Allergy in the Management of Chronic Rhinosinusitis

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May 2016

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Association of Allergy and CRS

- It remains controversial how allergy and chronic rhinosinusitis (CRS) are connected.
- A multitude of studies over the years have implicated allergy with CRS. Roughly speaking, the prevalence of allergy in the general population is about 30%. The prevalence of allergy in patients with CRS is closer to 40%.

Allergy and Immunology - an Otolaryngic Approach, 2002
Association of Allergy and CRS

- Not all CRS patients have allergy!!!
- Patients with allergy and CRS have a poorer outcome if the allergy component is not addressed.
- Patients that have allergy and CRS undergoing sinus surgery have increased surgical failure rates when allergy is not addressed

Allergy and Immunology - an Otolaryngic Approach, 2002
Management of Allergy

• 3 tiers of management exist for allergy
  • Avoidance strategies
  • Medical/pharmacological management
  • Immunotherapy
Immunology (BRIEF!)

Classic allergy is an IgE mediated process which may be tested (in vitro or in vivo).

T helper lymphocytes - TH1 cells promote response to bacteria, while TH2 cells promote a more “allergic” response.

Allergy in ENT Practice, 2005
Immunology continued

• Immunotherapy attempts to promote a TH1 environment and downregulate a TH2 environment, along with all of the associated inflammatory mediators.

• These inflammatory pathways/mediators are the targets for current drug therapies under investigation and will be discussed later in this lecture.
Immunotherapy targets the TH1/TH2 balance, tipping the scale in favor of TH1 and downregulating the associated TH2 inflammatory mediators.
Immunotherapy

• Approximately 80% of patients respond favorably to immunotherapy
  • Less symptoms of rhinorrhea, congestion, itchy eyes, etc.
  • Allergy/CRS patients that are on immunotherapy have better surgical outcomes
CRS with Nasal Polyps

• Classically, polyp disease was thought to be a more TH2 mediated disease that would respond favorably to immunotherapy
• Countless studies have been done showing both CRS with and without polyps may demonstrate TH2 mediated disease
• Allergy testing can be valuable in polyp patients, especially when history suggests allergy
  • I look at immunotherapy as a tool to use along with ESS and topical steroids in patients with positive allergy testing
Nasal Polyps and Endotypes

- CRS with and without nasal polyps - may need to further differentiate - possibly into several additional endotypes
- What about Aspirin Exacerbated Respiratory Disease (AERD)?
- Allergic fungal sinusitis?
- CRS with nasal polyps - eosinophils?
Polyps and Eosinophils

- What about eosinophils?
  - Often associated with polyps
  - Presence of eosinophils can indicate TH2 pathway
  - Associated with increased levels of IL-4, IL-5, and IL-13
  - Revision surgery required more often in these patients
  - Presence of allergy in these patients also increases risk of recurrence after surgery
  - May respond favorably to immunotherapy
Allergic Fungal Sinusitis

- Controversial as to the association of allergic fungal sinusitis and allergy
- At one point immunotherapy was thought to be contraindicated (make fungal sinusitis recur/worsen)
- More recent research has shown immunotherapy may actually be beneficial
- May be related to a “local” allergy response vs. systemic
Allergic Fungal Sinusitis

- Along with aggressive sinus surgery and topical corticosteroids, I look at immunotherapy as another potential tool to use to treat this difficult sinus disease
Aspirin Exacerbated Respiratory Disease (AERD)

- The classic triad of chronic rhinosinusitis, bronchial asthma, and aspirin intolerance
- Also known as Widal syndrome and Samter triad
- Not a TH2/IgE mediated disease, but does involve eosinophils
- Does not directly respond to immunotherapy
- Can be very difficult to treat with polyp recurrence and frequent asthma exacerbations
Aspirin Exacerbated Respiratory Disease

