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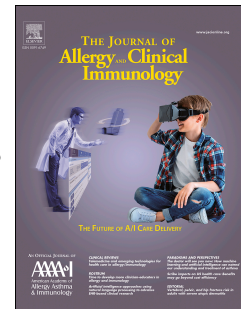
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Can asthma biologics change the course of disease and induce drug-free remission?

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Nearly forty years ago, we began to investigate and dissect the inflammatory pathways in asthma that drive disease chronicity. We learned that even when asthma seems well-controlled, airway inflammation is present and persists throughout life. This early period in asthma discovery in the 1980s closely followed novel studies that showed CD4 T cells could produce different patterns of cytokines and led to classification of CD4 Th subsets ¹. Later research showed that CD4 T cells in the airways producing type 2 cytokines promote features of asthmatic pathophysiology ¹. These studies laid the framework for development of monoclonal antibodies that are now widely used to treat type-2 asthma. This remarkable bench-to-bedside evolution has transformed our practice, as many of our most severely affected patients have finally gained control of their disease.

With long-term control achieved in some of our sickest patients and the continuing expansion of biological drugs, it is natural to consider shifting our focus from control of asthma to cure. A recent expert panel examined the robust literature on spontaneous remission in asthma and concluded that the “optimal outcome” is complete remission and should be defined by at least one year of absent symptoms off all asthma medications, a reduction in inflammation and improvement in lung function ². Is remission a realistic goal for future asthma care or are we setting the bar too high?

Achieving remission seems like a reasonable expectation in asthma since spontaneous remission, commonly referred to as “outgrowing” asthma, is considered a frequent

occurrence in children with asthma. Studies show that somewhere between 5 to 69% of children with asthma undergo spontaneous remission by adolescence or adulthood ³. This wide range in remissions in these study populations reflects differences in the criteria used to define asthma and remission, including asthma severity, age of disease onset and length of the follow-up period. By applying the above strict remission criteria ², the proportion of patients that achieved complete remission is small. In carefully documented mild to moderate asthmatic children, only 15% achieved complete remission at age 23 ³. Adult asthmatics followed over time with either childhood-onset or adult-onset disease may have even lower rates of spontaneous, complete remission of disease ³. The consensus from many studies indicates that spontaneous remission in children and adults is more likely in those with milder disease with a normal FEV1, less AHR and airway inflammation, and those using lower doses of ICS at their initial testing. Blood and airway eosinophils, serum IgE and local release of eosinophil inflammatory mediators were lower in childhood asthmatics that achieved remission compared to those with ongoing asthma ³. However, compared to never-asthmatic controls, children in remission from asthma had more airway inflammation and subepithelial fibrosis suggesting that those who have outgrown asthma may be merely asymptomatic ⁴. Consequently, relapses are high, occurring in 30-80% of childhood-onset asthmatics who had been in remission (Figure 1) ⁴. So, while spontaneous remission in asthma is observed, albeit at a lower level than collective belief, complete remission without relapse is probably uncommon. Asthmatics with moderate to severe disease, frequent exacerbations, low lung function, and more inflammation driving their disease, are

unlikely to undergo spontaneous remission. This more symptomatic population is most in need of long-term disease modification.

For decades, suppressing inflammation has been the mantra of asthma therapy.

Turning off the pathways that lead to persistent inflammation is the key to long-term remission and cure. Inhaled corticosteroids reduce eosinophilic airway inflammation, type 2 cytokines and asthma exacerbations, and improve lung function and AHR ¹. Yet, when corticosteroids are withdrawn, asthma recurs because airway inflammation resumes. Biologic drugs that target type-2 pathways reduce asthma exacerbations, hospitalizations, corticosteroid use and improve lung function and patient quality of life ⁵.

