not have qualified for any ICS by many guidelines, including recently updated US asthma guidelines [18]. Further, in SYGMA 1, even a single day of more than two, or more than four, inhalations of budesonide–formoterol reduced the short-term risk of severe exacerbations by 75%, compared with SABA alone [19]. This suggests that, even if patients have few interval symptoms, taking small extra doses of ICS–formoterol when symptoms worsen may be important in reducing the risk of progressing to a severe exacerbation.
4) A final important factor in the decision to move away from recommending SABA-only treatment in step 1 was the GINA policy of considering asthma treatment as an integrated patient-centred strategy, rather than as a series of isolated PICOT questions [2]. One of the paradoxes [20] of starting treatment with SABA alone is that the initial conversation with the patient is about symptom relief, and they are actively encouraged to rely on SABA as their only asthma treatment. This creates major barriers to patients' understanding and acceptance when, months or years later, they have more frequent symptoms, and are asked to take a daily preventer medication even on days when they have no symptoms [21]. This change in messaging partway through a patient's asthma journey is a major contributor to poor adherence. GINA believes that asthma treatment choices, and patient education, should focus on both symptom control and risk reduction from the time of first diagnosis.

Across many diseases, guideline recommendations are often based on indirect evidence, as can be seen if the relevant RCT study populations are scrutinised. This is particularly common in asthma, where only 5% of community patients would have been eligible for the major regulatory studies behind treatment steps 2–4 [22]. This problem continues, with only 10% of severe asthma patients likely to have been eligible for biologic RCTs [23]. In mild asthma it would (of course) be desirable to have a RCT comparing as-needed SABA alone *versus* as-needed low-dose ICS–formoterol in "a pure population of step 1 patients", as suggested by S. Ferretti and colleagues. However, there would be substantial difficulties and costs in recruiting patients who have asthma symptoms less than twice per month and with no risk factors for exacerbations, including no exacerbation in the previous year. Given the existing evidence of risks of SABA-only treatment, the cost and ethics of such a study would only be able to be justified if there was reasonable confidence that there was a real (rather than arbitrary) difference between such patients and the ~10 000 patients with mild asthma who have been included in studies of as-needed ICS–formoterol to date. We have not seen any evidence to support such a hypothesis, or any evidence to warrant excluding patients with infrequent asthma symptoms from being prescribed as-needed low dose ICS–formoterol to reduce their risk of infrequent but potentially serious adverse events.

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