• Disease mechanism is fairly well understood
  • Prostaglandin E2 usually inhibits leukotriene production - AERD patient lack this inhibition
  • AERD patients have increased gene expression of 5-lipoxygenase and leukotriene C4 synthase which results in increased mast cell and eosinophil expression
  • Aspirin, NSAIDS, and possibly salicylates in the diet can exacerbate the disease
Aspirin Exacerbated Respiratory Disease

• What about aspirin desensitization?
• Seems to help keep symptoms controlled, but difficult to maintain regimen
• Desensitization must be performed in supervised setting with ability to treat anaphylaxis available
• Must maintain daily dose of aspirin indefinitely. If patient misses even one dose, must go through desensitization again
• 30% of patients can not tolerate side effects
Aspirin Exacerbated Respiratory Disease

- Aspirin desensitization does not reduce polyp size - only helps maintain size or prevent enlargement
- Allergy immunotherapy has no direct impact on this disease, however, if concomitant allergy there may still be some improvement in patient symptoms and quality of life
• From Wikipedia: Monoclonal antibodies (mAb or moAb) are monospecific antibodies that are made by identical immune cells that are all clones of a unique parent cell, in contrast to polyclonal antibodies which are made from several different immune cells. Monoclonal antibodies have monovalent affinity, in that they bind to the same epitope.
On the Horizon - Biologics

- The general idea is to target a specific area of the immune system to alter immune function.
- In our field, the goal would be to decrease the inflammatory effects of the target leading to a decrease in sinus/respiratory symptoms.
Omalizumab

- Omalizumab is a humanized monoclonal antibody that targets free IgE.
- Currently approved in the US and Europe for severe allergic asthma
- Could theoretically improve disease burden/symptoms of CRS/polyp patients that exhibit a TH2/IgE form of the disease
Omalizumab

- A randomized, double blind, placebo controlled study was performed on patients with CRS/polyp patients that also had asthma.
  - Some with and some without allergic rhinitis
  - CT findings, nasal symptoms, sense of smell, and asthma all improved
  - Another study showed much less positive findings but included patients that did not have polyps
Omalizumab

- Due to the process of FDA approval and cost, it now appears unlikely that omalizumab will get the indication for CRS/polyps
- Could be used off label but is an expensive treatment (12,000$ per year?)
Reslizumab and Mepolizumab

- A monoclonal antibody that targets IL-5
- As stated earlier, IL-5 is one of the cytokines associated with TH2 and eosinophils
- Because of this IL-5 would theoretically make a good target to improve TH2 associated CRS/polyps
A study using mepolizumab was conducted with 30 patients with severe nasal polyposis refractory to topical steroids and surgery.

- 60% of patients showed a significant reduction in polyp size at 16 weeks.
- The positive responders showed continued benefit out to nearly one year from the treatment.
Dupilumab

- An anti IL-4/IL-13 monoclonal antibody
- IL-4/IL-13 share an α subunit which dupilumab targets
- 60 patients in a double blind, placebo controlled study were enrolled
  - The treatment group showed significant improvement in CT findings, Sino-Nasal Outcome Test, and University of Pennsylvania Smell Identification Test
What does it mean?

• Some of these drugs will likely get approved and make it to market. It remains to be seen whether they will be approved for CRS/polyps or just asthma

• They are going to be costly but may be a viable treatment option in the severe, recalcitrant polyp patient
Future Problems

- It seems that we currently lack viable and cost effective ways to differentiate accurately between the various endotypes for CRS, other than total IgE and specific IgE testing
- This is probably going to change as more biologics/targeted treatments become available
Final Thoughts

• Not all CRS with/without polyps is associated with allergy
• When allergy is present, immunotherapy is a valuable tool
• Just because a patient seems to fit into a type of CRS known to have no TH2 association does not mean they would not benefit from immunotherapy (history, history, history, history)
References

• Allergy in ENT Practice. King HC, et. Al 2005
• Allergy and Immunology - an Otolaryngic Approach. Krouse JH, et. Al.  2002