Specific Immunotherapy. What is the Best Practice?

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These are the topics I will cover in my chapter:

1. Is there a difference between subcutaneous, the so-called SCIT immunotherapy and sublingual (SLIT) immunotherapy?
2. In favor of what is that difference?
3. What protocols are currently available for you in your practice?
4. What do you have to tell your patients about possible side effects?

One hundred years ago, in 1906, Clemens von Pirquet defined the term "allergy" (**Figure 1**). At that time such cases were very rare. He was a pediatrician in Vienna and when an allergic patient appeared, all the doctors would come together to inspect (**Figure 2**.)

Figure 1. Clemens von Pirquet invented the term "allergy".

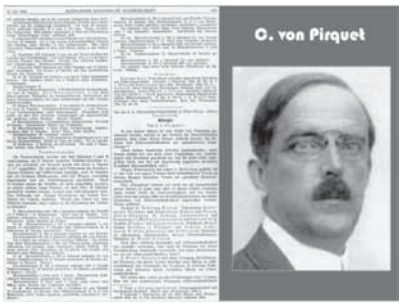


Figure 2. Dr. von Pirquet in his ward

This has changed a lot, we now have the Allergy-Tsunami and some people think it's going to take us away (**Figure 3**).

Figure 3. Allergy-Tsunami

Today one child in four has an ongoing allergic disease in Europe and we really do not know what will be the situation tomorrow [1]. There is this worldwide trend of increase, the ISAAC study has already been mentioned that in most regions of the world the allergies are still increasing [2].

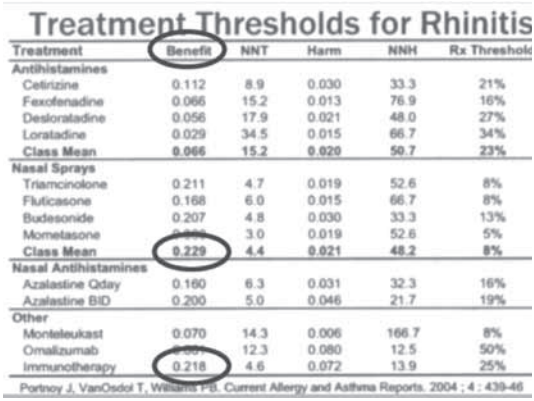
In some industrialized countries we have now reached a very high prevalence of allergy and asthma. In the NHANES-Survey in the United States they found that the prevalence of allergen-sensitization in US population was 42.5%. [3]. In another study with skin-prick tests in the US, 54% of the people in the US were tested positive to at least one of ten allergens. Allergic patients are now the majority of the population, but not only in the United States.

Some recent data published in Vienna show 50.8% of the Austrian population have some kind of sensitization [4].

Let us look at our patients, those in the age of three to 17. In a study conducted in Germany, they found that 45% of boys have an allergy in our population and 36% of girls. Around 40% sensitization is what is genetically determined in our genes. So sooner or later you will also reach such a high prevalence in Latin-America [5].

So many patients that wait for treatment and that is why the World Health Organization (WHO) has set up an initiative: how to deal with this global problem. They developed a treatment algorithm [6] for allergic rhinitis, with intermittent symptoms or persistent symptoms mild, or moderate to severe. It shows that you should consider specific immunotherapy (SIT) in the moderate to severe cases, be they intermittent or persistent. Also mild cases should be treated with immunotherapy, if patients have a persistent disease. So the majority of our patients qualify for SIT. There is good reason for that. In a recent meta-analysis from the United States they looked at the benefit of the different therapeutic options for allergic rhinitis. Immunotherapy had a benefit that was just as good as that of the steroid nasal sprays, for symptom control[7]. This analysis considered only subcutaneous immunotherapy (**Figure 4**). However, unlike symptomatic treatment, immunotherapy can prevent the development of asthma and new sensitizations that will alter the patient's situation to the worse.

Figure 4. Treatment Tresholds for Rhinitis.



Treatment Thresholds for Rhinitis

Treatment	Benefit	NNT	Harm	NNH	Rx Threshold
Antihistamines					
Cetirizine	0.112	8.9	0.030	33.3	21%
Fexofenadine	0.066	15.2	0.013	76.9	16%
Desloratadine	0.056	17.9	0.021	48.0	27%
Loratadine	0.029	34.5	0.015	66.7	34%
Class Mean	**0.066**	**15.2**	**0.020**	**50.7**	**23%**
Nasal Sprays					
Triamcinolone	0.211	4.7	0.019	52.6	8%
Fluticasone	0.168	6.0	0.015	66.7	8%
Budesonide	0.207	4.8	0.030	33.3	13%
Mometasone	[illegible]	3.0	0.019	52.6	5%
Class Mean	**0.229**	**4.4**	**0.021**	**48.2**	**8%**
Nasal Antihistamines					
Azalastine Qday	0.160	6.3	0.031	32.3	16%
Azalastine BID	0.200	5.0	0.046	21.7	19%
Other					
Monteleukast	0.070	14.3	0.006	166.7	8%
Omalizumab	[illegible]	12.3	0.080	12.5	50%
Immunotherapy	0.218	4.6	0.072	13.9	25%

Portnoy J, VanOsdol T, Williams PB. Current Allergy and Asthma Reports. 2004 ; 4 : 439-46

Therefore, it is hard to understand that, for example, in Germany, only 7% of all allergic patients that are treated for their allergic rhinitis receive immunotherapy. Still these 7% is the highest percentage worldwide. We, in Germany, have the biggest SIT-market worldwide. In the US this number is below 1%.

