INTRODUCTION
Chronic rhinosinusitis (CRS) is a condition caused by inflammation in the sinuses. The main treatment for CRS is a group of medications called steroids, which reduce inflammation. These medicines can be delivered directly into the nose by sprays or rinses, or taken by mouth (oral). While these medications are helpful in controlling the symptoms of CRS, they do have side effects. Oral steroids, in particular, may cause undesirable and sometimes dangerous complications. Physicians and researchers are working to develop ways to manage CRS with less potential treatment side effects.

Biologic therapies (biologics) are medications that target specific cells or inflammatory pathways associated with a disease. Because they have specific targets, biologics are thought to have less side effects. For this same reason, biologics may also potentially be more effective than steroids. These medications have already been investigated in the treatment of other inflammatory diseases. For example, biologics have been remarkably effective at controlling inflammation in asthma. These medications are currently undergoing clinical trials to determine their safety and efficacy in the treatment of CRS.

In this section we will discuss the biologic therapies that are under investigation for use in CRS. Here we will also provide some background on how they work.

INFLAMMATION IN CHRONIC RHINOSINUSITIS
There are two different types of inflammation involved in CRS. One type causes CRS without nasal polyps (CRSsNP) and the other causes CRS with nasal polyps (CRSwNP). Currently, the only biologics being investigated for CRS target the type that causes polyps.

CRSwNP inflammation is caused by a type of white blood cell called a type 2 T-helper cell (Th2 cell). Once triggered, these cells elevate levels of signaling proteins called interleukins (IL). These signaling proteins help white blood cells communicate. When elevated, interleukins signal the body to increase inflammation. There are a number of interleukins in CRSwNP and Th2 type inflammation. Interleukins IL-4, IL-5, IL-10, IL-13 are elevated. As the inflammatory process continues, these signaling molecules activate another type of white blood cell called eosinophils. These white blood cells are the end result of Th2 type inflammation. Eosinophils are also found in asthma and allergic reactions. Eosinophils interact with another signaling molecule called immunoglobulin E (IgE). IgE is elevated in patients with nasal polyps and allergies.

In CRSwNP, three of the signaling molecules have been targeted for biologic therapies. These include IL-5, IL-4, and IgE. The medications being investigated for these will be discussed below.
ANTI-INTERLEUKIN-5 (IL-5) THERAPY
IL-5 is one of the signaling molecules seen in CRSwNP type inflammation. IL-5 is often elevated in patients with nasal polyps. This molecule activates eosinophils, the white blood cells involved in the Th2 type of inflammation pathway. By reducing the amount of IL-5, these white blood cells may not be activated. This, in turn, would stop or reduce the inflammation seen in the sinuses. Medications that have been developed that target IL-5 include reslizumab and mepolizumab. Benralizumab is a similar medication which targets the IL-5 receptor. These medicines are antibodies that block the effects of IL-5. Once in the body, they find and attach to their target and deactivate it.

These medications are currently undergoing clinical trials (phase 3). The trials will determine the safety and efficacy of the medications in patients with CRSwNP. Thus far, these biologics have been examined in small trials (24 to 30 patients) over short durations (4 weeks). They were found to decrease the size of polyps seen in the nasal cavity. However, they did not improve patients’ symptoms. These results have encouraged researchers to look further at the medications. Trials are being performed in larger groups and for longer treatment durations. As the results become available, they will help physicians decide if these medications should be used in CRSwNP.

ANTI-INTERLEUKIN-4 (IL-4) AND (IL-13) THERAPY
IL-4 and IL-13 are other molecules being targeted in CRSwNP. IL-4 and IL-13 may play an important role in the activation of cells to form polyps in the nasal cavity. The medication that has been developed to target IL-4 is also an antibody. This antibody finds the receptor IL-4 attaches to in order to deliver its signal and block it. Blocking this receptor stops IL-13 from delivering its inflammatory message as well.

Dupilumab is an IL-4 receptor antibody. It was originally developed for use in patients with atopic dermatitis. Atopic dermatitis is an allergic-like inflammation of the skin. After dupilumab was approved for use in atopic dermatitis, a study examined its effects in CRSwNP. This study looked at 60 patients for 16 weeks to examine the effects of the medication. The researchers found both a reduction in polyp size and patient symptoms. This is currently the only biologic therapy that has been shown to do both. Dupilumab is currently in Phase 3 clinical trials.

ANTI-IGE THERAPY
IgE is an immunoglobulin that is found in elevated levels in patients with CRSwNP. It is not clear what exactly IgE does in CRSwNP. However, when IgE levels are elevated, so are eosinophils. Anti-IgE therapies have been shown to be useful in other diseases with increased eosinophils, like asthma.

Omalizumab is an antibody, which binds to IgE and deactivates it. Two studies have examined the effects of omalizumab in CRSwNP. These were both small trials (14 and 24 patients) over 16-24 weeks. Both of these studies noted an improvement in sinus inflammation on computed tomography scans (CT). One of these studies also found a reduction in polyp size. However, neither study saw improvements in patient symptoms. Phase 3 trials are currently ongoing for omalizumab as well.

BENEFITS OF BIOLOGIC THERAPIES
Although in the early phases of development and investigation, these therapies have shown promising results. Biologics offer the potential to reduce inflammation in CRSwNP without the
need for oral steroid treatment. Early evidence suggests that patients on omalizumab have reduced steroid requirements compared to before therapy. If biologic therapies can control the inflammation, patients may need less sinus surgery as well. These potential benefits could change the way patients with CRSwNP are treated.

RISKS OF BIOLOGIC THERAPIES
While serious complications are less than 1%, biologic therapies are not without risk. Patients receiving these medications can develop allergic reactions, including anaphylaxis. Anaphylaxis can be life threatening. Reactions at the injection site are also common (10-45%) but are temporary. Such reactions usually resolve within days. Headaches are the next most common side effect, affecting 6-19% of patients. Other reactions are less common. Dupilumab has been associated with conjunctivitis (inflammation of the eye) in 10% of patients. Reactivation of the herpes virus has occurred in 2-4% of patients. Omalizumab carries an increased risk of heart complications. Heart attacks (3%) and blood clots in the legs or the lungs (3%) may occur. Increased rates of respiratory tract infections (common cold or flu) may occur less commonly.

Initially there concern that omalizumab could increase the risk of cancer developing. Subsequent research in asthma patients over 9 years has shown there is no increased risk of cancer with omalizumab therapy compared to the general population.

SUMMARY
Biologic therapies are medications that target specific cells or inflammatory pathways within CRS. These medications are still under investigation, but show promise as a potential therapy for CRSwNP. Advanced clinical trials are currently underway for four biologic therapies. However, additional study of the risks and benefits is required before they can be recommended for routine use. In summary, biologics may be a useful and safe alternative to current therapies.