Update on the Treatment of Allergic Rhinitis

Fuad Baroody (author) and Tania Sih (edited)

The goal of this chapter is updating on allergic rhinitis in children. we will show you some data that we have generated in adults, because it is just easier to do studies in adults, and some of the data applies to children also.

So let us introduce you practical aspects in allergic rhinitis in children. If you look at North America, some 40 million Americans are affected by allergic rhinitis[1] and the prevalence is estimated to be 10% to 30% in adults[1] and up to 40% in children[1]. So it is one of the most common chronic conditions in childhood.

There has been recently a substantial increase in the prevalence of allergic rhinitis in the developed countries for a variety of reasons, including things like the hygiene hypothesis, deregulation of the immune system that we will not discuss[1-3].

There is a very nice study that was published not too long ago, looking at quality of life data, targeted at children, published by Meltzer [4], who is a very prolific researcher in allergic rhinitis[4]. This was a national telephone screen of 35,000 US households. Identified children between 4 and 17 years of age. They talked to the parents of the kids when they were younger, and to the kids themselves and the parents when they were older.

They had two groups: a group with allergic rhinitis and a group of control without nasal allergies. And then they showed different effects on quality of life in these two populations. They looked at family practitioners diagnosed allergies, allergists, otolaryngologists, etc. and they had a variety of other healthcare worker input, which I will not go over with in detail.

It is important to mention that most environmental allergies do not start showing up until the age of 2+. And at under 3 and there is not a whole lot of prevalence of age at diagnosis, but the majority is diagnosed between 3 and 6 years of age, and they continue to be diagnosed as they get older (**Figure 1**).

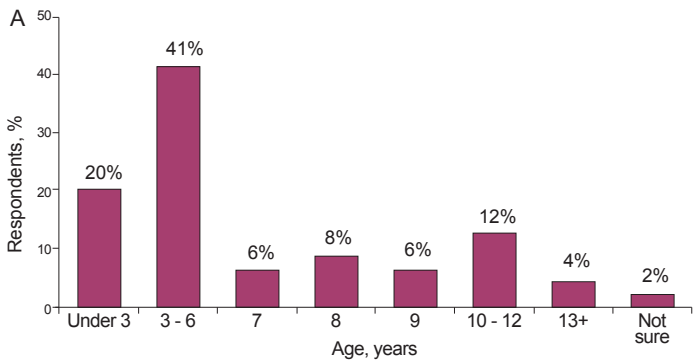
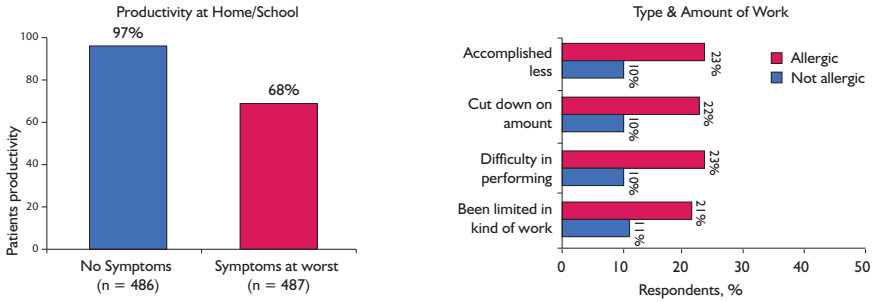


Figure 1. Allergic rhinitis age of presentation

Now looking at how allergic rhinitis affects quality of life, like in sinusitis that also affects qualify of life, infection problems also affect quality of life and allergic rhinitis does too. This is parental perception of productivity at home or school in patients with symptoms and when they have no symptoms at their worse, and that there is about a 30% decrease in the children's productivity.

When you also look at the type and the amount of work that these children do (**Figure 2**), and if you then compare allergic children in red to the non-allergic children in blue, they accomplish less, they cut down on the amount that they can do, they have difficulty in performing their tasks and they are limited in different activities in school and otherwise, but mostly at school. So this is a significant burden on the children, just because their nose is obstructed and they have a runny nose, and it is a problematic issue.



Figures 2 A and B. A-Productivity at home and school. B-Type and amount of work

Let's briefly review the pathophysiology, which will be relevant in discussing the different treatment options (**Figure 3**). In a sensitized child with allergic rhinitis, specific IgE antibodies sit on the mast cell, and when you are exposed to an antigen that you are allergic to, it leads to crosslinking of the IgE receptor, and in the acute stage leads to the release of histamine and multiple other mediators. This leads to the acute symptoms of the early phase reaction. So these children sneeze, have a runny nose, are congested and also have itching. Remember that this is often referred as rhino-conjunctivitis, it is not just rhinitis.

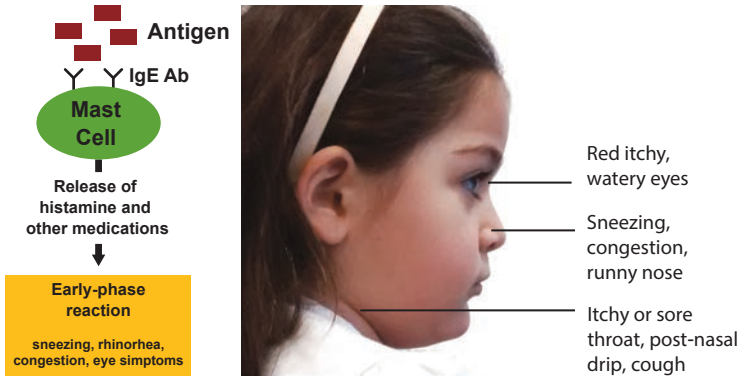


Figure 3.Early phase reaction in a sensitize child with allergic rhinitis

More importantly, if you continue to follow these kids, or you look at kids with repeated exposure during the allergy season, you will see that there is what we call a late-phase reaction or a chronic inflammatory infiltrate of the nasal mucosa, the hallmark of which is the eosinophil (**Figure 4**). Other studies have shown that there is a predominance of TH2-type cells in this inflammatory influx. And the TH2-type cells typically produce IL4, IL5 and IL13, and IL5 keeps the eosinophils happy and the IL4 and IL13 have significant roles in the IgE switching of plasma cells to the production of specific IgE.

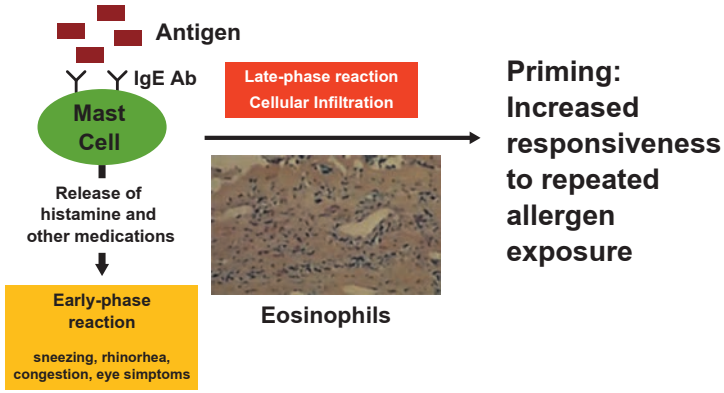


Figure 4. Late phase reaction in allergic rhinitis

The state of chronic inflammation is very important and leads to heightened responsiveness of the nasal mucosa. So these patients are increasingly more responsive to repeated allergen exposure during the season, and even to exposure to non-specific stimuli. For example, you will see that children and adults in allergy season are much more responsive, for example, to cigarette smoke, or to polluters, or to strong odors, or to perfumes. And that state of heightened activity of the nasal mucosa is related primarily to the chronic inflammation.

Now, what is the clinical picture like? These kids often have telling signs, one of them is the allergic salute, where they keep sniffing their nose and they get a small supra tip creek (**Figure 5**). Then many of them have significant nasal obstruction and they get venous congestion under the eyes, otherwise known as allergic shiners.

