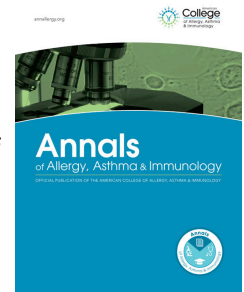


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Choosing the right biologic for severe asthma: precision medicine through the lens of patient-centered decision making

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Title Page

Choosing the right biologic for severe asthma: precision medicine through the lens of patient-centered decision making

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1 In the past few years, we have seen the emergence of numerous biologics on the market for
2 severe type 2 (T2) asthma. In addition to omalizumab (a monoclonal anti-IgE antibody), three
3 anti-interleukin (IL) 5 agents are approved for eosinophilic asthma and an anti-IL4Ra biologic
4 recently received FDA approval for the indication of severe asthma. For patients with severe T2
5 asthma (about 5% of the asthma population), this translates to newer, targeted therapeutic
6 options that have been shown to reduce asthma exacerbations and that generally have a favorable
7 side effect profile(1). Many factors, notably likelihood of treatment responsiveness as well as
8 patient values and preferences, need to be factored in when designing a treatment plan that is
9 tailor-made to the individual patient. This will truly bring us into the realm of precision
10 medicine.

11 Omalizumab is typically used for allergic asthma in patients with elevated serum IgE
12 and evidence of perennial allergen sensitization. However, anecdotally clinicians have found the
13 predictive value of these biomarkers to be limited. This has been reinforced by recent evidence
14 that suggests that high levels of other T2 biomarkers, such as peripheral eosinophil count,
15 exhaled nitric oxide level and serum periostin, may have predictive value in determining the
16 likelihood of therapeutic response (2). Anti-IL5 biologics (mepolizumab, benralizumab,
17 reslizumab) appear to have greatest benefit in patients with severe eosinophilic asthma, with
18 varying cutoffs of peripheral blood eosinophil counts indicated on their approved labels. There
19 are some differences between these agents, regarding mechanisms, dosing and administration,
20 however it is not clear which is the best choice with regards to efficacy. Benralizumab
21 potentially leads to more complete eosinophil destruction by blocking the IL-5 receptor, but we
22 are uncertain of the clinical impact of this on asthma control. There is some evidence showing
23 that some patients who failed mepolizumab, responded to reslizumab dosing, perhaps because it

is weight-based and may be a better choice in obese asthmatics (3). Certainly, further research is needed. Dupilumab is the newest monoclonal antibody on the market, blocking both IL4 and IL13 pathways. Although there is no strict eosinophil cut point for its use, studies suggest better therapeutic response with higher eosinophil counts. Although all showed an improvement in the primary endpoint of asthma exacerbation, there were different effects on secondary endpoints, such as lung function and symptoms. Notably, at present there are no approved targeted therapies for non-T2 asthma.

Choosing the biologic agent that is the "best" for the patient can be challenging. Although comparative studies would be ideal, these are unlikely to occur due to the exorbitant costs associated with performing large comparative studies. We are therefore left looking at "real world" studies, meta-analyses, network meta-analyses, and our own clinical experience (4). There are limitations to each of these types of studies; for example, some meta-analyses reach different conclusions and network meta-analyses rely upon direct evidence (from head-to-head trials) and indirect evidence from common comparator trials.

Refined phenotypic discrimination of severe asthma will hopefully improve treatment selection over time. Real world data regarding patient response and critical evaluation of treatment non-responders will be important to improving our understanding of how best to use these medications. As trends in our understanding of asthma and other chronic diseases suggest, personalized (precision) medicine will likely become more precise over time. In the future, we will hopefully have a better understanding of predictive biomarkers, or a combination of biomarkers that predict treatment response. Perhaps we will concede that there is no "best"

biologic, or “one size fits all” approach, but rather accept that some patients will respond better to one agent than another.

Our treatment choices will also be influenced by other factors: frequency of dosing, route and location of administration (dupilumab for example is the only biologic that is self-administered, omalizumab is the only one approved for young children aged 6 and up), and cost/insurance coverage issues. Existence of poorly controlled co-morbidities may also be a consideration in the future - biologics are currently being investigated in nasal polyps, atopic dermatitis and eosinophilic esophagitis. There may be a role in combinatorial biologic therapy, or this need may be averted by newer biologics that have more upstream targets such as TSLP or IL33 blockade.

Another consideration is the extremely high costs associated with biologic therapy that work against the medications being considered cost-effective (5). Patient education, environmental controls, measures of adherence, and control of co-morbidities are important to implement early to identify patients truly with severe asthma. For those asthmatics who truly have severe asthma, we could greatly improve the cost effectiveness of biologics if we could better identify those likely to respond based on phenotype before initiating therapy. Likewise identifying characteristics of those responding once therapy has been initiated (and discontinuation if efficacy is not established), will play an important role in improving cost-effectiveness. There is not consensus at this time regarding when it is best to evaluate treatment response and/or consider switching agents.

As we move into the era of personalized medicine, patients are playing a larger role in their health care. The Institute of Medicine defines patient-centered care as care that incorporates individual patient preferences, needs and values, and promotes this as a fundamental approach to

improving health care quality in the United States. Shared decision making is described as “the joint involvement of patients and health care providers in making health care decisions that are informed by the best available evidence in regard to possible options and potential benefits and harms and that consider patient preferences and values” (6). This approach can be particularly important in the management of chronic diseases, such as asthma, and should be incorporated into treatment algorithms. For example, a patient with severe asthma may feel more comfortable starting a medication that has been approved for a long time versus one that has only recently been approved, or another might prefer home versus infusion center injections due to lifestyle and work considerations. Patient preference regarding medication choice, and dosing as well as risk considerations must be important to consider. Physicians should be prepared to have these important discussions with patients, many of which are well informed. Patients now oftentimes research online, and have information from direct-to-consumer marketing, prior to entering the physician’s office.

Precision medicine, applied through the approach of patient-centered decision making, will likely bring forth the best outcomes. In the future, treatment choices will likely continue to expand and become more complex. We will likely see more biologics emerge- anti-TSLP, anti-IL33 and hopefully agents for non-T2 asthma. With these advancements, also comes a need to better understand asthma phenotypes and treatment responders, acknowledging that likely no one medicine fits all. This will allow us to offer precision medicine with a patient-centered approach, in a cost-effective manner.

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