Anti-inflammatory reliever therapy (AIR) for asthma

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Shareable abstract (@ERSpublications)
SABA overuse is prevalent and dangerous in asthma. Use of anti-inflammatory relievers (ICS/formoterol) in asthma mitigates against risk associated with SABA overuse and poor ICS adherence, and is the preferred approach for asthma management. https://bit.ly/4aHOLn8

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In 2019, the Global Initiative for Asthma (GINA) made ground-breaking recommendations to change the way asthma had been managed for the previous 50 years [1]. The established norm of using short-acting β_2-agonist (SABA) "reliever" inhalers, with or without separate corticosteroid containing "preventer", "controller" or "maintenance" inhalers (ICS), was no longer recommended for most people with asthma. Recognising the dangers associated with over-reliance on SABA relievers and insufficient or no ICS use, GINA called for a new treatment paradigm. Two-in-one anti-inflammatory reliever inhalers (AIRs), containing a combination of ICS and the fast- and long-acting β_2-agonist formoterol fumarate (ICS/formoterol), became the preferred reliever in asthma; either as reliever-only for mild asthma or as both maintenance and reliever therapy (MART) for moderate-to severe asthma. But the use of ICS/formoterol as a reliever-only in mild asthma, without additional regular maintenance doses, remains unlicensed in many countries, potentially impacting adoption.

In order to consider the potential impact of widespread implementation of GINA's recommended approach, it is important to consider the harms posed by: 1) the scale and consequence of SABA over-reliance in asthma; and 2) the misconception that so called "mild asthma" is risk-free.

SABA over-use is common in asthma and is a global phenomenon [2–5]. Regular use of SABA inhalers is associated with poor asthma control and the link between excess use (three or more 200-dose SABA canisters per year) and risk of asthma exacerbation and death is well evidenced [6–8]. But SABA's ability to rapidly relieve symptoms caused by bronchial smooth muscle constriction can lead patients to become over-reliant and, in some cases, deeply psychologically dependent on them [9]. The clearly observed association between SABA use and symptom relief strengthens patients' perception that SABA is the most important treatment for their asthma, despite SABA's failure to address the underlying airway inflammation. Indeed, the harms associated with SABA over-reliance go beyond simply failing to reduce risk, with excessive SABA use implicated in contributing to eosinophilic airway inflammation [10] and, when used without ICS, potentially resulting in β_2-receptor downregulation, decreased bronchoprotection, rebound hyper-responsiveness and decreased bronchodilator response [11]. SABA overreliance is therefore clearly unsafe [12] and enabling such health behaviour illogical at best.

Defining an individual's asthma severity as mild is fraught with challenges, not least because different criteria have been used to describe so-called mild asthma by different researchers and expert groups [13]. However, it is important to understand that patients who have infrequent asthma symptoms, even if these are once a week or less, may still be at risk of severe attacks (potentially triggered by viral infections and/or sudden allergen exposure) [14].

Asthma control is defined by GINA in two domains: symptom control and future risk of poor asthma outcomes. Symptom control refers to an individual's current status and can be defined using the Asthma

Control Test (ACT) or Asthma Control Questionnaire (ACQ), which provide information on the previous 4 or 1 week(s) respectively. Identifying future risk is more complex and requires consideration of multiple factors known to be associated with adverse outcomes, such as exacerbations (see box 2-2 in the GINA report [1]). COUILLARD *et al.* [15] developed a prototype asthma attack risk scale based on data extracted from the control arms of clinical trials spanning asthma severities. The resulting prototype tool incorporates asthma exacerbation history, existing asthma treatment, type 2 (T2) biomarkers and clinical risk factors (ACQ ⩾1.5, forced expiratory volume in 1 s <80% predicted, poor adherence, SABA overuse (more than a cannister per month), previous intensive care unit admission, significant comorbidities and environmental exposures). Eosinophilic inflammation, evidenced by blood eosinophils and fractional exhaled nitric oxide, is associated with increased exacerbation risk across asthma severities. The risk associated with elevated T2 biomarkers at baseline appears to be mitigated through appropriate ICS use in mild asthma [16]. However, limited access to T2 biomarker testing within primary care and low levels of adherence with regular ICS therapy in this population creates potential for individuals to remain at risk of future exacerbation and, in some cases, preventable asthma deaths. When considering a population approach to asthma management, it is therefore essential not to conflate apparent "mild asthma" with risk-free asthma and to adopt an approach to manage asthma that mitigates against the inevitable risk of ICS nonadherence. This has been the approach recommended by GINA where the preferred option (track 1) is to replace SABA as the reliever with a two-in-one ICS/formoterol anti-inflammatory reliever inhaler. "When a patient at any step has asthma symptoms, they use low-dose ICS-formoterol as needed for symptom relief. In Steps 3–5, they also take ICS-formoterol as regular daily treatment" [1].