If you look at the typical symptoms that seem to bother patients, and this is again from that survey of families, and these are symptoms that are bothering them every day or most days. You see that nasal congestion is a very, very prominent nasal symptom. Unfortunately, it is a symptom that is harder to control with medical therapy. Now, you also see sneezing, running nose, watery eyes, postnatal drip, itchy eyes, nasal itch and less frequently other things. So these kids have significant symptoms.

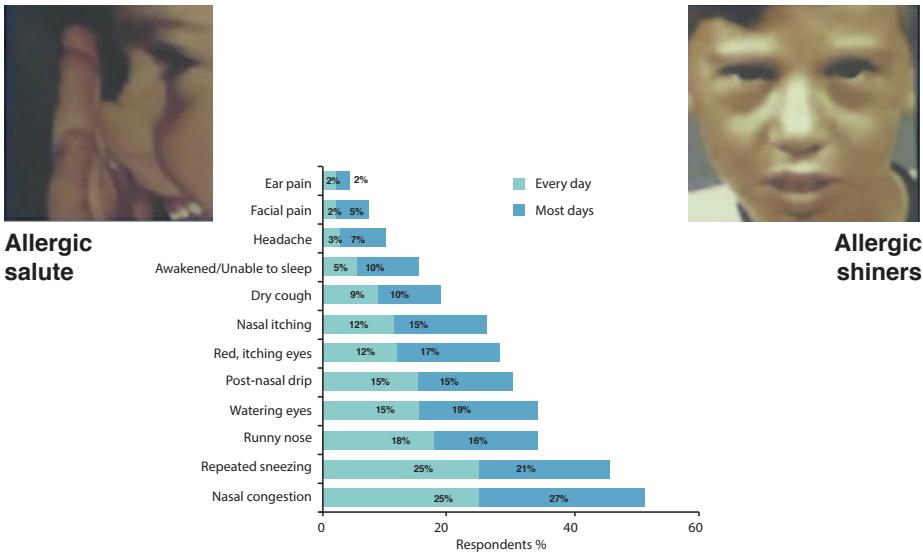


Figure 5. Allergic salute, allergic shiners and typical allergic symptoms

Now, how do we classify allergic rhinitis? Many of you might know the ARIA classification[5]: allergic rhinitis and its impacts on asthma, spearheaded in Europe by John Bousquet and his colleagues that set the guidelines[5].

ARIA also mentions intermittent symptoms. In the US we refer to them as seasonal allergy or seasonal allergic rhinitis. And also persistent symptoms which mean year-round. So where I (author FB) come from (Chicago), we have trees, grasses and outdoor pollen in the spring, we have ragweeds in the fall and then we have indoor molds, dust mites and pets for the patients who have pets in their homes, that lead to year-round symptoms.

How do we diagnose these patients? Skin tests and RAST testing are reasonably equivalent. Many people suggest that skin testing is a little more sensitive, it gives you a quick result. You have to make sure that your patients when they come for a skin test are not on antihistamines, some for longer times than others. There is a very, very small risk of a systemic reaction and some kids do not like to get multiple pricks.

Most allergists do a prick test (**Figure 6**), it is not an intra-dermal test, necessarily, you do intra-dermal only if you are very suspicious of an allergen, and the prick test is negative. It cannot be performed on patients with atopic dermatitis, or dermatographism because their skin is very sensitive.

RAST testing takes a little longer. It's one stick, you draw blood one time, and its gives you specific IgE levels to a variety of allergies. It takes about ten days for the result in our facility. Most we see are very amendable to this a little bit more than that (skin testing).

In a survey, many people were diagnosed by history and did not have these tests. But among the other half, almost half were skin tests and a smaller proportion was blood test only.

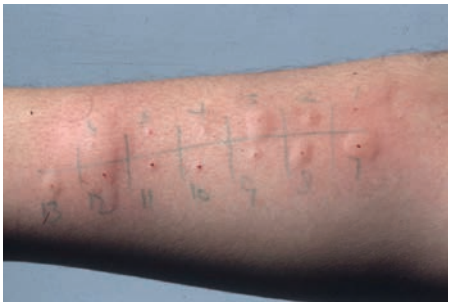


Figure 6. Skin prick test

If we look at comorbidities (**Table 1**), like in sinusitis there is a lot of data suggesting that allergic patients have systemic inflammation, so it is an allergic predisposition that not only affects the nose but also affects the lungs and leads to asthma. If you look at comorbidities in these patients, you will see that the patients with allergic rhinitis compared to the patients with no allergic rhinitis had, for example 2.8 (headaches), 7.0 (face pressure) and 4.9 times more ear pressure, there were more likely to have tubes placed, they were a little bit more likely to have tonsils and/or adenoids removed, they were much more likely to have sinus problems. And many of them snored.

Table 1. Allergic rhinitis comorbidities

	Patients or parents (%)		
	AR	No AR	Fold difference
Pain or pressure			
Headache *	54	19	2.8
Face *	28	4	7.0
Ear *	24	5	4.9
Surgery			
Tube placed †	16	9	1.8
Tonsils and/or adenoids removed ‡	18	11	1.6
Sinus problems*	43	4	10.8
Snoring*			
Every day	14	5	2.8
Most days	10	4	2.5

*$P < .001$. †$P < .05$. ‡$P < .01$.

As far as asthma (**Table 2**)[6], again, comparing patients with documentation of asthma, allergic rhinitis vs non allergic rhinitis, the allergic rhinitis were three times more likely to have a diagnosis of asthma and four times as likely to have had asthma in the past twelve months. Again, important comorbidities, there is actually some data in adults that suggests that if you treat the nose, you improve the reactivity of the lower airway and that treatment, typically, is done with steroids.

Table 2. Comorbidity of allergic rhinitis and asthma

	Patients or parents (%)		
	AR	No AR	Fold difference
Asthma diagnosis*	39	13	3
Asthma in last 12 mo*	28	7	4

*$p < .001$

What are our treatment strategies? Clearly, if you could avoid all allergens you would be fine. But we also know in practicality that this is really not feasible. So we move to pharmacotherapy, and we will discuss briefly some of these treatments, including antihistamines, decongestants, receptor antagonists, anticholinergics. We will not discuss cromoline, as cromoline is mildly effective. It is very safe but compliance is a problem because you have to give the drug about 3 to 4 times a day, and it's a nasal spray. And finally, intranasal steroids. We will touch on immunotherapy briefly and we will discuss combination treatments.

So let's talk about antihistamines. We have two options for antihistamines: we have systemic and intranasal. And the systemic includes the sedating and the non-sedating. In children the preference is to use the non-sedating antihistamines and we will show you why in a second. We also have the option of using infranasal antihistamines which seem to be slightly more effective than their systemic counterparts. We will present you data to support that.

A lot of the studies in the United States are made in environmental chambers, where you put a large number of people, you expose them to the allergen and you test different therapeutic entities.

In this study (**Figure 7**)[7], specifically, they tested levocetirizine, desloratadine and placebo. And they had two consecutive days and gave them the pills, and they sat in the chamber and were exposed. There is a reduction from baseline is what is marked on the Y access, so up is better, and you will see that everybody gets a little bit better when they get placebo. There is a strong placebo effect in the allergic rhinitis trials, but the people on desloratadine in yellow and levocetirizine in the Xs do better, and levocetirizine is a little bit better than desloratadine.

