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COMMENTARY

Asthma and COVID-19: In Defense of Evidence-Based SABA

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Abstract: There have recently been major objections to the use of short-acting beta-agonist (SABA) in episodic acute asthma culminating in a call for replacing SABA with combination of inhaled corticosteroids and long-acting beta-agonists despite little evidence supporting this point of view. It is regrettable to note that this attack on SABA occurs in the midst of an unprecedented demand for, and shortage of, SABA inhalers during the current COVID-19 pandemic, and the worldwide efforts to increase SABA supplies. In this commentary, we defend the well-established role of SABA and argue that the call for the phase out of SABA is inappropriate, since it is not solidly evidence based.

Keywords: asthma, beta-agonists, COVID-19, inhalers

Commentary

There have recently been major objections to the use of SABA in episodic acute asthma culminating in a call for replacing SABA with combination of inhaled corticosteroids and long-acting beta-agonists despite little evidence supporting this point of view. In a recent European Respiratory Journal editorial by Charriot et al,[1] the editors repeatedly and forcefully attempt to convince the reader that we should "get rid of SABA", that SABA "is misused" and that there is need "for change in real-life rescue asthma management" as well as a "need for change in the organization of SABA phase-outs". The authors hailed GINA for "down-rank(ing) SABA whenever it was possible".

The verdict on SABA is supported, in part, by reports of deleterious effects of regular (not transient acute) use of SABA and compares these attacks with the previous fight against the use of oral corticosteroids (OCS). The fight against SABA is, in our view, inappropriately compared to "detrimental OCS side effects" and remind us that SABA (compared to OCS) "has its own set of consequences".

It is a pity to note that this type of attack on SABA occurs in the midst of an unprecedented demand for, and shortage of, SABA inhalers during the current COVID-19 pandemic,[2,3] and the worldwide efforts to increase SABA supplies.[4] SABA treatments have become the first line of defense for COVID-19 patients that also suffer from asthma, COPD or other pulmonary exacerbations, particularly in the elderly population.[5] With regards to asthma, a recent nation-wide large scale (220,000 participants) study from Korea,[6] showed a significantly greater risk of SARS-CoV-2 infection and severe clinical outcomes of COVID-19 among patients with allergic rhinitis and asthma, especially nonallergic asthma. The Center for Disease Control (CDC) has recently (Sep 11, 2020) followed suit with a warning

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that people with moderate to severe asthma may be at higher risk of getting very sick from COVID-19.[7] Due to the potential risk of infection by nebulizers,[8,9] the need for SABA in the forms of MDIs has dramatically increased during the COVID-19 pandemic.[2,3]

There is wide agreement that management of asthma exacerbation with or without COVID-19 should continue as before with increased frequency of SABA therapy delivered through metered-dose inhaler using a spacer, particularly during the first hour of presentation to the emergency department.[10]

We are, in our view, fortunate that both numerous and intense attacks on SABA have not been successful. To phase out SABA, as emphatically called for by these authors, would in our opinion, be a critical error. Indeed, it is our view that what they and other SABA critics suggest is "putting the cart before the horse" since it is likely that overuse of SABA is the result of asthma deterioration not its cause! Furthermore, we would like to emphasize that nowhere in the study referred to in the editorial,[11] was it suggested that SABA was the cause, rather than the result of asthma deterioration!

The editorialist clearly wishes to convince us that their prejudiced view that "over-use" or "over-reliance" on SABA, is the cause of the poor outcomes, including more frequent exacerbations, and increased asthma deaths.

Stating their hypothesis in this way is, at first sight logical, yet we suspect that their SABA-related "cause and effect" assumption may have been, influenced by the sponsors of the study who may have a commercial interest in the SABA phase out, as well as previous research, similarly prejudiced! Looking at the question through this lens (ie, SABA causes exacerbations) makes us judgmental. To assume that SABA causes more death and uncontrolled asthma, and then use the association between the two to support our prejudice that SABA overuse is the cause of death rather than the corollary—that deteriorating asthma leads to SABA overuse is, in our view, a very one-sided position.

