

# Journal Pre-proof

So, you've prescribed a biologic. Now what?

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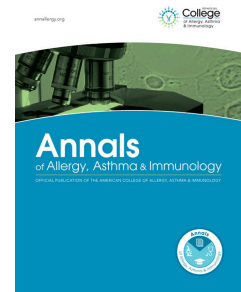
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Title Page

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Abbreviations: GINA: Global Initiative for Asthma, eNO: exhaled nitric oxide; FEV1: forced expiratory volume in 1 second; ICS: inhaled corticosteroid; IL-5: Interleukin 5; EGPA: eosinophilic granulomatosis with polyangiitis; HES: hypereosinophilic syndrome

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1 This is an exciting time in the field of allergy and immunology. The advent of biologic medications has  
2 undoubtedly revolutionized the landscape of asthma management. Many patients previously  
3 condemned to frequent hospitalizations, emergency department visits, and prednisone bursts can now  
4 live with minimal symptomatology. However, the fact that these biologics remain in their infancy poses  
5 several questions beyond eligibility criteria, choice of biologic, and dosing. Questions regarding duration  
6 of use, switching biologics in non-responders, and stepping down therapy have all arisen.

7  
8 While it is gratifying to see patients responding positively to treatment with a biologic, there is little  
9 guidance regarding time to follow up after initiating therapy, frequency of office visits, type of  
10 monitoring to be performed, and deciding on treatment failure. Some aspects of the individual patient's  
11 care should be considered when making these decisions including comorbidities (atopic dermatitis,  
12 chronic urticaria, nasal polyposis), and goals of therapy such as symptoms, exacerbations, and  
13 spirometric values (Table 1). Given that patients are started on a biologic due to insufficient asthma  
14 control, maintaining close follow up is logical. If frequent exacerbations were the main precipitant for  
15 starting a biologic, it may take several months to determine effectiveness. However, if daily  
16 symptomatology, quality of life, or decreasing spirometric values prompted initiation, improvements  
17 may occur within the first few doses (depending on the biologic chosen). GINA guidelines recommend  
18 an initial evaluation in 4 months to assess efficacy.<sup>1</sup> If there is an excellent response, continue the  
19 biologic and follow-up every 3-6 months. If no response, consider a trial of an alternative biologic, if the  
20 patient is eligible. If the response is unclear, consider extending the trial period another 6-12 months. In  
21 this author's experience, a 4-month initial follow-up from the time the prescription is written is ideal.  
22 This allows time for prior authorization processing/insurance approval, and the patient has typically  
23 received 2-3 doses. At follow-up, the patient often has a general idea of whether they feel the  
24 medication is beneficial.

Some biologics have stronger evidence than others regarding improvement in spirometric values, so frequency of monitoring may be based on physician's preference. Dupilumab, for example, has been shown to increase FEV1 within 2-3 weeks.<sup>2</sup> Thus, repeat spirometry may be considered earlier in those using this biologic. Earlier, or more frequent, measurement should certainly be considered if the patient's clinical picture is declining. At a minimum, spirometry should be monitored every 1-2 years per current GINA guidelines.<sup>1</sup> Although useful in determination of patient eligibility and selection of a biologic, there is no consensus as to the utility of monitoring eosinophil levels or exhaled nitric oxide (eNO) during biologic therapy. The degree to which each of these biomarkers is impacted depends greatly on the biologic chosen. Studies show that patients with higher baseline eosinophil counts are more likely to respond to IL-5 targeted therapy, although this is also shown to be predictive of responses to omalizumab and dupilumab.<sup>1-3</sup> Mepolizumab and reslizumab significantly reduce peripheral eosinophil counts.<sup>1</sup> If a patient fails to show benefit, or shows only partial benefit after initiating an IL-5 targeted agent, it may be reasonable to repeat an eosinophil count to determine if they are sufficiently suppressed. In these patients, persistently high eosinophil levels ( $\geq 300\mu\text{l}$ ) may be an indication of treatment failure. In these select cases, a trial of benralizumab, which more completely depletes eosinophils, may be warranted. Indeed, cases have been reported where transitioning from mepolizumab to benralizumab provided added benefit.<sup>4</sup> Alternatively, a trial of dupilumab would also be reasonable in this scenario.