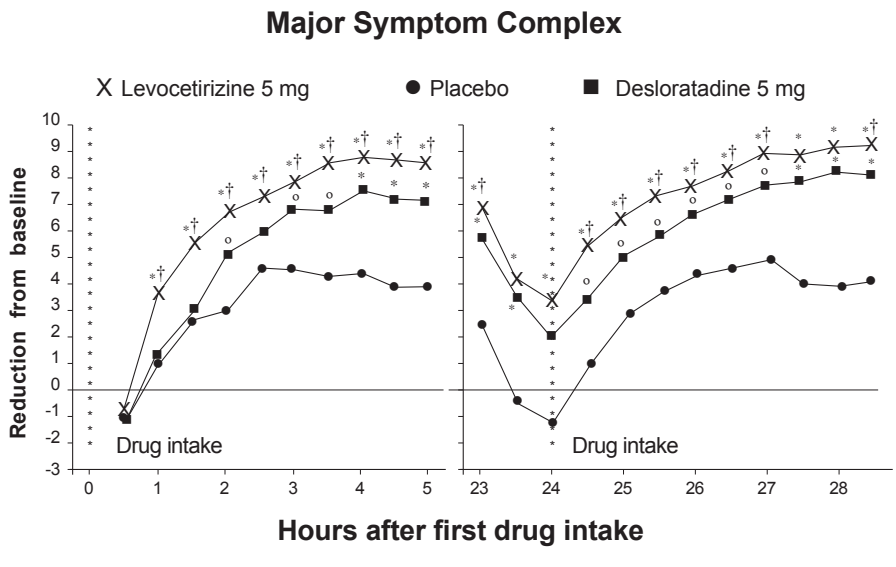


Figure 7. Reduction of major symptom complex comparing placebo, levocetirizine and desloratadine[7]

When you bring them in the second day, their symptoms are starting to happen again, remember, lower is worst, but you give them a drug again and again they benefit from the placebo but more benefit from the antihistamines. There are many, many studies like that and there are also many seasonal studies that suggest the efficacy of antihistamines and we use them routinely.

Now, why not to use sedating antihistamines? There is a very good example of why not. There is a study (**Figure 8**)[8] looking at performance in kids, the learning score on the Y-axis, and these were normal children; children with allergic rhinitis on loratadine, a non-sedating antihistamine; children with allergic rhinitis on placebo, and then children with allergic rhinitis on diphenhydramine or Benadryl. This is a very potent antihistamine and it also has additional anti-cholinergic properties, so it actually dries the nose up. Unfortunately, it also affects your performance.

So, look at a few points. First of all, normal children do best, children with allergic rhinitis not treated, have impaired learning score. If you treat them with loratadine they improve a little bit, but they don't get as good as the normal children, but they get worst when you treat them with diphenhydramine (Benadryl). So, this is caution for kids who go to school not to treat them with a sedating antihistamine and to resort, preferentially, to the non-sedating.

There is also some data that suggests that even if your give diphenhydramine at night you might have some lingering sedative effects the next day. So, it is important to be careful with that, as long as it does not affect your patient.

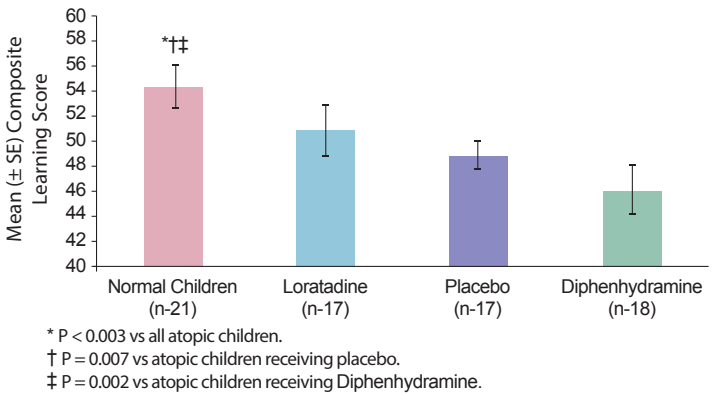


Figure 8. Learning score in children with allergic rhinitis receiving loratadine, placebo and diphenhydramine[8]

There is a study (**Figure 9**)[9] a comparison between a systemic antihistamine and a topical antihistamine, azelastine. Azelastine is marketed in the United States as a topical medicine and cetirizine is marketed as a systemic, and you will see in this study for itchy nose equal benefits, nasal congestion, the intra-nasal does a little bit better than the systemic, the same for sneezing. The stars indicate statistical significance. So, it's a little added efficacy, it is perceived that the intra-nasal do a little bit better than the systemic antihistamines.

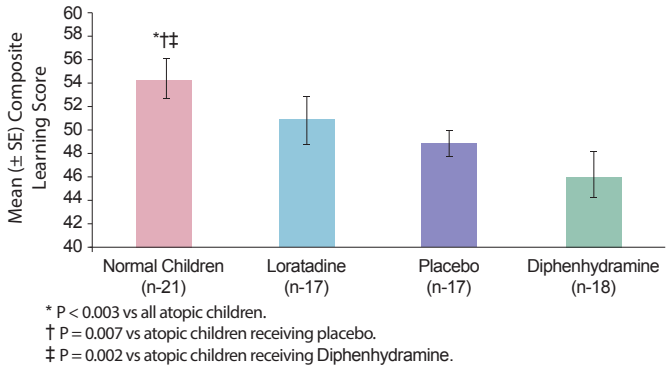


Figure 9. Comparison between a systemic antihistamine (cetirizine) and a topical antihistamine, azelastine (Az)[9]

There is another antihistamine that is available in the United States, it is called Olapatadine. Looking in another study (**Figure 10**)[6], on changes in total nasal symptoms causes. Lower, it is better, they all start at the same baseline. You will see again a little bit of improvement with placebo and better improvement on two separate doses of 0.6% and 0.4%. The 0.6% is what it is marketed at in the United States, it is called Pataday and is available as an intra-nasal spray.

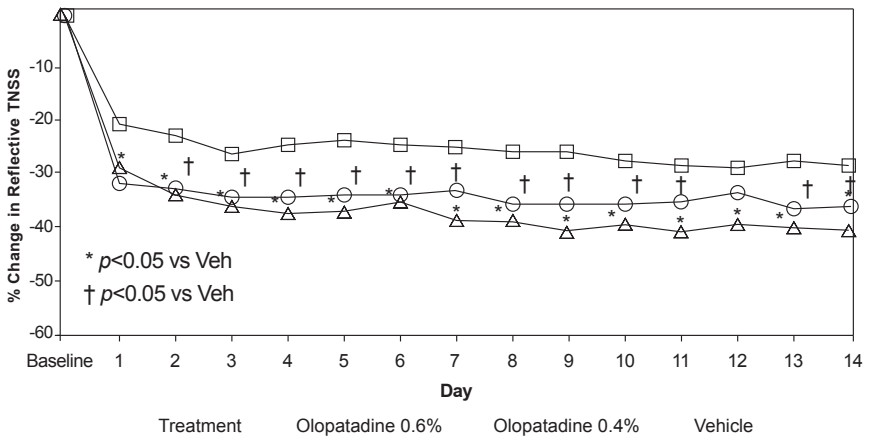


Figure 10. Nasal symptoms treated with olopatadine 0.6%, olopatidine 0.4% and placebo[6]

One small problem with these intra-nasal antihistamines is that as Azelastine has about 20% incidence of bitter taste compared with the vehicle, so children might not like that very much, and Olapatadine is a little bit better but still has a 12.6 incidence of bitter taste vs placebo which only has 0.8%. So a word of caution: some children might not like these when they are sprayed in the nose.

Let's move to Leukotriene receptor antagonist, the most common and most widely used in the United States is Montelukast, otherwise known as Singulair. This is based on the fact that this is lipid metabolism, this is arachidonic acid it is metabolized through the 5LO pathway and goes to Leukotriene C4-A4-B4 (**Figure 11 A, B**). The C4 seems to be important in allergic rhinitis, there is data that shows that they are released after the nasal allergic reaction and that if you come and put LTC4 in the nose it leads to significant nasal congestion. This is the development of a Leukotriene receptor antagonist, that's what Montelukast is.

