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Reply to “Exploring the long-term effects of biologic initiation in severe asthma: Insights from the International Severe Asthma Registry”

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To the Editor:

We agree with many points made by Cheng et al¹ and offer our clarifications. We agree that severe asthma is heterogeneous, and unraveling asthma phenotypes and endotypes can pave the way for precision medicine in asthma management, which is within the scope of the International Severe Asthma Registry (ISAR). The referenced GLITTER study was focused on a more severe subgroup of patients who had guideline-defined severe asthma and high exposure to oral corticosteroids (OCS).² The study has investigated the phenotypes of OCS-dependent and frequent OCS users with severe asthma, in particular treatment effect variations with regard to biologic-associated reductions in exacerbations across various demographic, clinical, and phenotypic parameters. Figure 4, as depicted in the reference paper, showed a consistent reduction in exacerbations after biologic initiation; the reductions were observed across categories such as age, sex, smoking status, body mass index, and, notably, eosinophilic phenotypes, characterized by type 2 inflammation, allergic predisposition, the presence of nasal polyps, and responsiveness to various asthma treatments. These findings demonstrated treatment efficacy across asthma phenotypes. However, the extent of reduction indeed slightly varied. A pertinent study of Chen et al³ demonstrated that a combination of core prognostic factors has the capacity to predict multi-domain treatment responses to mepolizumab, in particular, to identify a small subset of patients with severe asthma who will not benefit as much from the treatment. As we move forward, ongoing studies with ISAR are delving deeper into the subject matter. The Effectiveness of biologics in patients with different combinations of T2 biomarkers (IGNITE) study, for instance, seeks to assess the impact of several T2 biomarkers on the treatment effects of various types of biologic therapy in severe asthma. These studies may continue to offer valuable insights into the nuances of precision medicine strategies for asthma management.

Regarding the consistency and representativeness of study findings, it is important to emphasize that ISAR stands as the largest and most comprehensive database dedicated to this complex medical condition. The commitment to quality assurance and continuous improvement has laid the foundation for the establishment and ongoing success of ISAR. The utilization of the Delphi process,⁴ a widely recognized approach to reach consensus among experts, enabled ISAR to harness the collective expertise of professionals worldwide, which ensures that data collection, categorization, and analysis adhere to the rigorous standards in clinical guidelines. All participating sites, individually or as part of a local or national registry, gather data for submission to ISAR that is of the highest quality achievable. The clinical care provided at centers is also of high quality as reflected in improved outcomes seen in the non-initiating subjects of the GLITTER study.² The database's extensive reach has facilitated pioneering research in severe asthma management and precision medicine and has yielded numerous scientific breakthroughs.

Therefore, it is important to clarify that the multi-centered settings in the referenced study are, in fact, an advantage rather than limitation. Earlier evidence on the real-world effectiveness of biologics in patients with asthma mainly came from single settings such as the United Kingdom, the United States, and Japan.⁵⁻⁷ In contrast, ISAR's multi-centered approach offers a more diverse and comprehensive perspective, which improves the generalizability of findings.

Lastly, although we agree that the use of biologic therapies may not be universally cost-effective in patients with moderate-to-severe asthma, it is important to clarify that ISAR was not designed to address questions related to the cost-effectiveness of medications due to the nature of registry data. Moreover, the referenced GLITTER study was tailored to a more severe subset of patients with severe asthma,² which did not cover the entire target population for cost effectiveness analyses of biologics. Rather, the core clinical implication of the GLITTER study is that we confirmed that the identified treatment benefits of biologics in the restricted, artificial environment of randomized controlled trials can be replicated in real-world clinical practice, which provides an evidence base for payers and funders of more costly health care interventions to make informed decisions.

This study was conducted by the Observational and Pragmatic Research Institute (OPRI) Pte Ltd and was partially funded by Optimum Patient Care Global and AstraZeneca Ltd. No funding was received by the OPRI for its contribution.

Conflicts of interest:

T. N. Tran is an employee of AstraZeneca and may own stock or stock options in AstraZeneca. M. Sadatsafavi has received honoraria from AstraZeneca, Boehringer Ingelheim, Teva, and GlaxoSmithKline for purposes unrelated to the content of this manuscript and has received research funding from AstraZeneca and Boehringer Ingelheim directly into his research account from AstraZeneca for unrelated projects. R. B. Murray is a consultant for Observational and Pragmatic Research Institute (OPRI), which conducted this study in collaboration with Optimum Patient Care and AstraZeneca. N. Ali was an employee of OPRI at the time this research was conducted. OPRI conducted this study in collaboration with Optimum Patient Care and AstraZeneca. C. Ariti was an employee of the OPRI. OPRI conducted this study in collaboration with Optimum Patient Care and AstraZeneca. L. Bulathsinhala is an employee of the OPRI. OPRI conducted this study in collaboration with Optimum Patient Care and AstraZeneca. E. G. Gil was an employee of AstraZeneca at the time this research was conducted. AstraZeneca is a co-funder of the International Sociological Association Registry. J. M. FitzGerald previously declared grants from AstraZeneca, GlaxoSmithKline, Sanofi Regeneron, and Novartis paid directly to UBC, and has received personal fees for lectures and attending advisory boards from AstraZeneca, GlaxoSmithKline, Sanofi Regeneron, and Teva. M. Alacqua was an employee of AstraZeneca at the time of manuscript development and is currently employed at CSL Behring SpA. M. Al-Ahmad has received advisory board and speaker fees from AstraZeneca, Sanofi, Novartis, and GlaxoSmithKline, and received a grant from Kuwait Foundation for the Advancement of Sciences (KFAS). A. Altraja has received lecture fees from AstraZeneca, Berlin-Chemie, Menarini, Boehringer Ingelheim, GlaxoSmithKline, MSD, Norameda, Novartis, Orion, Sanofi, and Zentiva; sponsorships from AstraZeneca, Berlin-Chemie Menarini, Boehringer Ingelheim, GlaxoSmithKline, MSD, Norameda, Novartis, and Sanofi; and has participated in advisory boards for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, MSD, Novartis, Sanofi, and Teva. R. Al-Lehebi has given lectures at meetings supported by AstraZeneca, Boehringer Ingelheim, Novartis, GlaxoSmithKline, and Sanofi, and received advisory board fees from GlaxoSmithKline, AstraZeneca, Novartis, and Abbott. M. Bhutani has received speaker and consultant fees from AstraZeneca, GlaxoSmithKline, Sanofi, Covis, Boehringer Ingelheim, and Valeo. L. Bjermer has (in the last 3 years) received lecture or advisory board fees from Alk-Abello, Astra-Zeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mundipharma, Novartis, Sanofi, Genzyme/Regeneron, and Teva. A. Bjerrum has received

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