POINT OF VIEW

Grass pollen sublingual immunotherapy and paediatric allergic rhinitis: A patient-oriented decision

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Abstract Guidelines and systematic review report that allergen immunotherapy (AIT) is, in general, effective in the treatment of allergic rhinitis. However, experts suggest not generalising the results of different clinical studies: for example, it would not be advisable to translate the results found in an adult population to a paediatric population or the results on the efficacy of AIT against a specific allergen to the AIT against a different allergen. Moreover, according to Evidence Based Medicine (EBM), clinical decisions are individualised and should derive from the "integration of best research evidence with clinical expertise and patient values". Taking into account the high specificity of the AIT and EBM principles, we tried to answer the question on how advisable it is to prescribe the AIT for the management of grass allergic rhinitis in children. To do this, we revised the scientific literature in order to solve a specific case scenario. © 2015 SEICAP. Published by Elsevier España, S.L.U. All rights reserved.

Introduction

The aim of our study was to evaluate the usefulness of a grass pollen immunotherapy for paediatric grass pollen rhinitis. To do this we chose a particular case scenario and we kept in mind the needs of a particular child and his family. We also considered that, as suggested by the experts, the allergen immunotherapy (AIT) has its own specificity: for example, it is not advisable to compare different brands of AIT, or transfer the results of adult patients to the paediatric population.

We described a decision path, as could happen to any doctor. We started from a guideline and then, when necessary, we continued our search until the primary studies.

Case scenario

We met GS, a nine-year-old boy, in September 2013. In the last three years, during the spring (April–June), he presented sneezing, watery rhinorrhoea, itching and nasal obstruction. Sometimes he had cough and breathlessness during physical activity. At the moment of the visit, we found mild pale oedema of the nasal mucosa and mild pulmonary

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wheezing. Skin prick test with the most common Aeroallergens showed a single positivity against grasses. We suggested the daily use of mometasone furoate nasal spray from the end of March to the end of June, and the management of eventual acute asthmatic symptoms with salbutamol spray. A spirometry testing (at rest, after exercise and after salbutamol) performed one month after the first visit was normal.

GS carried out two more visits at the end of April 2014 and in August 2014; on this latter occasion, he told us that he needed the salbutamol spray to control asthma symptoms for a total of 15 days in 11 months (all the episodes were due to physical exercise); he had also used the steroid nasal spray as prescribed (one puff for each nostril in the morning and, sometimes, one more puff in the afternoon) with an almost complete prevention of rhinitis symptoms. He went to the seaside in July and he had no symptoms even without administering any drug. What GS would like to know now is if there is something more to do; we hinted at the possibility of using the grass pollen AIT, which is presented as a possible option in two authoritative position papers on rhinitis.1,2 His father, affected by allergic rhinitis, tried AIT for five years without advantage but he trusts us and backs our decision.

The patient values

Evidence Based Medicine (EBM) suggests to take clinical decisions taking into account: "(1) integration of best research evidence with (2) clinical expertise and (3) patient values".3 However, the third point is often unfulfilled because patients do not express a real preference but they just want the doctors to suggest what would be the best for them. So we identified some issues of interest:

- Will GS heal from his rhinitis through the AIT?
- Will the AIT prevent a worsening of his allergic symptoms, for example of the asthma?
- Will the AIT reduce the rhinitis symptoms? If yes, more or less than the steroid spray?
- Does the AIT have adverse effects? If yes, more or less than the steroid spray?
- Is the AIT administration more or less disturbing than the steroid spray?
- Is the AIT more expensive than the steroid spray?

It is important to know that today (May 2015) in Italy, both the AIT and the steroid nasal spray are charged to the patient if symptoms are controlled by drugs as it is in the case of GS.

The clinical expertise

This is the second pillar of the EBM, consisting in the ability of doctors to shift the best scientific evidence available to the single patient with his specificities. Going back to our patient:

- Like all the children of his age, GS does not want an injective therapy. That is why we cannot consider for him the subcutaneous AIT and so the sublingual AIT (SLIT) is our only option.
- His father is a teacher and his mother is a housewife, there are four people in his family and they cannot afford the tablet SLIT, which is too expensive; only the drop SLIT is left.
- GS is a child, affected by rhinitis, with a monosensitisation to grass pollen; this is the population we have to refer to (not others like children with asthma and sensitisation to mites or adults with grass pollen allergic rhinitis).
- In the last spring, GS administered daily steroid nasal spray with good results; he has already found a solution to his symptoms. An eventual different therapy should have clear and methodologically well-demonstrated advantages (deriving, for example, from double-blind randomised controlled trials, DB RCT).

