Clinical Remission in Severe Asthma: How to Move From Theory to Practice

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ACKNOWLEDGMENTS

Medical writing support was provided by Dan Jackson, PhD, CMPP, of CiTRUS Health Group, which was in accordance with Good Publication Practice (GPP4) guidelines. AstraZeneca (Cambridge, UK) funded this support. AMG and DBP both conceived and refined the topic for this manuscript. Both authors contributed to the discussion and revision of the content and approved the final version.

DISCLOSURES

Andrew Menzies-Gow has attended advisory boards for AstraZeneca, GlaxoSmithKline, Novartis, Regeneron, Sanofi, and Teva; has received speaker fees from AstraZeneca, Novartis, Sanofi, and Teva; has participated in research with AstraZeneca for which his institution was remunerated and has attended international conferences with Teva; and has had consultancy agreements with AstraZeneca and Sanofi.

David B. Price has board membership with AstraZeneca, Boehringer Ingelheim, Chiesi, Mylan, Novartis, Regeneron, Sanofi Genzyme, and ThermoFisher; consultancy agreements with Airway Vista Secretariat, AstraZeneca, Boehringer Ingelheim, Chiesi, EPG Communication Holdings Ltd, FIECON Ltd, Fieldwork International, GlaxoSmithKline, Mylan, Mundipharma, Novartis, OM Pharma SA, PeerVoice, Phadia Ab, Spirosure Inc, Strategic North Limited, Synapse Research Management Partners SL, Talos Health Solutions, Theravance, and WebMD Global LLC; grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute Pte Ltd) from AstraZeneca, Boehringer Ingelheim, Chiesi, Mylan, Novartis, Regeneron, Respiratory Effectiveness Group, Sanofi Genzyme, Theravance, and the UK National Health Service; received payment for lectures/speaking engagements from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Mylan, Mundipharma, Novartis, Regeneron, and Sanofi Genzyme; received payment for travel/accommodation/meeting expenses from AstraZeneca, Boehringer Ingelheim, Mundipharma,

Mylan, Novartis, and ThermoFisher; stock/stock options from AKL Research and Development Ltd, which produces phytopharmaceuticals; ownership of 74% of the social enterprise Optimum Patient Care Ltd (Australia and United Kingdom) and 92.61% of Observational and Pragmatic Research Institute Pte Ltd (Singapore); 5% shareholding in Timestamp, which develops adherence monitoring technology; served as peer reviewer for grant committees of the UK Efficacy and Mechanism Evaluation programme and the Health Technology Assessment; and served as an expert witness for GlaxoSmithKline.

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Asthma is the most common nontransmissible respiratory disease worldwide, affecting nearly 340 million people; about 3% to 10% of people with asthma have severe asthma (SA).[1] Patients with SA have a heavy disease burden, including impacts on social, mental, and emotional well-being as well as frequent symptoms, exacerbations, and adverse effects of treatment.[1] For example, recent cohort studies indicate that about 50% of patients with SA have received long-term treatment with oral corticosteroids (OCS),[2] despite the well-established adverse effects.[3]

Biologics can reduce the burden of asthma exacerbations and OCS use in patients with asthma; as such, they have enabled a paradigm shift away from treat-to-failure toward an era of precision medicine, thereby invigorating conversations about the potential for patients to achieve and maintain asthma remission.[4] In 2020, an expert consensus group defined asthma remission as ≥12 months with zero significant symptoms, patient and provider agreement regarding remission status, zero use of systemic corticosteroids for asthma, and optimization/stabilization of lung function.[5] We recently performed a post hoc analysis of clinical remission across three phase 3 trials in SA, using a composite definition of remission.[4] We reflect here on the following questions engendered from that study:

- Which aspects of remission can be measured in routine clinical practice and are they reflected in the current definition?
- In which populations is clinical remission achievable (eg, asthma vs SA) and could earlier administration of targeted therapies (ie, before excessive OCS exposure, high symptom burden, and low lung function have developed) empower more patient subgroups to achieve remission?
- What are realistic treatment goals for patients who do not meet the consensus definition of asthma remission?