Our hope was that a reduction in specific inflammatory pathways would recalibrate the airway milieu and modify the course of disease. Omalizumab binds IgE and reduces mast cell and basophil activation resulting in reduced exacerbations and airway inflammation ⁵. Omalizumab led to fewer CD3 and CD4 T cells, type 2 cytokines and eosinophils in airway biopsies and modified markers of airway remodeling ⁶.

Mepolizumab (anti-IL-5) reduces eosinophils and is highly effective in preventing asthma exacerbations and improving asthma control ⁵. Yet, after withdrawal of omalizumab or mepolizumab in long-term-treated study subjects, more than half had exacerbations in the following year, a proportion similar to control subjects ⁷. Drug withdrawal studies in dupilumab (IL-4/IL-13 pathway inhibitor)-treated asthmatics have not been published. Subjects with atopic dermatitis who received a short course (16 weeks) of dupilumab followed by withdrawal or dose reduction exhibited increased symptoms that were inversely proportional to the dupilumab dose ⁸. The impact on

asthma after a long course of treatment with dupilumab remains unknown. Overall, studies to date suggest that in a large proportion of subjects with severe asthma, withdrawal of biologic drugs, even after long-term use, does not reverse the pathologic inflammatory program that drives disease.

Interestingly, observations extended for up to six years after discontinuation of omalizumab indicate that some subjects had long-term improvement in symptoms and fewer exacerbations ⁹. (Follow-up studies of other biologic drugs beyond one year are not yet available.) Successful discontinuation of omalizumab was associated with a longer course of therapy, better asthma control during omalizumab treatment, childhood disease and fewer allergic comorbidities ⁹. There are also data to suggest some asthmatics fared well with omalizumab dose-reduction without loss of asthma control ¹⁰. Therefore, in patients treated with omalizumab, there appears to be a subset of asthmatics whose disease becomes milder, or who might achieve remission or possibly cure, within a larger group of asthmatics whose disease resumes its inflammatory course.

If our patients are well-controlled on a biologic drug, how will we know if their disease has gotten less severe or gone into remission? Either of these outcomes would be deemed a triumph for asthma biologic drugs. If we continue biologics on a standard schedule, we can't measure these successes nor identify the features associated with a positive response. Only through careful reduction in drug dosing will we identify this small subset of responders. We should advocate to adopt the personalized, step-down

approach similar to how we adjust corticosteroids in well-controlled asthma. Our goal should be good control on the least amount of drug. As we adjust biologic therapies, we may find some patients can reduce or even stop, whereas others' disease may resume with a ferocity like that in the past. To identify potential responders, providers need clear guidelines to reduce the dosing interval of biologic drugs while closely monitoring symptoms, exacerbations, and biomarkers (Figure 2).

The future brings hope that biologics in the pipeline, such as those that affect epithelial inflammatory signals, will more permanently turn-off the signals that drive asthma. For now, though, we should focus on interval improvement in severity and celebrate these decades of advances in asthma.

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Figure Legends

Figure 1. Asthma Remission and Relapse. Asthma symptoms are caused by airway inflammation. In cases of spontaneous asthma remission, airway inflammation is reduced. Drugs including corticosteroids and monoclonal antibody biologics reduce inflammation and control asthma symptoms, but when the drug is stopped, asthma commonly relapses. There may be some asthmatics who remain well-controlled after drug withdrawal. Further adapted from original figure ³.

Figure 2: Proposed approach to reduce asthma biologics. How will you know if you can reduce the dose of a biologic drug in your asthmatic patient? One approach would be to monitor control based on symptoms, exacerbations and lung function. If the patient is well-controlled, then the biologic drug would be reduced to determine the minimal dose required to achieve good control. For drugs that are supplied in pre-filled syringes, the dosing interval could be increased. For drugs supplied in different doses, the amount of drug could be reduced. Control would be assessed every 3-6 months and if the patient remains well-controlled, the dose could be further reduced. If not well-controlled, the dose would be increased to the higher dose that had stabilized the patient. Dose reduction, stopping or restarting biologics drugs does not appear to cause adverse consequences.