We believe that it is equally legitimate, scientifically justifiable and appropriate to turn the question around-namely, is it not more likely that patients with more frequent and severe exacerbations, having obviously less well controlled, more severe asthma, would use SABA more frequently?

Is it not also possible that many patients simply do not like to take ICS because of confusion with OCS and the well-known associated numerous and severe adverse effects? Alternatively, patients simply prefer to use SABA for rapid relief of shortness of breath regardless of our somewhat "rigid" clinical guidelines? Studies have repeatedly confirmed the latter point of view. Patients, given their fear of corticosteroids and lack of an obvious rapid response, inherently prefer the almost immediate relief of breathlessness provided by the SABA compared to ICS that provides no immediate discernable benefit![12,13] Thus, these authors (and previous investigators that initiated the SABA cause-effect hypothesis many years ago[14]) are not, scientifically-speaking, entitled to attribute deterioration in asthma severity to overuse of SABA, since the evidence merely demonstrates an association, not cause and effect! To attribute the cause of asthma deterioration simply to overuse of SABA when the supporting evidence is merely for an "association", is therefore not justifiable using evidence-based criteria!

Would it not be reasonable to suggest that increased SABA use simply signifies and warns of deterioration of asthma control reflected in a marked increase in patients' symptoms and, at least initially, be given equal weight. Considered in this way, there should, in our opinion, be a major difference in how the problem is approached and interpreted! That is, the issue is not simply in the excessive use of SABA, but rather in the response of the patients to the increased symptoms reflecting asthma deterioration for which increased (excessive!) SABA is "required"! Is this not where our efforts should be focused in order to achieve a solution to the problem of deterioration of asthma control and increased morbidity and mortality related to overuse of SABA?

In fact, in another recent study, funded by the same sponsor, Amin et al have identified underuse of ICS and overuse of SABA as the manifestation of poor adherence which was shown to be related to patients' low-perceived need for asthma medications, inadequate communication between patients and physicians, perceived medication concerns, and suboptimal patient knowledge, including incorrect inhaler technique.[15]

Indeed, having identified the symptom (shortness of breath-causing overuse of SABA) of the "fire" and the ease with which an early warning system ("fire alarm") could nowadays be devised, could not the abuse of the SABA device be the signal that initiates a rapid response from the health-care system? Despite their one-sided attacks on SABA, towards the end of the editorial the authors agree that SABA abuse is "an excellent surrogate marker of poor asthma control" and that

their prescription (e.g. frequency of renewal) can easily be monitored by their pharmacist and communicated to their physician) and can generate automatic warnings … by smart inhaler devices.

Phasing out SABA will not solve the problem eloquently identified and defined by Amin et al. Thus, we should not throw away the SABA "baby with the bathwater" but rather apply overuse intelligently for our patients' benefit.

In a recent-published paper, Wang et al[16] analyzed data (March 3, 2020 to June 8, 2020) from the Massachusetts-based Mass General Brigham (MGB, formerly Partners HealthCare) health system's electronic health record, the largest volume of hospitalized patients with COVID-19 in New England. Interestingly, among 1827 cases with asthma and positive COVID-19 diagnosis, the authors found that patients with mild asthma who were previously prescribed SABA alone, were more likely to triaged to outpatient care and less likely to be hospitalized. No such differences in risk for hospitalization or ICU care were found in patients treated with ICS or combined ICS-long-acting beta-agonists.

SABA has a well-established role and the call for the phase out of SABA is inappropriate, since it is not solidly evidence based. In particular, given the COVID-19 pandemic, we strongly resist phasing out this important medication, now inexpensively, widely and appropriately used by many patients with reversible airflow obstruction.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

I Amirav is currently affiliated with Dana-Dwek Children's Hospital, Tel Aviv, Israel. M. T. Newhouse is employed by InspiRx Pharmaceuticals Inc as the Chief Medical Officer and has patents through InspiRx Pharmaceuticals Inc (6,470.882; 8,119,016; D 689,602; D 685,085; and D 686,725; Pending: US 2012/0318261 and 2012/0318265). The authors report no other conflicts of interest in this work.

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