Our experience with the Asthma Control Questionnaire, 6-item (ACQ-6; and other patient-reported outcome measures, such as the asthma control test) has shown that it is not an ideal symptom assessment tool in SA. The ACQ-6 only evaluates only one domain of control in SA and emphasizes bronchodilator use while

excluding other important aspects of SA (eg, exacerbations, OCS use, and >1-week recall). Additionally, the ACQ-6 was not developed for use in this subset of patients. Indeed, the ACQ-6 may not accurately capture symptom control from SA itself given the high rates of airflow limitation and remodeling changes.[4,6] Moreover, physical deconditioning, comorbidities, and subjective attributes of disease can drive symptom perceptions, making the ≤0.75 ACQ-6 score threshold a prohibitive criterion for SA remission; notably, in the UK Severe Asthma Registry, the median ACQ-6 score was 2.9.[2,6] There are also challenges with including a lung function criterion in definitions of SA remission, principally because of a lack of consensus in defining "optimization and stabilization of [lung] function." Several studies have reported interpatient variability in lung function in association with the expected loss of lung function that occurs with aging, making it necessary to define patient populations according to changes over time (ie, trajectories such as non-decliner, slow decliner, and rapid decliner); furthermore, pathologic alterations in the airway and changes in lung function over the course of the disease may make it impossible for patients to return to "normal" lung function.[6] For example, in the UK Severe Asthma Registry, the median clinic forced expiratory volume in 1 second was 65.3%.[2] Taken together, these factors make it challenging to include measures of lung function in the definition of SA remission, particularly if applied retrospectively to clinical studies.

One challenge with applying the consensus definition to patients with SA is that it raises questions about the type of patients for whom asthma remission is achievable. Baseline factors associated with remission include milder disease, shorter asthma duration, better lung function, greater asthma control, younger age, and earlier age at asthma onset.[7] Conversely, it may be difficult for patients in later stages of SA to achieve that same definition of remission, especially the asthma control and lung function criteria.[6] These observations suggest that the consensus remission definition might be more relevant and achievable earlier in the disease course; whereas, for some patients with SA, it may be more appropriate to focus on exacerbations, OCS use, and symptoms and impairments (eg, individualized disease characteristics) to define the aim of treatment.[4,6,7] Indeed, those observations also suggest that earlier identification of patients at risk of SA and/or use of biologics earlier in the disease course could enable earlier intervention and thereby change the trajectory of asthma to achieve remission and reduce or prevent long-term disease progression.[4,6,7]

Given the challenge in meeting the consensus remission definition for some patients with SA, the question remains—in clinical practice, how should we describe the outcome for patients who meet some, but not all, of the criteria for remission? For some patients, reductions in exacerbations and OCS use (ie, stable disease) could be substantially beneficial, whereas for other patients reductions in background medications, symptoms, and/or impairments could substantially reduce their burden of disease.[6] Ultimately, treatment goals likely vary among individuals based on many factors, including the stage of their disease and their clinical presentation.[4,6,7] Nevertheless, it is important to remember that these questions can be answered clinically

through direct health care professional-patient shared decision-making, further highlighting the importance of including patient preferences when defining or identifying remission in asthma.[5]

In conclusion, there are challenges with applying extant definitions of asthma remission to patients with SA. Although an SA-specific revised/modified remission definition or alternative nomenclature, specific to SA, could be useful, exacerbations, OCS use, and symptoms are likely the key criteria. Recent studies and anecdotal clinical observations suggest clinicians should consider treating certain asthma phenotypes with targeted therapies (eg, biologics) earlier in the disease course, to increase the likelihood of achieving and maintaining asthma remission. Efforts must be made to relegate the treat-to-failure and elevate the treat-to-target approach to managing SA.

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