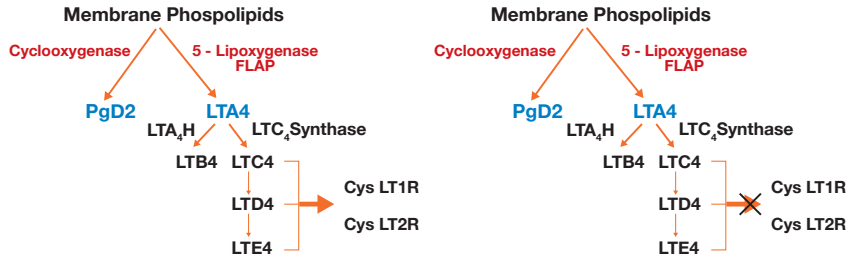


Figure 11 A, B. Phospolipids metabolism

We will mention an example of a study that led actually to the approval of this drug in the United States for the treatment of allergic rhinitis. This is a study[10] where they looked at placebo, Montelukast and Loratadine. This is an adult study (**Figure 12**). Montelukast was given at 10mg per day and what you see is, you always see some improvement in placebo and these are all the nasal symptoms. This is broken down into congestion, rhinorrhea, itching and sneezing. You see equivalent improvement in Montelukast and Loratadine, which study after study has shown the same. The Leukotriene antagonist and the systemic antihistamines have shown the same. The Leukotriene antagonist and the systemic antihistamines have almost equal efficacy.

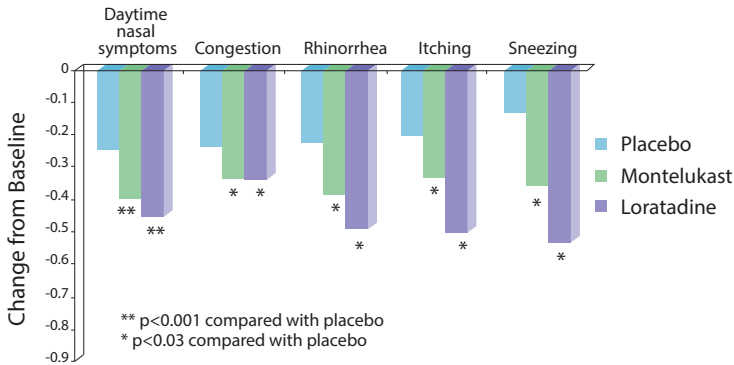


Figure 12. A study where it was looked at placebo, Montelukast and Loratadine for the treatment of allergic rhinitis.[10]

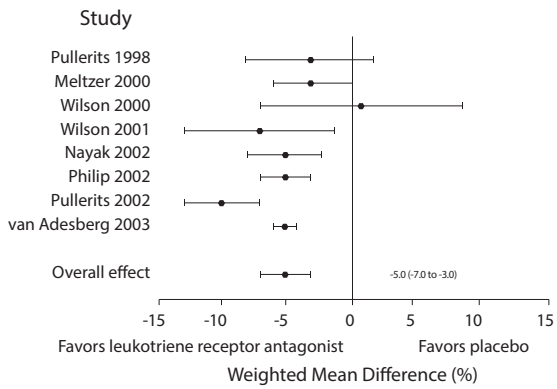


Figure 13. Comparison of leukotriene receptor antagonist and placebo. The plot of weighted mean difference with 95% confidence intervals for composite rhinitis symptom scores is expressed as a percentage of the maximum score. There was significant variation in results among studies (P=0.001 for heterogeneity).[11]

If you look at meta-analyses, this is a meta-analysis looking at the Leukotriene receptor antagonist, multiple studies[11] comparing them to placebo and it always favors the drugs (**Figure 13)**. So they are effective. When you do a meta-analysis comparing the Leukotriene receptor antagonist to the antihistamines (**Figure 14**), most of the studies favor the antihistamines, but the difference is not specifically significant, but just showing that they are, essentially, equivalent products as far as efficacy is concerned.

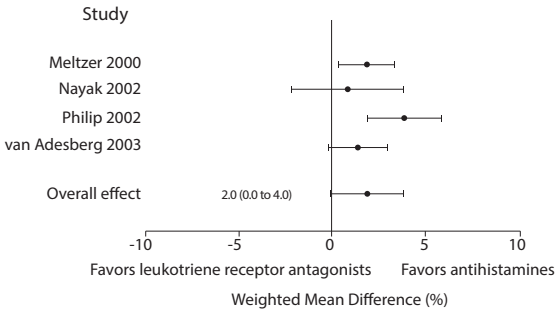


Figure 14. Comparison of leukotriene receptor antagonist and antihistamines, The plot of weighted mean difference with 95% confidence intervals for composite rhinitis symptom score is expressed as percentage of the maximum score. The results did not vary among the studies (P = 0.13 for heterogeneity). There was no significant difference between leukotriene receptor antagonists and antihistamines. [11]

Now let's move to anticholinergics. One word about anticholinergics, the only one that is marketed in the United States is called Ipratropium bromide, otherwise known as Atravine. It is a mono-symptomatic treatment or nasal rhinorrhea, it does not help congestion, it does not help sneezing. If you have the occasional patient with allergic rhinitis where despite your best efforts at therapy the nose continues to run significantly, a surgeon in the operating room might have a problem with that. Then you can use Atravine and it is marketed in two concentrations: one for colds and one for allergic rhinitis. And you see, in this study (**Figure 15**)[12] compared to placebo, Leudokrine decreases the duration of rhinorrhea and the severity. So it is very effective. And you can titre it to needs between one and three titres a day. But it only works for a runny nose, it cannot be used as a sole treatement for allergic rhinitis.

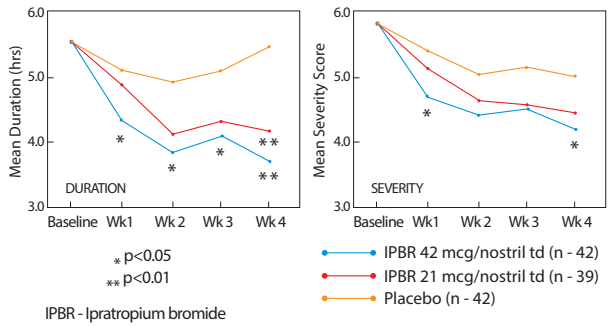
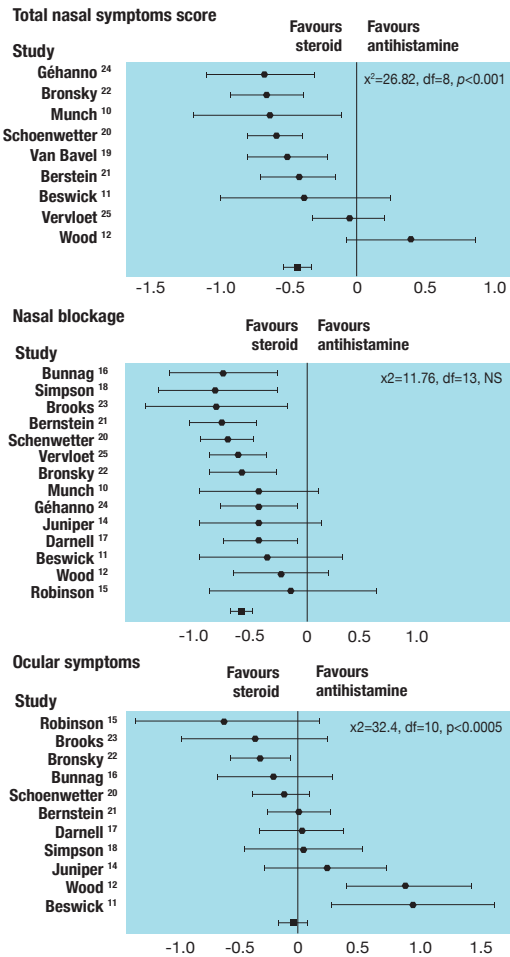


Figure 15. Ipratropium bromide (marketed in two concentrations) compared to placebo[12]



Figures 16 A, B, C. Meta-analyses studies comparing antihistamines to intra-nasal steroids for total nasal symptoms and ocular symptoms.[13]

Let's move to what we think is the most effective modality of treatment of allergic rhinitis: intranasal steroids. We will show you meta-analyses comparing antihistamines to intra-nasal steroids (**Figures 16 A, B, C**). In every study[13] when you look at total nasal symptoms except one, and this is the overall effect, the intra-nasal steroids work better than the antihistamines for total nasal symptoms. They work much better in every study compared to the antihistamines for nasal blockage, and even for eye symptoms, almost half the studies show an effect of intra-nasal steroids in helping eye symptoms almost equivalent, if not better, than the effect of antihistamines. We have actually shown that the eye symptoms are generated by a nasal ocular reflex, and that by giving the intranasal steroid in the nose affects the symptoms by blocking the reflex, without getting into the eye or generating any problem with the eye as far as this is concerned.

