CHEST

International Severe Asthma Registry

Closer to the Full Picture of Asthma Care and Outcomes?

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The recent arrival of biological agents, a new therapeutic class in asthma, has revived the interest in patients with severe asthma (SA), a subset with impaired quality of life and high use of health care resources.[1,2] To investigate the history and care of SA and the effect of biologics, several national registries have recruited large samples of patients with well-characterized asthma, generally including clinical, functional, and biological data. As a rule, registries have been initiated at a national level to assess the impact of biologicals in the specific context of local health care systems. More recently, large-scale international initiatives such as the Severe Heterogeneous Asthma Research Collaboration, Patient-Centered (SHARP) and International Severe Asthma Registry (ISAR) have been launched to aggregate data from national registries.[3] Beyond extending considerably the number of patients included, they allow cross-national comparisons to be conducted. In this issue of *CHEST*, the ISAR Consortium investigated exacerbation rates in patients with SA across the world.[4]

The primary purpose of the study by Lee et al[4] published in this issue of *CHEST* was to perform cross-national comparisons of the rates of severe exacerbations in populations of patients with SA. The authors investigated a total of 7,510 patients from 17 countries and observed 1,939 severe exacerbations over a 1-year period, that is, 0.27 exacerbations/person-year. A first analysis producing crude results found a wide range of rates, from 0.04 in Argentina to 0.88 in South Africa, that is, a more than 20-fold difference (crude interquartile range, 0.13-0.54). An adjustment on available effect modifiers or potential confounding factors had a limited impact on the findings (adjusted interquartile range, 0.15-0.39), leading the authors to conclude that similar patients with SA in different countries showed markedly different risks of severe exacerbations even after controlling for several patient characteristics and randomness resulting from the finite sample, suggesting that unknown patient-level or system-level factors explained the observed differences.

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Although widely accepted, the definition of exacerbation nevertheless should be reassessed because part of the outcome measures, that is, the use of oral corticosteroids, originates from patient-reported outcomes.[5] As such, apart from possible recall biases, they are impacted by patients' experiences and understandings of asthma, as well as by personal behaviors. When asthma deteriorates, patients with asthma may or may not change the use of therapy as a result of personal decisions based on expectations, identification of the trigger(s), perceived risks of adverse outcomes, use of validated action plans, as well as local care organizations.[6,7] Indeed, the prescribing behavior of the physician who sees a patient with uncontrolled asthma also may impact the recorded rate of exacerbation, with marked differences among physicians and among countries, illustrated by the more frequent prescription of oral corticosteroids to control clinical deterioration of patients with asthma in some jurisdictions.

It is also notable that exacerbation rates generally were lower during the 12-month follow-up period than in the 12 months preceding inclusion (0.27 exacerbations/person-year vs 0.67 exacerbations/person-year; $P < .01$, Wilcoxon test). Although these figures may be flawed by recall bias, they also may reflect the awareness of patients and health care professionals of the ability to improve asthma control after inclusion in the registry, without necessarily resorting to new therapy (only 8% restarted biologic therapy). Of particular interest,

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overall exacerbation rates observed in the ISAR were low compared with the rates recorded in the trials that established the value of biologics in severe Type 2-high asthma, which implies that most patients would not qualify to receive a biologic agent in most European countries.[8]

Added to the potential confusion between severity and control,[9] unassessed or unreported patient characteristics (particularly quality of life, adherence, and socioeconomic status) and unverified occurrence of exacerbations may lead to misclassification of severity, and patients who do not have SA may end up being included in SA registries. This may impact the representativeness of some registries, particularly when the samples are of limited size; it also may affect recorded rates of exacerbations, and hence the validity of cross-national comparisons, when misclassification differs among countries, for instance because of varying levels of expertise in asthma care or because of distinct guidance for identifying exacerbations. Of note, at least in some countries, the quality of the patient sampling can be tested by comparing the data from local registries with the data that can be retrieved from local health care data sets by using similar selection criteria; discrepancies may signal a need for corrective actions.

Some methodologic limitations may have affected the findings, for instance, the 6-year inclusion period (2015-2021, including the global COVID-19 pandemic), because the last years have witnessed a rapid and profound transformation of many health care systems, with an impact on asthma care.[10] Also as mentioned, the variations of outcome identification by local health care professionals may be larger than acknowledged by the authors. To circumvent this limitation, an alternative approach would have included a direct sampling at the population level, similar to the one used by Asthma Insights and Reality in Europe in 1999,[11] with a random population screening to identify patients with asthma and the use of standardized questionnaires by interviewers through direct contacts with all patients.[12] If the choice of a registry is understandable to assess the effects of therapy, parallel initiation of data collection across all countries using identical selection and outcome assessment criteria would have produced more robust findings. Clear guidance is available now, with the essential elements of good registry practice for research, also listing indicators of quality that may enhance registry validity and reliability.[13]

In conclusion, the study by Lee et al[4] should prompt us to reassess the methods for identification and collection of outcome measures in asthma studies by acknowledging the key role of patients as data providers and by developing a deeper understanding of patients' and health care professionals' behaviors that impact on the rates of recorded exacerbations. Such an approach would enhance the capacity of ISAR further to deliver the high-quality evidence needed to support efficient asthma care.

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