In mild asthma, ICS/formoterol as needed for relief of symptoms has been shown to be superior to SABA-only therapy in terms of exacerbation reduction and asthma control [17, 18]. Compared to fixed-dose ICS with SABA reliever (where adherence with ICS maintenance was high), ICS/formoterol as needed was comparable for exacerbation prevention (exacerbations requiring oral steroids) and was associated with lower risk of asthma-related hospital admission, emergency department attendance or urgent care visits. In moderate–severe asthma, use of ICS/formoterol reliever with additional regular daily dosing as MART has consistently been shown to be superior in terms of exacerbation reduction compared to fixed-dose ICS/LABA combinations plus SABA reliever at both comparable and higher ICS doses [18, 19].

Faced with this evidence and GINA endorsement, use of AIR in asthma may be expected to be common practice. But evidence and guideline endorsement does not necessarily lead to clinical practice change, as was observed in a UK region where despite local guidelines recommending MART, <5% of asthma patients were receiving this treatment [20]. When adding the lack of regulatory approval for ICS/formoterol as a reliever-only in mild asthma across Europe, the adoption of this approach appears less certain.

However, in this issue of *ERJ Open Research*, BRUSSELLE *et al.* [21] provide hope that GINA recommendations are gaining traction. They report that among 981 patients treated for mild asthma in 56 centres across four European counties, 56.3% were receiving ICS/formoterol as needed (without maintenance ICS), 32.2% were prescribed regular low-dose ICS (either alone or with additional ICS/formoterol or SABA reliever) and only 11.6% were receiving SABA as needed (without maintenance ICS) at enrolment. In this multicentre observational study, sites were asked to enrol all eligible participants to minimise selection bias and followed patients over ∼6 months (window of 5–9 months from enrolment for the final study visit), with all treatments prescribed as part of routine clinical care. An electronic diary was used to capture medication-use data and revealed self-reported adherence with regular ICS dosing to be <80% among almost 40% of patients for whom this was prescribed.

Despite all participants being treated for mild asthma (defined in this study as receiving GINA steps 1 and 2 treatment), asthma control at baseline based on the five-item ACQ and ACT definitions was only achieved in between 54.9% and 61.3%, depending on treatment group. This fell to less than half (45.1–49.6%) when future risk was considered within the asthma control definition, as per GINA. Despite this, ∼90% of patients remained on the same therapy throughout follow-up. Among those receiving SABA-only as-needed at enrolment, around 50% were uncontrolled at baseline, yet 88.2% remained on SABA as-needed at the end of the study. While the study findings could be considered to reflect real-world prescribing practice, the mere fact that the treating centres participated in this study suggests that they have a degree of asthma expertise and therefore may be expected to be more aware of asthma treatment evidence and more responsive to risk than other less engaged centres. As such, the observed lack of treatment escalation despite apparent risk provides a compelling argument for widespread adoption of ICS/formoterol as the default reliever in asthma. SABA-containing regimes should therefore only be used where ICS/formoterol is unavailable and the clinician is sure that adherence with ICS-containing maintenance therapies can be guaranteed (see GINA track 2 [1]). Such an approach helps to mitigate against hidden/

unidentified risk at a population level, ensuring patients receive an ICS when it is needed. Indeed, although the study was not designed to enable between-group comparisons with regard to clinical outcomes, it is interesting that the SABA as-needed group had the highest proportion of patients experiencing a severe exacerbation (2%) and was the only group in which lung function decline was observed during follow-up. This provides some evidence that randomised controlled trial findings are applicable to the real world.

In an era where advanced therapies are enabling highly effective, targeted and personalised approaches to managing severe asthma [22], enabled by detailed phenotyping and risk stratification, it is important not to overlook the need for a coherent, population-level strategy to reduce risk and improve outcomes for all people with asthma. GINA recommended such an approach in 2019 and Brusselle *et al.* [21] provide hope that this is becoming established practice across Europe. However, continued efforts are needed to ensure that nobody with asthma is exposed to the risk of SABA-only treatment, either through lack of prescribing or suboptimal ICS adherence.

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