If you look at the leukotriene receptor antagonist, again, there is no surprise. Comparing Leukotriene receptor antagonist with nasal corticosteroids, all the studies

show in favor of nasal corticosteroids (**Figure 17**)[14]. So clearly, intra-nasal corticosteroids are more effective than systemic antihistamines or Leukotriene receptor antagonists.

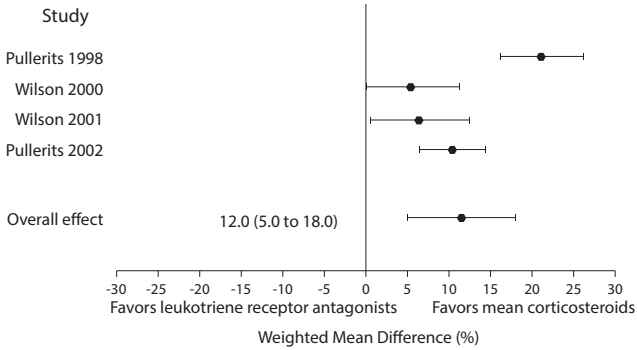


Figure 17. Comparison of leukotriene receptor antagonist and nasal corticosteroids. The plot of weighted mean difference with 95% confidence interval for composite rhinitis symptom scores is expressed as percentage of the maximum score. There was significant variation in results among studies ($P = 0.0002$ for heterogeneity).[14]

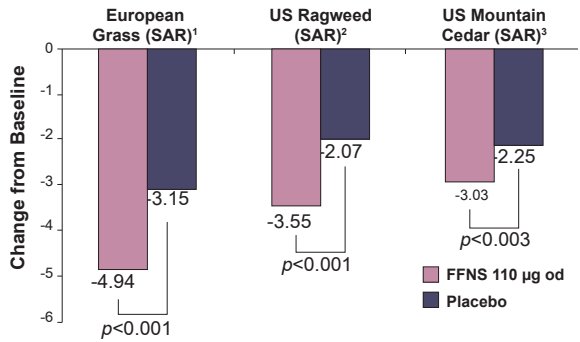


Figure 18. The efficacy of fluticasone fuorate nasal spray in total nasal symptom score compared to placebo in 3 studies.[15-17]

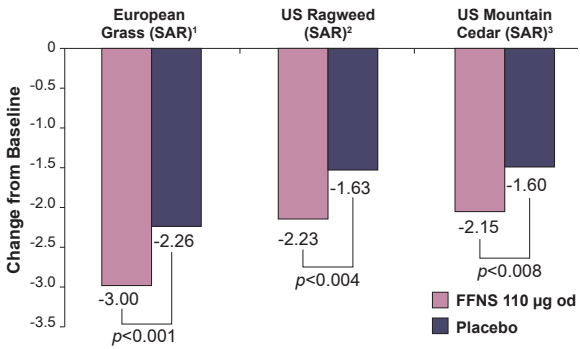


Figure 19. Effects of intra-nasal steroid sprays in the nose and on eye symptoms during allergy season in 3 studies.[15-17]

Let us give you an example. The latest of the intra-nasal steroids on the market in the United States, it is called fluticasone fuorate nasal spray. There are three studies: a European grass study[15], a United States ragweed study[16] and a United States mountain cedar pollen study,[17] all seasonal allergic rhinitis (**Figure 18**). The study shows its efficacy (fluticasone fuorate nasal spray) in total nasal symptom score and you see significant efficacy compared to placebo in all of these studies.

We also looked at total ocular symptoms score, so the effects of this sprays in the nose on eye symptoms during the allergy season and, again, you can see a nice, statistically significant improvement in eye symptoms (**Figure 19**). So in many of your patients

who have eye symptoms they will get better when you treat their nose with an intra-nasal steroid. We will also mention that if they continue to struggle with their eyes despite your best efforts, there are intra-ocular antihistamine drugs that work very well, Olopatadine is one of those, but we have no data for you on that.

Are intra-nasal steroids safe for children? That is always the concern of parents who come. We are careful for every parent when we prescribe an intra-nasal steroid to explain that this is a steroid, and explain to them how we think it is safe, and what the data that supports safety is. Therefore they are more likely to give it. Because we have had problems. Initially, when we started to practice a few parents would go home, open the package, see 'steroids' and not treat their kids. So it is very important.

If you look, the three latest additions to the intra-nasal steroids market: mometasone, fuorate fluticasone propionate, fluticasone fuorate they have very low systemic bio-availability after intra-nasal administration (**Figure 20**).[18-21] Thus, they are safe.

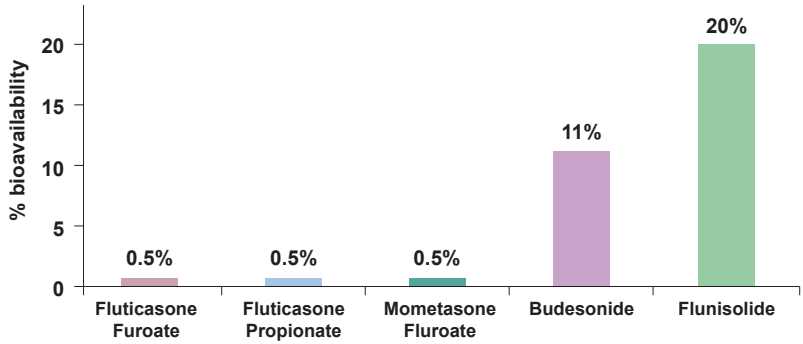


Figure 20. Bioavailability of mometasone, fuorate fluticasone propionate, fluticasone fuorate compared with budesonide and flunisolide.[18-21]

If you look at child's growth? This is another concern. There is a study with mometasone and placebo (**Figure 21**).[22,23] They tested these kids growth over a whole year, and they were in a placebo controlled study and you see that the steroid and the placebo were not different at all. Actually, they grew a little bit more with steroids, we think this is sort of a chance occurrence. You also see the same data with inhaled fluticasone propionate, even when it is inhaled you see very good data on safety.

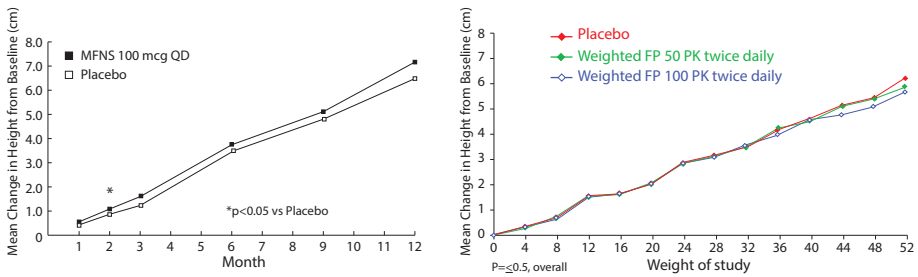


Figure 21. Mometasone and placebo at children's growth.[22,23]

In most of these studies the investigators also obtained blood and video cortisone simulation test every month, and there was absolutely no difference between the placebo and the intra-nasal steroids treated patients. Thus the safety of these. Most of these agents are approved starting age 2 or 4 years of age by the FDA in the United States. And we use them very liberally in our practice.

