

Adding a Biologic to Asthma Therapy: The Role of Adherence in Selecting the Right Patient



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The addition of biologics to the treatment of severe asthma has been a notable advance for patients previously unable to gain control of their asthma despite an optimized treatment plan. In this month's issue, Bender et al¹ describe the suboptimal levels of adherence for many patients escalated to biologics and provide evidence that a third of these patients do not meet the criteria for having moderate or severe asthma. The publication offers insight into the variability in prescribing biologics and how this differs from guideline step-care for selecting appropriate patients for these life-changing therapies. Their observations depict a wide range in clinical practice decision making.

Biologics are licensed for patients with severe uncontrolled asthma. The Global Initiative for Asthma (GINA)² uses high-dose inhaled corticosteroid (ICS)-containing therapies as a marker of asthma severity. Before ICS dose escalation, GINA recommends assessment of adherence and inhalation technique. Although not a focus of the present article, it is apparent that there is still the need for greater clarity and understanding regarding assessing disease severity and adherence as they pertain to patients being treated with these high-cost medications.

The prescribing information (PI)³ for biologics in the United States recommend that biologics are indicated for patients primarily with severe asthma (1 indication includes moderate to severe) on maintenance therapy. The clinical studies sections of PIs highlight that most patients studied had a history of 2 or more severe exacerbations or required daily oral corticosteroids. The National Institute for Health Care and Excellence⁴ recommends biologics for patient with severe asthma who have "agreed and followed the optimized standard treatment plan." GINA² provides an algorithm for escalating patients with severe asthma to biologics and, as noted above, suggests assessing factors that may contribute to uncontrolled asthma, including adherence and inhalation technique. The wording in GINA, National Institute for Health Care and Excellence, and the PIs appears to

be intentionally nonprescriptive to preserve provider decision making on a patient-by-patient basis. But in so doing they do not identify standards for assessing an optimized treatment plan, including the threshold level of adherence, evaluating adequate inhalation technique, or appraising the disease burden. The result is that the patient's advocacy, provider preference, type of health insurance, and patient socioeconomic status may be significant determinants of advancing therapy to include a biologic.

Bender et al¹ report that many patients escalated to biologics have suboptimal adherence to their ICS-containing maintenance medication and suggest inappropriate escalation to high-cost medications. Nearly a third of patients were using low-dose ICS or low-dose ICS/long-acting bronchodilator (LABA) maintenance. This diverges from the GINA report, which defines severe asthma "as asthma that remains uncontrolled despite optimized treatment with high-dose ICS/LABA or that requires high-dose ICS/LABA to prevent it from becoming uncontrolled."² On the basis of GINA severity steps, a third of patients from this report do not meet the criteria for moderate to severe asthma.¹

Although GINA² presents an algorithm for step-care, further scrutiny of prescribing patterns identifies that the patient's insurer or country of residence, health care provider, the patient's health care literacy, and the marketing of the products may all impact the decision of who is prescribed a biologic. The threshold level of adherence, how to assess adherence, and whether adherence to ICS is predictive of adherence to biologics are still unanswered subjects.

Asthma severity is a primary criterion for stepping up care. But how appropriate is it to determine severity on the basis of present dosing of controller medications? Beasley et al,⁵ in their clinical review of the dose response to ICS, found that 80% to 90% of the clinical therapeutic response was achieved with daily doses of fluticasone propionate 200 to 250 µg or equivalent. They note that in contrast to efficacy, the systemic adverse effect profile does have a significant dose response. The article highlights that 50% to 65% of prescriptions for ICS-containing medications in Australia and Scotland are high-dose ICS. This suggests that either most patients in these 2 representative countries have severe asthma or that many patients are inappropriately prescribed high-dose controller therapy. Beasley et al⁵ acknowledge that there is significant patient variability in response to ICS but that this high proportion of high-dose ICS use would not account for the prescribing practices. Assessing burden of disease rather than the ICS dose may be more appropriate.

Bender et al¹ highlight several limitations of their study. First is the dependence on claims data for the determination of disease severity and adherence. Important to note is that insurers frequently use this same claims data to determine which patients meet their criteria for biologics. Missing from the present

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analytics are the personalized decision-making factors that are not recorded in claims data and not easily accessible from the electronic health record. The present study is also limited by the paucity of data from the Medicaid population, which bears much of the asthma disease severity burden in the United States.

The Bender et al¹ study reported that most patients escalated to biologics had less than 80% adherence to maintenance medication irrespective of GINA severity classification. For patients with oral corticosteroid use and GINA step 4/5, this improved to 68%. Inadequate adherence in patients prescribed biologics has also been described in a report by Jeffery et al.⁶ An additional study by Maddux et al⁷ found adherence to both ICS and biologics to be suboptimal. They reported a higher level of adherence to biologics than to ICS, although only 61% achieved a greater than or equal to 75% proportion of days covered for their biologic. ICS adherence was weakly associated with adherence to biologics. Confounding the role of adherence was their finding that neither ICS nor biologic proportion of days covered greater than or equal to 75% was associated with a reduction in asthma exacerbations.

These publications highlight the issue of adherence and suggest the need to have a consensus statement defining an “optimized standard treatment plan.” Other articles on adherence suggest that the adherent phenotype,⁸ including patients conforming to both medication and lifestyle recommendations, may additionally be an important determinant of response to care. In clinical practice, adherence to an ICS/LABA may be based on provider prescribing records, patient report of utilization, pharmacy dispensing reports, and occasionally electronic medication monitoring. All of these methods have advantages and limitations, but at a minimum there needs to be consensus on how to assess adherence and an established threshold for appropriate adherence. In addition, enhanced determinants of disease burden and more specific biomarkers may augment the criteria for patients who are appropriate for biologic therapy.

The present article highlights the need for greater clarity on appropriate escalation to biologics. More universal and patient-centric evidence is needed to establish criteria. GINA² discusses modification in recommendations in low- and middle-income nations, but health care inequities occur also in higher income countries where socioeconomic status and health care literacy are important determinants of which patients receive higher cost therapies. Inner-city patients in the United States, as an example, frequently experience the greatest asthma morbidity and mortality from asthma and often have the least access to biologics due to cost considerations. For example, Akenroye et al⁹ demonstrated that biologic use is lower in publicly insured

patients, particularly publicly insured Black patients, compared with privately insured patients.

“Step-therapy” has been implemented as an administrative program to balance the goals of safe-guarding a patient’s access to high-quality care and preventing the inappropriate use of high-cost medications.¹⁰ If step-therapy is to be successful in management of severe asthma, there needs to be confidence that the evidence supports the thresholds for decision making. One of the criteria for step-up to a biologic is that the provider-patient team have “agreed and followed the optimized standard treatment plan.” Bender et al¹ demonstrate that for many patients this is not true. Acceptable parameters for adherence to treatment before escalation to high-cost biologics need to be established. The presence of severe asthma determined by use of high-dose ICS needs to be reassessed if the Beasley et al⁵ review is correct and the dose-response is relatively flat. Maybe it is time to step back and reevaluate the evidence that supports present stepwise care and restructure and reassess the use of high-dose ICS as a determinant for biologics. Additional clinical parameters of disease burden and/or specific biomarkers of disease severity are needed to affirm stepping up to biologics. Equally important is that all appropriate patients, especially the medically underserved, should have equal access to indicated biologics irrespective of their insurer or their health literacy.

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