Look at the levels of clinical efficacy you have with SIT:

1. an early effect right after the initiation;
2. you have a persistent effect during treatment;
3. you have a long-term carry over effect;
4. you have the preventing effect;
5. preventing new sensitizations;
6. preventing the onset of asthma.

That has been brilliantly shown by Stephen Durham from the United Kingdom in an article published in the New England Journal just 10 years ago, when he demonstrated the long term effect of subcutaneous immunotherapy [8].

A European study published by Bodo Niggeman, from Berlin could show that immunotherapy prevents the onset of asthma - not in all patients, there are still 20% of children treated with immunotherapy that will develop asthma, but this is a much lower figure than in those patients who just receive symptomatic treatment (40%) [9].

Friedrich Horak, an ENT-specialist from Vienna places his allergic patients during winter time in a chamber and then blows allergens on them to determine their allergen susceptibility (**Figure 5**). Within few minutes they all become very symptomatic, when they breathe this allergenic air. In a recent study on sublingual immunotherapy, he conducted these examinations after seven days, after one month, after two months, after four months in a placebo-controlled, double-blind design. Within four months of sublingual immunotherapy treatment, these patients improved a lot, and had much less symptoms under immunotherapy. This is what we had expected. Surprisingly however, already after seven days of taking sublingual immunotherapy tablets, patients were much better off than those on placebo. The first publication on these tablets that have been used by Friedrich Horak was in 1999 but now they are available in Europe [10].

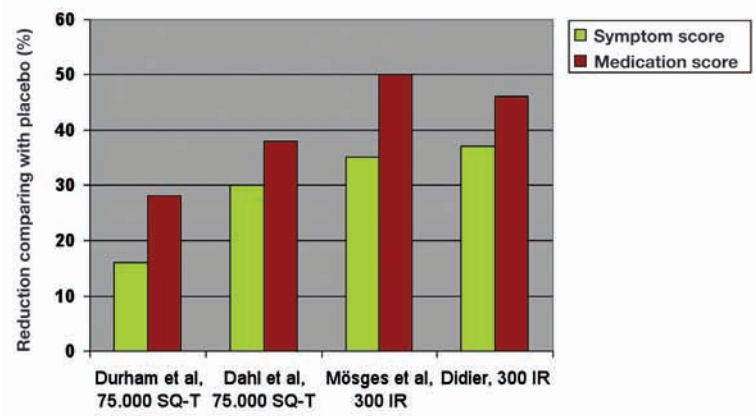
Figure 5. Chamber of Horak

We have also conducted a clinical trial in Germany where we could demonstrate the efficacy [11]. The landmark trial about this new treatment has been published by a French group [12].

There is another sublingual tablet in the market in the German market the so-called GRAZAX tablets [13]. This has also been extensively tested [14]. With these tablets, it is better to treat the patients for four months before the season, then they get much less.

We compared all these trials (Mösges et al [11] and Didier et al [12], Durham et al [13], Dahl et al [14] on **Figure 6**). You can tell your patients that they will have a relieve of at least 30% more than with placebo, which is quite a lot if you compare it to other treatment modalities. In the original paper by Steven Durham[8] he compared sublingual immunotherapy tablets with subcutaneous immunotherapy, nasal steroids, antileucotriens and anti H1 drugs. His group concluded that SLIT tablets (sublingual immunotherapy) are the gold standard of treatment [8, 13].

Figure 6. Symptoms score reduction in different trials



A German study with SQ-standardized grass tablet [15] and another international study with SLIT tablets [16] have demonstrated their efficacy and safety for children of the age of 5 years and more.

One interesting point is also, that there is such an early onset of the efficacy within a few days of treatment. That gives you the chance to start therapy during the season, when the patients are already symptomatic. Already during the first season these patients improve a lot.

What do you have to tell your patients about side effects? They are mostly local and rarely systemic. Local effects are very frequent: oral pruritus, edema in the mouth, throat irritations, these are typical side effects. They add up to 73% of your patients experiencing that in the beginning of therapy. So you have to tell every patient, that he will most likely experience such side effects, but these are transient effects that will go away after one or two weeks. Systemic side effects are very rare and there's only been one clearly documented case of anaphylaxis, but no deaths so far. So this is a very safe procedure to do.

What can you do to improve these local side effects? Do SVIT instead of SLIT. That means, specific vestibular immunotherapy. If you tell your patient to put the tablet in front of the teeth (in the vestibulum of the mouth - between anterior inferior teeth and inferior lip) where they have less mast cells and more Langerhans cells. There they will develop less local side effects, as has been shown in a paper by the group from Bonn, in Germany [17].

So to answer the questions that I asked in the beginning: is there a difference between SCIT and SLIT? Yes, it is in favor of SLIT, surprisingly. What protocols are available? Many – (high-dose, cluster, seasonal, tablets) and you must tell your patients that they will experience some side-effects transient and mostly local.

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