Now what is our treatment algorithm? In patients with mild or episodic like they go to a house with a cat that they are allergic to, every once in a while, they can take an antihistamine before they are going and they will be just fine. When they get slightly more persistent anti-viral disease we always go to a nasal corticosteroid and then we step up or step down the therapy depending on how they do. And we will give you some examples.

A step-down approach, if symptom relief is achieved or maximized with other approaches you can step-down therapy. And we will show you as needed treatment and how that may be effective.

A step-up approach, if the treatment is inadequate, or when the patient is doing their best and they still have no relief we always look for potentially switching the medication class, adding another medication, or investigating for other causes, such as sinusitis that accompanies allergic rhinitis.

"As needed" therapy, is the data we generated about six, seven years ago now, which is very interesting. We tried to, we speculated that an intra-nasal corticosteroid given as needed would be more effective than an antihistamine given as needed, and we originated a trial during the allergy season to show that. There is a study a 28-days trial[24] during the ragweed season in the United States (**Figure 22**). There was no placebo arm in this trial, these patients were told to take Loratadine as needed for symptoms, or fluticasone propionate as needed for symptoms. And you will see, remember that there is no placebo, so we are sure that Loratadine would have been better than placebo, but the intra-nasal steroid was better than loratadine in many

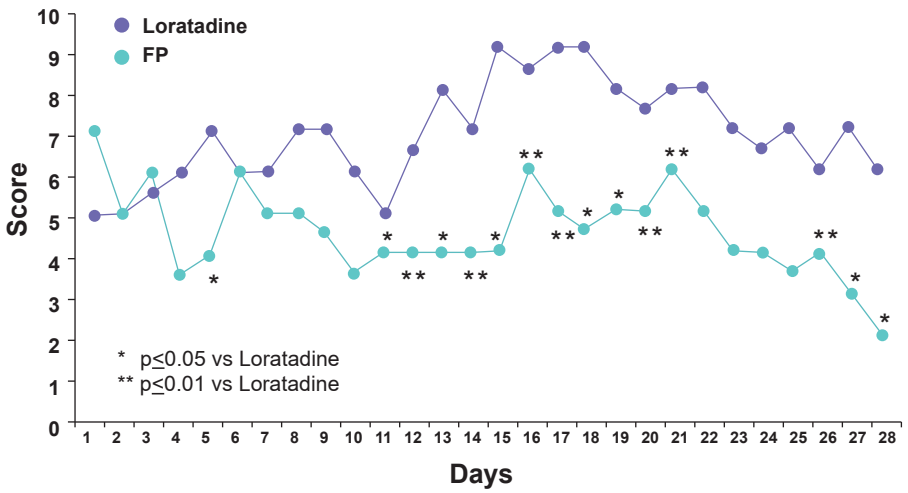


Figure 22. A 28-days study trial during the ragweed season in the United States. No placebo arm in this trial. These patients took Loratadine and fluticasone propionate as needed for symptoms.[24]

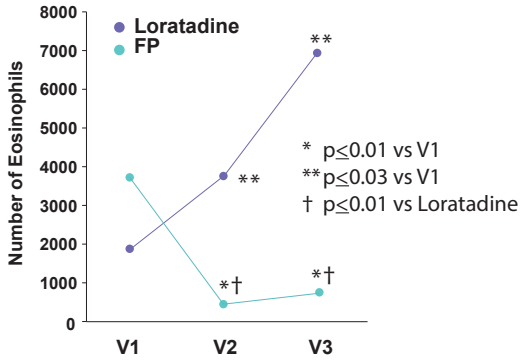


Figure 23. Number of eosinophils (before season started, peak of the season, end of the season). The children under loratadine and the eosinophils in the nose: go up dramatically, no effects on inhibiting eosinophilia. Children under fluticasone the eosinophils are shut down.[24]

of the timepoints. And we think the main reason for that is that the intra-nasal steroid decreases the inflammation in the nasal mucosa, while the antihistamine does not. Look at the eosinophils (**Figure 23**), this is before season started, peak of the season, end of the season. You will see loratadine and the eosinophils in the nose go up dramatically, no effects on inhibiting eosinophilia, whereas if you use fluticasone you see the eosinophils are shut down. And we think that is the reason for the superior efficacy of the intra-nasal corticosteroids. They are a much better anti-inflammatory medication.

How about the step-up approach? You can give antihistamines with decongestants, antihistamines with Leukotriene modifiers, or intra-nasal steroids with a variety of other drugs. Let us share some data with you about that. This is a simple example of how an antihistamine decongestant combination works better for a total nasal symptoms score, including nasal congestion (**Figure 24**).[25] This is a pseudoephedrine (PSE) alone, Desloratadine (DL) alone and the combination (DL/PSE). Or most of these are labeled as antihistamine D or the decongestant part. We are sure you are all familiar with these preparations. So they do help, they are not perfect but they do help.

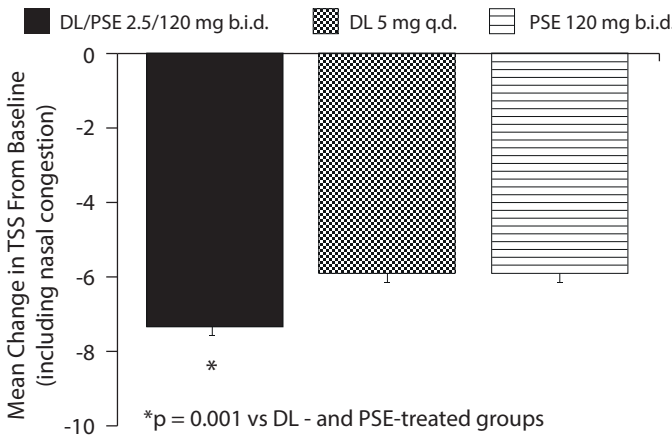


Figure 24. Total nasal symptoms score, including nasal congestion, using pseudoephedrine (PSE) alone, Desloratadine (DL) alone and the combination (DL/PSE). Antihistamine decongestant combination works better for a total nasal symptoms score, including nasal congestion.[26]

There is an attempt (the producer marketed this) that the combination of Montelukast and Loratadine provided superior benefit but it actually does not. So this is a seasonal study (**Figure 25**), you see again the placebo effect. Montelukast is better than placebo, loratadine is about the same as montelukast. The combination is not very different. So initially there was a thought about manufacturing a combination pill, but they dropped that because they would not get approved because there is really no added efficacy. It sometimes helped in some patients.

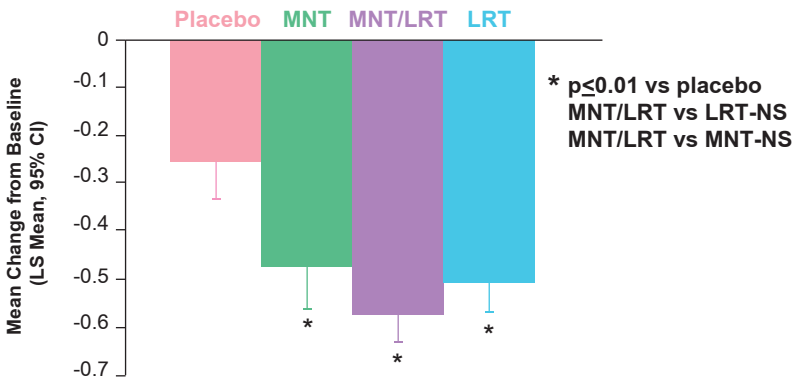


Figure 25. Daytime nasal symptoms score using placebo, Montelukast (MNT) alone, Loratadine (LRT) alone and a combination of both (MNT/LRT)

What about the leukotriene receptor antagonist? Will it help if added to fluticasone? Again, we did a seasonal study in grown ups, and what we did for this study is we brought them, and they were perennial rhinitis, they had symptoms all the time. We put all of them on fluticasone and they got better, but a proportion out of 102 some patients continued to have a mean total nasal symptom score over 4, which we labeled as residual, or uncontrolled disease. And then we randomized these patients, about 54, into either continuing on fluticasone and getting either placebo or montelukast. And then this is the data (**Figure 26**), you see that there really was no difference. So adding Montelukast to an intra-nasal steroid did not enhance efficacy in this case.

