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

To the Editor:

"GINA 2019: a fundamental change in asthma management." This is how Reddel *et al.* [1] headline their editorial on the report in question. Reddel *et al.* [1] express a fundamental concept: "GINA no longer recommends treatment of asthma in adolescents and adults with SABA alone. Instead, to reduce their risk of serious exacerbations, all adults and adolescents with asthma should receive either symptom-driven (in mild asthma) or daily inhaled corticosteroid (ICS)-containing treatment." We have some doubts about the full suitability of this change.

For a long time, the therapy suggested for asthmatic patients at step 1 has been as-needed albuterol or another short-acting β_2-agonist (SABA). This is, for example, what the international guidelines on asthma of the British Thoracic Society [2] and the National Institute for Health and Care Excellence [3], suggest. In 2019, the Global Initiative for Asthma (GINA) for the first time questioned this traditional indication [4]. GINA classifies asthma severity based on the level of therapy needed to control symptoms. According to its report, asthma controlled with as-needed therapy or daily low dose inhaled corticosteroids (ICS) is defined as "mild" and this group is composed of step 1 and step 2 patients. Since 2019, GINA has recommended as-needed low dose ICS–formoterol as the "preferred controller option" for step 1 asthma patients [4], transferring for the first time the preferable use of this association (or otherwise use of low dose ICS whenever SABA is taken) from step 2. The reason for this significant management change arises from the high importance that was given by GINA to ICS in reducing exacerbations and asthma-related deaths, and the risks of SABA-only therapy [5]. The GINA report highlights the frequency of severe exacerbations and the importance of their prevention [4], and also in mild asthma [6]. Of course, the GINA report has an excellent intention. But is it well supported? Some questions can be raised about this new step 1 approach.

Regarding GINA 2019, the recommendation was based on indirect evidence from the corresponding step 2 studies, in particular the SYGMA report [7]. According to this study, the use of as-needed budesonide–formoterol resulted in a 64% lower rate of severe exacerbations than as-needed terbutaline (annualised exacerbation rate 0.07 *versus* 0.20; rate ratio 0.36, 95% CI 0.27–0.49; p<0.001). The recommendation was reinforced in GINA 2020 by two further studies, the PRACTICAL [8] and Novel START [9] trials. According to the first, the rate of severe asthma exacerbations was lower with as-needed budesonide–formoterol than budesonide maintenance plus as-needed terbutaline therapy (absolute rate per patient per year 0.119 *versus* 0.172; relative rate 0.69, 95% CI 0.48–1,00; p=0.049) [8]. As for the second, the number of severe exacerbations in the as-needed budesonide–formoterol group was lower than the number in both the albuterol group (9/223 *versus* 23/220; relative risk 0.40, 95% CI 0.18–0.86) and the budesonide maintenance group (9/223 *versus* 21/225; relative risk 0.44, 95% CI 0.20–0.96) [9]. However, these studies involve both step 1 and step 2 patients, with no specific differences described in results.

So, how can we understand that there would be a benefit even for the patients at step 1 only? It is currently true that mild asthma can lead to severe exacerbations with a frequency ranging from 0.12 to 0.77 per patient-year [6], but this data may be affected by the presence in the study population of step 2 patients, not allowing differentiation to be made between them and step 1 patients. No direct evidence is today available about the frequency of severe exacerbation in patients who before were classifiable to step 1. Probably, this frequency is lower than that of a step 2 patient having a severe exacerbation. Thus, the

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Cite this article as: Ferretti S, Gelsomino M, Miceli Sopo S. About the recommendation of the GINA strategy report on asthma step 1. *Eur Respir J* 2021; 57: 2003324 [https://doi.org/10.1183/13993003.03324-2020].

difference in the incidence of severe exacerbations between patients treated with only as-needed SABA and patients treated with as-needed low dose ICS–formoterol may not be significant nor clinically irrelevant in step 1 patients.

Trying to avoid a hypothetical risk could lead to an unmotivated overtreatment this way. The currently unavailable evidence demonstrating the real need for use of ICS–formoterol association for step 1 could arise from a randomised controlled trial comparing treatment with SABA alone *versus* low dose ICS–formoterol in a pure population of step 1 patients.

Thus, we think that there is not yet sufficient evidence to transfer the use of ICS–formoterol, recommended in step 2, to step 1. Treating intermittent as mild persistent asthma could mean killing step 1: are you sure it would be fair?

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Received: 31 Aug 2020 | Accepted: 23 Sept 2020

Conflict of interest: None declared.

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