Mass General Brigham

Pamphlet #11: "Biologics" to Treat Asthma

For more than half a century, corticosteroids ("steroids") have been the mainstay of our anti-inflammatory therapy for asthma (and for many other inflammatory conditions elsewhere in the body, such as in joints (e.g., rheumatoid arthritis), skin (e.g., psoriasis), eyes (e.g., uveitis), intestines (e.g., ulcerative colitis), and many others. Steroids treat inflammation with a "broad brush," having effects on many groups of chemicals throughout the body, some of which we understand, some of which are unknown. The result is successful suppression of many types of inflammation, but also, when carried throughout the body via the bloodstream, many undesirable and harmful side effects. Those who have needed to take steroid tablets for any length of time know that they are a "double-edged sword," cutting for both good and bad (see Pamphlet #6: "Steroids in Tablet Form" by the Mass General Brigham Asthma Center).

As for many medicines, steroid use came about as the result of empirical observation. Extract from the adrenal glands of cows was observed to have beneficial effects; the active substance was then purified and chemically synthesized, and this purified derivative became part of our medical armamentarium. Over time, as science advanced, some of the chemical pathways by which steroids exert their effects have been identified.

But what if one could approach the treatment of asthma in a different way? What if with our modern techniques of cell and molecular biology, we could begin by identifying the chemicals that are important in asthma, in particular those that are important in causing the characteristic inflammation of asthma, and then develop medications to block the activity of those chemicals? Presumably, the more targeted our medicines, the fewer the undesirable ("off-target") side effects the medicines will have. Therein lies the remarkable revolution in many fields of modern medicine, including the treatment of severe, persistent asthma, with the widespread use of targeted monoclonal antibodies.

Monoclonal antibodies

One way to create a medicine that is very specific for its target and not broadly active (like steroids) is to make a protein – in particular, an antibody -- shaped specifically for the important molecule that one is trying to block. You may already know from your readings about allergic asthma that the body naturally makes these narrowly directed antibodies against allergens in our environment. These antibodies are very specific: the ones shaped to attach to cat dander allergen will not bind to dust mite allergen, and vice versa. A great advance in medical therapeutics has been the ability to synthesize in the laboratory similarly targeted antibodies.

These manufactured antibodies all share the exact same size and shape; they are made in the laboratory from only one group of antibody-producing cells. Hence, they are "monoclonal." When monoclonal antibodies are administered and distributed throughout the body, they "seek out" and attach to the particular molecules for which they have been designed, blocking them from reacting with other chemicals in the body and thereby inhibiting the biologic processes (in this case, asthmatic inflammation) that they would otherwise cause. Because these medicines are secreted by cells in culture rather than assembled from atoms using chemistry, they are referred to as "biologics."

What Are the Targets for Monoclonal Antibodies in Asthma

Asthma is a complex disease caused by mechanisms that differ among different persons. No single "key asthma molecule" has been identified or is likely to exist. However, for some people with asthma, particularly those who suffer some form of allergic asthma, key molecular targets for monoclonal antibodies have been identified. To date, these are targets that are most important in persons with allergic asthma – asthma characterized either by excess allergy protein (immunoglobulin E, "IgE") or by excess allergy cells (the white blood cells called eosinophils [pronounced ee-oh-SIN-o-fills]), or both. In particular, there now exist monoclonal antibodies that bind to immunoglobulin E protein (regardless of which allergen it has been designed to recognize); to the proteins that signal from one cell to the next, called interleukins (pronounced in-ter-LEW-kins); and to the immune-activating protein made by the lining cells in the airways, thymic stromal lymphopoietin (pronounced LIM-foe-po-EE-it-tin), referred to as TSLP). Among the interleukins, monoclonal antibodies effective in the treatment of asthma target interleukin-5 (referred to as IL-5), interleukin-4 (IL-4), and interleukin-13 (IL-13). Interleukins 4, 5, and 13 and TSLP all play important roles in activating and drawing into the airways the eosinophils that are key to asthmatic inflammation in many people.

So here they are the current monoclonal antibodies used to treat allergic/eosinophilic asthma:

Generic Name	**Brand Name**	**Target**
Omalizumab	*Xolair*®	Immunoglobulin E
Benralizumab	*Fasenra*®	Interleukin 5
Mepolizumab	*Nucala*®	Interleukin 5
Reslizumab	*Cinqair*®	Interleukin 5
Dupilumab	*Dupixent*®	Interleukins 4 and 13
Tezepelumab	*Tezspire*®	TSLP

You can see the naming convention for monoclonal antibodies: they all end in *-mab*. It is very likely that as more key proteins involved in asthmatic inflammation are identified and more monoclonal antibodies are produced to inhibit their action, this list of novel "biologics" for the treatment of asthma will grow longer. There already exist monoclonal antibodies to treat other inflammatory diseases, in which different molecules drive the inflammatory processes,

including the examples of inflammation cited above: rheumatoid arthritis, psoriasis, uveitis, ulcerative colitis, and many others.

Who Might Benefit from These Biologics?

Not everyone with asthma would benefit from -- or find necessary -- treatment with a biologic. The greatest impact of these medicines has been among persons with very severe asthma characterized by recurrent severe attacks that require steroid tablets For most of these drugs, treatment is limited to persons who have excess numbers of eosinophils in the blood or evidence for allergies together with high immunoglobulin E levels In these cases the biologics have proved to be a "game changer." In most instances they have successfully reduced symptoms, reduced the frequency of asthma attacks, and lessened the need for oral or very high-dose inhaled steroids. For those who had been dependent on frequent or even daily steroid tablets to control their asthma, freedom from these oral steroids can feel miraculous.

How Are Biologics Administered?

All but one of the biologics used to treat asthma are administered by injection under the skin. The exception, reslizumab (*Cinqair*®) is given directly into the veins (intravenously). Some are administered every 2 weeks, others every 4 weeks (and one, benralizumab [*Fasenra*®] is given every 8 weeks after the initial 3 months of therapy). Often, for safety's sake, the first dose of medication is given in the doctor's office, and you are asked to wait under medical observation for 30-60 minutes to ensure that you experience no immediate adverse reaction. However, all the biologics used in asthma have been approved for self-administration at home. All those that are given by injection are made available in easy-to-use "auto-injectors," facilitating self-administration in the skin of your abdomen or thigh … or you can enlist the help of family or friends to give the injection.

Side effects

Unpleasant side effects have been relatively few. Depending on which biologic your doctor chooses for you, side effects might include generalized achiness, a slightly increased risk of varicella zoster infection (shingles), an inflammatory conjunctivitis, and very rare anaphylactic-type reactions (with omalizumab, *Xolair*®). The safety of these new medicines during pregnancy and breast feeding is for the most part unknown (with at present the most evidence for safety during pregnancy having been collected for omalizumab, *Xolair*®).

The cost of the biologics is very high, several times greater than the most expensive inhaler for asthma.

On the plus side, several of these biologics designed to treat asthma have been shown to have beneficial effects in other inflammatory conditions, as below. The specific molecules that they are designed to block are active not only in asthma but also in these other, related inflammatory disorders. In choosing a biologic to treat your asthma, your doctor will likely

consider whether you would benefit from any of these other favorable actions of the medication.

Generic Name	Brand Name	Also Approved for Use in:
Omalizumab	*Xolair*®	Food allergies; chronic hives; sinusitis with nasal polyps
Mepolizumab	*Nucala*®	Asthma with allergic vasculitis; sinusitis with nasal polyps
Dupilumab	*Dupixent*®	Eosinophilic esophagitis; eczema; sinusitis with nasal polyps