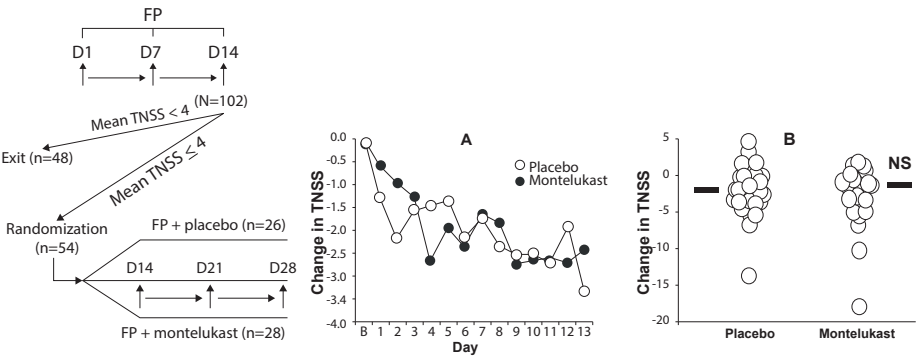


Figure 26. Adding leukotriene receptor antagonist (montelukast) to fluticasone (FP). So adding montelukast to an intra-nasal steroid did not enhance efficacy in this case.

There is a medication where the combination is actually better than the individual product. This is now marketed as a combination product in the Unites States and it has azelastine and fluticasone propionate, and you see that there is added efficacy. **Figure 27** shows azelastine alone,[27] fluticasone alone, both better than baseline so they do work, but if you combine them, you get better efficacy. And this drug is given twice a day, so you split the fluonate dose into morning and evening and you give the antihistamine with it, they are available as a single combination in the United States, but it is cheaper actually to give a prescription for fluticasone and a prescription for azelastine. You can certainly do that here if you don't have the combination product. We go to this when they fail with intra-nasal steroids.

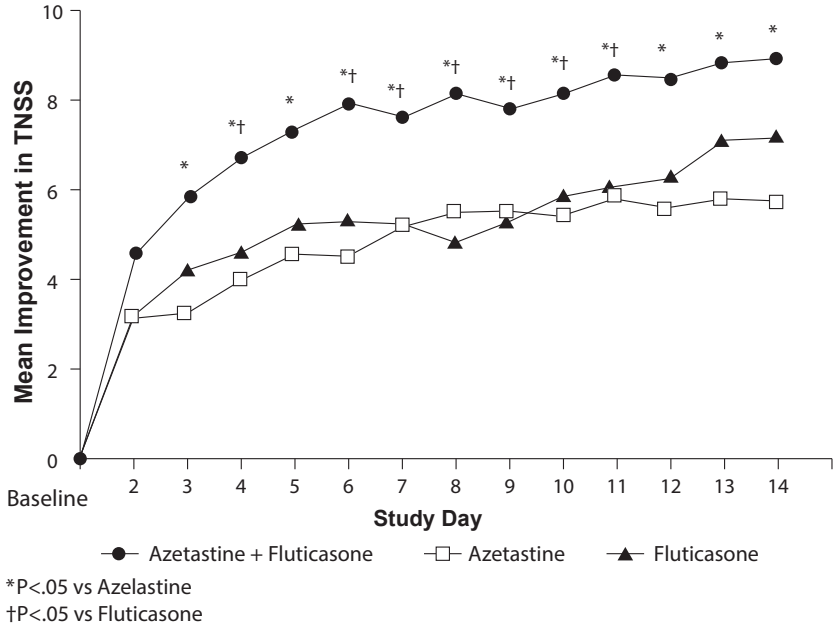


Figure 27. Combination product with azelastine and fluticasone propionate compared with azelastine alone and fluticasone alone. When you combine them you get better efficacy.[27]

Oxymetazoline added to intra-nasal steroids is an interesting concept, it's always the concern about rhinitis medicamentosa, but we also did a study adding fluticasone with oxymetazoline over a 4-week trial, and shows that it enhances efficacy without rebound nasal congestion after cessation (**Figure 28**).[28] We followed these patients for two weeks after stopping treatment and there was no rebound nasal congestion. A recent study published by Eli Meltzer, published in 2013, supports that concept, but that study was a small study.

So the management approach, by the time they get to my office they are significantly affected and we put them on an intra-nasal steroid. If they have zero response we look for other diagnosis, adenoidal hypertrophy, sinusitis, other problems. If they have a very good response we try to reduce the dose or give it as needed. If they have a partial response, we will try other therapies.

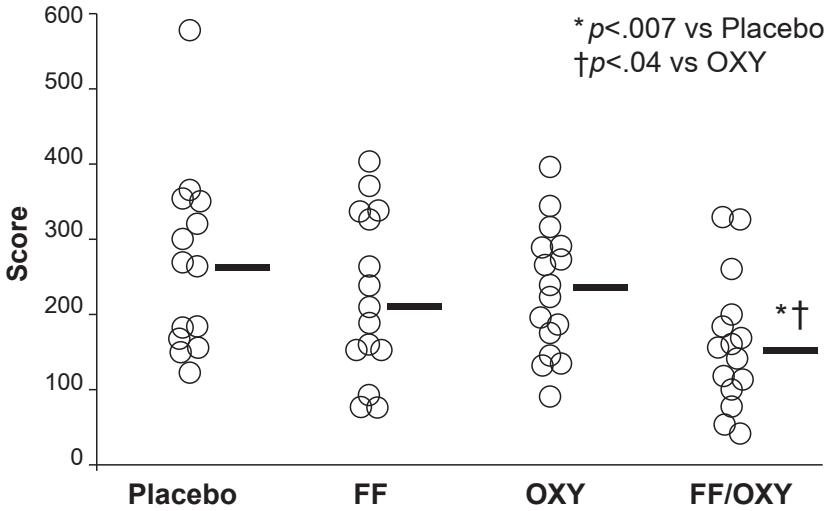


Figure 28. A 4 week trial study with oxymetazoline (OXY) added to intra-nasal steroid – fluticasone (FF). There is always the concern about rhinitis medicamentosa, but its combination enhances efficacy without rebound nasal congestion after cessation. These patients were followed for two weeks after stopping treatment and there was no rebound nasal congestion.[28]

A few words about immunotherapy. Immunotherapy is the only treatment, very effective, and it is available both in subcutaneous and sublingual now, and it is the only therapy that is known or has been shown to alter the natural course of the disease. So, if you receive immunotherapy for a year or two, you can stop and you continue to see benefits. This is not available in any if the pharmaco-therapies that we discussed. It does a couple of things over the years. It decreases skin test hyper-reactivity. Initially there is a little bump in Ig then the IgE goes down, and there is an increase in what is known as blocking antibodies or IgG4 (**Figure 29**).[29]

