

The Challenges and Opportunities of Maximizing the Benefits of Severe Asthma Registries



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Severe asthma affects a small minority of patients with asthma, but, despite this, these patients drive 50% of the overall costs of asthma management.¹ In addition, they represent a major challenge to the treating clinician. Historically, patients with severe asthma have been difficult to manage, but as we have gained a greater understanding of the biology underlying these patients' disease, in parallel we have now seen the emergence of multiple new targeted therapies for such patients. Historically, omalizumab was our only available biologic, and, although effective in many patients, there remained patients who were ineligible to use it. More recently, the availability of therapies targeted at anti-IL-5 and the recent approval of dupilumab for asthma have transformed our management options for these patients.

The availability of these newer therapies has the potential to transform the care of patients with severe asthma, but along with the opportunities come challenges. It is in this context that the report in this issue of the journal from the Italian Severe Asthma Network needs to be assessed.²

In the current study, the investigators report the baseline characteristics of 437 patients who have been enrolled into this network. They provide some interesting findings but also a chance to look at the role of severe asthma registries, given the new therapies that are available. Registries have a potentially important role in contributing to our understanding of severe asthma management. This potential can be looked upon under various headings.

Registries provide an opportunity to phenotypically describe a range of patients in a "real-world" setting. Unlike randomized controlled trials, where patients are enrolled with very strict inclusion and exclusion criteria, registries can adopt a more liberal

framework. Such data can then serve to inform the clinician's real-world assessment of these patients. It also comes with risks in that, if the data collected across sites are not standardized, important information may be missed. The Italian registry highlights this issue in that, in such a large cohort, gastroesophageal reflux disease (GERD) and vocal cord dysfunction (VCD) were not identified as comorbidities. Based on the Severe Asthma Research Program (SARP) data, where, in a similar patient population, GERD was shown to be significantly associated with asthma exacerbations, its absence from this data set is surprising.³ Although less frequent, the absence of VCD is similarly surprising. The importance of critically evaluating and treating these and other comorbidities before categorizing a patient as having severe as opposed to uncontrolled asthma, which is potentially modifiable, is critical.⁴ The authors enrolled subjects at their first visit, and this highlights the fact that patients with GERD and VCD may be missed and be categorized as having severe asthma before these and other modifiable comorbidities such as sinusitis have been aggressively treated.

An important, not always recognized, comorbidity that the Italian registry highlights is that of bronchiectasis, which occurred in 16% of patients. This figure likely underestimates the frequency, because computed tomography scans of the chest were not routinely carried out. There are 2 important clinical caveats that follow. The presence of atypical mycobacterial infection has been identified in patients with severe asthma,⁵ and its treatment may improve the patient's overall status but also, given that we now recognize that azithromycin is an effective intervention for severe asthma, its casual prescription without ensuring the absence of bronchiectasis and associated atypical infection is very important.⁶

Part of this initial evaluation also requires a systematic assessment of nonadherence, which has been shown in multiple studies to be prevalent across patients of all severities. In the current registry, this has not been done and one must assume that there is a substantial problem with nonadherence. Several features highlight this possibility. The patients in the registry report taking a mean dose of 1084.3 ± 489.0 µg of fluticasone propionate or equivalent, and in the overall population, 64.1% of subjects were taking systemic oral corticosteroids. Despite this very high intake of anti-inflammatory therapy, close to 60% of subjects had peripheral eosinophil counts of greater than $300/\text{mm}^3$ and a similar percentage had an exhaled nitric oxide level of 25 parts per billion or greater. Both these measurements suggest significant ongoing inflammation, and, based on the almost universal elimination of peripheral eosinophils by systemic corticosteroids, this suggests that maintenance therapy was not taken with the high level of adherence reported in this registry.⁷

Although this may be looked upon as the benefit of a real-world study, it may reduce a very important role that registries can provide. In this study, a very high proportion of subjects were on

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omalizumab or mepolizumab, and the authors have been able to identify those who might be candidates for either, both, or neither of these drugs, but such categorization into a potential eligible subject depends on baseline characteristics and especially ones that take into account adherence. Recently, it has been suggested that randomized controlled trials are required to compare the current and emerging new biologics in severe asthma, but, unfortunately, such trials are not likely to occur because of cost and the need for collaboration between pharmaceutical companies.⁸ Registries provide an important alternate structure for pragmatic randomized trials, but including a well-characterized cohort of patients is necessary for success in this endeavor.

Registries help us gain better understanding of different phenotypes for asthma and their clinical implications. A study from the British Thoracic Society severe asthma registry demonstrated the differences in severity of asthma in adult patients and the differences in inflammatory markers in late-onset asthma.⁹

An additional important role for registries is to provide safety data and also outcomes in populations such as pregnant patients with asthma. Although such outcomes cannot be expected from the current publication, it highlights the importance of integrating the many current and emerging national severe asthma registries into a global registry. This is currently being achieved with the development of the International Severe Asthma Registry.¹⁰ Such a registry with its anticipated recruitment of more than 10,000 patients will truly provide a bridge to Big Data for this very important patient population. By integrating a biomarker repository into such a registry, we can further leverage its benefit by linking it to current and future yet unidentified biomarkers and treatments.

An added consideration for the utility of registries is to provide real-world health outcomes within a cost-effectiveness framework for the use of biologics. This may provide important information for payers in terms of granting access to these expensive therapies. Lesson learned from the early phases of the introduction of biologics for the treatment of rheumatological disorders may be valuable in the emergence of biologics for asthma.¹¹

In conclusion, the current publication is an important addition to the literature and provides an opportunity to critically evaluate the role of registries in severe asthma. As outlined in the published recommendations for optimizing registries,¹² it is important that baseline and follow-up characteristics are carefully

collected and data collection is standardized across sites. Careful attention to such detail will provide the practicing clinician, payer, and most importantly patients with valuable information for the successful management of severe asthma in the community.

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