Although indicated for eosinophilic asthma, worsening eosinophilia has been reported in patients after initiating treatment with dupilumab, despite overall improved asthma control.<sup>2</sup> Some experience side effects secondary to eosinophilia,<sup>2</sup> although a causal relationship has not been established. In those that do experience eosinophilia, levels typically return to near baseline even when therapy is continued.

Repeating an eosinophil count would be prudent in patients taking dupilumab who present with new symptoms possibly associated with eosinophilia.

Both dupilumab and omalizumab reduce eNO levels<sup>2,5</sup> while eosinophil targeted agents do not.<sup>6</sup> The utility of following these values after initiating a biologic has not been established. For patients taking dupilumab or omalizumab, lack of clinical improvement paired with a rising or unchanged eNO may be an indication of treatment failure or poor adherence. eNO levels may still be useful for monitoring adherence to ICS use, particularly in patients treated with IL5/IL5R biologics.

Once control has been achieved after starting a biologic, the process of stepping down baseline therapy and even cessation of the biologic may seem unclear. The order of reduction/cessation of treatments should be based on several factors, including observed benefit at initiation, patient risk factors, side-effects, cost, and patient satisfaction.<sup>1</sup> For those patients requiring daily systemic glucocorticoids, careful tapering and elimination, with caution regarding remaining adrenal function, should be paramount. Although only mepolizumab, benralizumab, and dupilumab performed trials specifically dedicated to proving efficacy with oral steroid reduction, the same approach can likely be taken for all biologics. GINA guidelines advise subsequently reducing inhaler therapy every 3-6 months to a minimum baseline treatment of medium dose ICS. De-escalation beyond this becomes tricky, and additional consideration should be given to the aforementioned factors. Patients often ask, "When can I stop my biologic medication?" Definitive duration and timing of biologic discontinuation has yet to be determined. None of the current biologics show convincing evidence of asthma remission or improvements in airway remodeling. Some patients may be able to maintain control with less frequent administration of their biologic medication, which may be more convenient and economical. However, in patients with long histories of uncontrolled asthma with inhaler therapy alone, it is unlikely that

temporary treatment with a biologic will provide a “cure.” Cessation of the biologic will likely result in return of symptoms, exacerbations, and loss of control. Though data is limited, expert consensus suggests that trial discontinuation should not be considered for at least 12 months in biologic responders.<sup>1</sup> Importantly, allergic asthmatics should ensure sustained avoidance of known allergic triggers. Discontinuation should only be attempted if asthma control is excellent and adherence is maintained.

No biologic works for every asthma patient, and unfortunately some patients do not show improvement. Before deciding on treatment failure, the allergist should consider factors that may impact asthma control. These may include local pollen seasons, cold/flu season, and other environmental exposures. For example, patients with allergic asthma who start a biologic during winter months may not be able to assess effectiveness until peak pollen seasons. Careful assessment of all domains of asthma control should be evaluated including exacerbation frequency, spirometric changes, symptom frequency, and quality of life. While many patients have improvements in all categories, improvements in even one category may justify continuation of therapy in certain patients.

Biologics have brought a new world of treatment options to patients. With time and further longitudinal studies, hopefully we will gain more insight into the appropriate duration, evaluation of responder status, stepping down therapy, and biomarker monitoring for each biologic therapy. For now, we rely on our strong foundation of traditional asthma care by assuring trigger avoidance while taking into consideration the patient’s response, side effects, and preferences.

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| Condition           | Biologic Agent |             |            |              |           |
|---------------------|----------------|-------------|------------|--------------|-----------|
|                     | Omalizumab     | Mepolizumab | Reslizumab | Benralizumab | Dupilumab |
| Allergic Asthma     | X              |             |            |              |           |
| Eosinophilic Asthma |                | X           | X          | X            | X         |
| Chronic Urticaria   | X              |             |            |              |           |
| Atopic Dermatitis   |                |             |            |              | X         |
| Nasal polyposis     |                |             |            |              | X         |
| EGPA                |                | X           |            | X            |           |
| HES                 |                | X           | X          | X            |           |

Table 1: Conditions that, if present, may help to decide on the most appropriate biologic medication.  
*EGPA: eosinophilic granulomatosis with polyangiitis; HES: hypereosinophilic syndrome.*