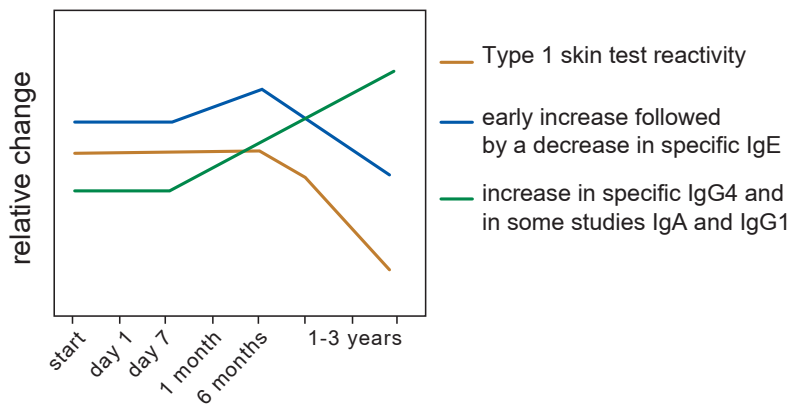


Figure 29. Immunotherapy. Initially there is a little bump in Ig then the IgE goes down, and there is an increase in what is known as blocking antibodies or IgG4.[29]

As far as the patophysiologic events, it leads to a decrease in mast cell and basophile activity, it improves or switches the T-cell profile and enhances T-regulatory cells, which shut down and control the immune response, and it decreases tissue mast cells over the long term (**Figure 30**). This is the typical switch from a TH2 to a TH1 response and it increases the blocking antibody, decrease IgE and blocks the inflammation.[29] So it is very effective. However, it has concerns. You have to take it for 3 years, you often will have to get a shot weekly for a long time. There is a small risk of fatal reactions and the most recent review, 8 million injections, .01% systemic reactions and no fatalities.

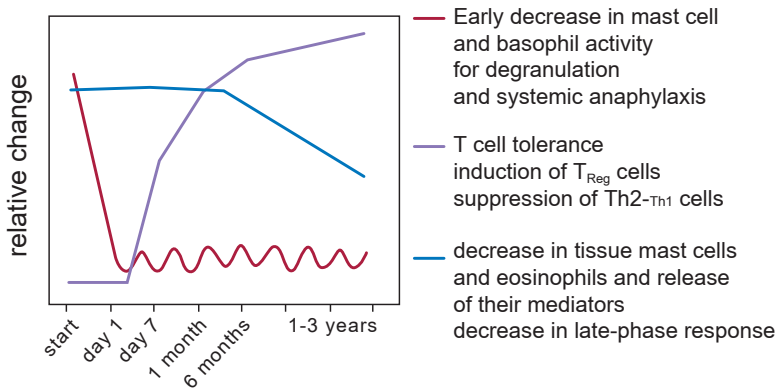


Figure 30. Immunotherapy. This is the typical switch from a TH2 to a TH1 response and it increases the blocking antibody, decrease IgE and blocks the inflammation.[29]

The recommendation in the United States currently, is if you give immunotherapy the patient has to be in your office prepared to deal with anaphylactic shock, and has to stay in the office for 30 minutes after injection to watch for side effects. And that has reduced the fatalities from 1 per 2.5 million to like none in the second period of the review.

There is a meta-analysis[30-31] looking at subcutaneous immunotherapy, multiple publications. And it shows that they almost all favor treatment for symptoms score and for medication score. And if you look at sublingual therapy, it is the emerging immuno-therapy now, it has been given in Europe for several years and it's starting to be looked at by the FDA in the United States.

There is one meta-analyses[32,33] about that It shows that it is effective and improves symptoms compared to placebo. It is given under the tongue or swallow tablets, and has much less adverse events. Most of the adverse events are a little oral itching and bother, but no airway problems. This is a most recent study[34] where grass immunotherapy was given in the United States (**Figures 31 A, B, and C**) and you see during the grass season, that the patients with placebo have a lot of symptoms, the patients with the grass tablet treated for about 7 weeks before the season have a significant improvement. So this is a very promising, potentially take home medication which can alter the natural history of the disease. And we are all looking forward to these products being approved in US.

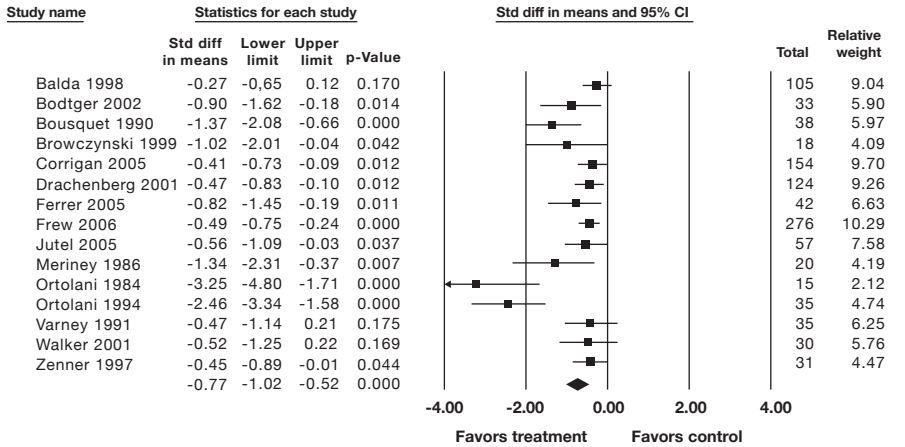


Figure 31 A. Immunotherapy: sublingual therapy. The patients with the grass tablet treated for about 7 weeks before the season with the grass tablets have a significant improvement.[32]

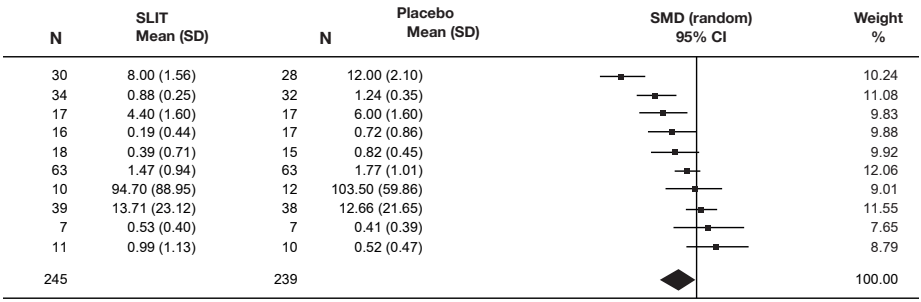


Figure 31 B. Immunotherapy: sublingual therapy. The patients with the grass tablet treated for about 7 weeks before the season with the grass tablets have a significant improvement.[33]

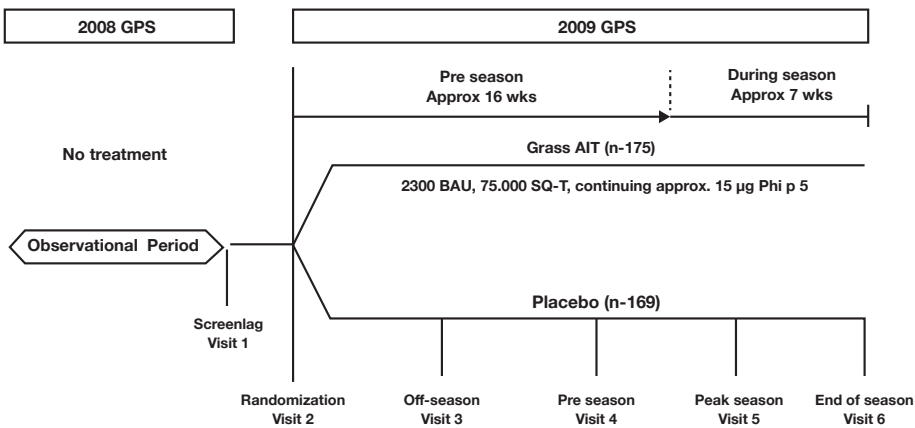


Figure 31 C. Immunotherapy: sublingual therapy. The patients with the grass tablet treated for about 7 weeks before the season with the grass tablets have a significant improvement.

So, in summary allergic rhinitis is a common problem. Significant impairment in quality of life, so look for it and treat it. There are multiple very safe pharmacotherapy options and the combinations will usually get you enhanced control, and immunotherapy is left as a last resort because of the tenuous and tediousness of it, until sublingual becomes approved.

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