We have to take into account advantages and disadvantages in terms of efficacy, adverse effects and economic costs.

The best research evidence

Since, as said above, we are oriented to the drop SLIT, the World Allergy Organization (WAO) position paper (PP) on this topic4 may be an important source of basic scientific information. This PP reports as follows: "The literature suggests that, overall, SLIT is clinically effective in rhinoconjunctivitis and asthma, although differences exist among allergens... The relative change versus placebo, when reported, ranged between 20% and more than 35%". The WAO PP4 refers to the systematic review (SR) with meta-analysis (MA) of Radulovic et al.5. They compared SLIT vs. placebo, finding that the standardised mean difference (SMD) for symptoms was −0.42 while the SMD for the use of symptomatic drugs was −0.43. However, according the WAO PP,4 the reliability of these results is limited by the great heterogeneity of the trials considered in the review. Anyways, thanks to the increasing number of available trials, it is now possible to do more specific SR with MA, thus reducing the statistic heterogeneity of resulting data. An example of these SR is the one published by Di Bona et al.6 (also reported in the WAO PP), regarding the efficacy of SLIT in grass allergic rhinitis.

The specificity of the SLIT efficacy

In their SR, Radulovic et al.,5 consider different parameters on specific SLIT efficacy, taking into account, for example, the culprit allergen or the age of the patient. Through this SR they learned that the SLIT is significantly more effective than placebo in reducing symptoms (both in adults and in children) and that grass pollen SLIT itself is effective (even if, unfortunately, this last result is presented without distinction between adults and children). The importance of the concept of specificity in this particular field is stressed by Bachert et al.7 who replied to the De Bot et al.8 paper entitled “Sublingual immunotherapy not effective in house dust mite-allergic children in primary care” saying that “The title suggests that sublingual immunotherapy for house dust mite (HDM) ‘in general’ is not effective, but should clearly state that SLIT for HDM with a specific product is not effective... We therefore suggest to specify the SLIT product
in the title of the publication and to avoid unjustified general statements on application routes or patient groups. Therefore, going back to our patient and trying to be as specific as possible, we analysed the Di Bona et al. SR.

Di Bona et al. SR with MA

In this SR, Di Bona et al. look at the efficacy of SLIT in the management of grass pollen allergic rhinitis from two different points of view: symptoms improvement and rescue drugs reduction. They also considered separately both tablet and drop SLIT. However, as previously said, GS did not need to use rescue drugs during the period of the mometasone furoate spray treatment, and his family probably cannot afford the cost of the tablet SLIT. Thus, we have to focus only on the results about the improvement of symptoms obtained through the drop SLIT. These show a small, but statistically significant, difference between SLIT and placebo (SMD $-$0.23; IC $-$0.43; $-$0.02). However, if we look specifically at the three paediatric studies included, we find that none of them is favourable to the SLIT: there are not significant differences in any of them between the groups regarding the primary outcome. We have also checked another SR with MA and we found that their inferences about these three studies were the same as Di Bona et al. Finally, we have directly analysed these papers and we drew the same conclusions: in these three studies the grass pollen drop SLIT does not offer significant advantages over placebo in reducing AR symptoms in children.

The subsequent studies

The WAO PP considers three more recent RCT DB studies, useful for the management of AR in children. Stelmach et al. randomised 60 Polish children, with a grass pollen mono-sensitivity, to receive either pre-/co-seasonal (6 months/year) drop SLIT (Stalarol 300, Stallergenes), or continued (12 months/year) drop SLIT or placebo. After one year, the group undergoing the pre-/co-seasonal SLIT showed a statistically significant reduction of 42% in the score of nasal symptoms; the reduction detected in the continued SLIT group was not significant while there were not differences in the placebo group. This result might be interesting for GS (even if it the lack of significance in the continuous SLIT group is surprising). Anyway, as reported by Durham et al., we know that there could be a direct correlation between AIT efficacy and pollen concentration and, as described by website www.polleninfo.org (http://www.polleninfo.org/GB/en/current-data.html?poll=5&month=6&tabber=6&time=1), pollen concentrations in Poland are higher than in Italy, and GS lives in Lazio, an Italian region. Twenty-four Iranian children were enrolled in a study by Ahmadiasfshar et al. and they were randomised to receive a grass pollen drop SLIT (Stalarol 300, Stallergenes) or placebo for 24 weeks. Twenty of them completed the study; the author’s conclusion was that “the symptom scores in treatment group and placebo were similar at the beginning of study until 21st week; after that, significant reduction was seen in treatment group up to the end study.” A deeper quantification of this advantage is not possible through the data shown in the article.

Wahn et al. randomised 207 children (most of whom were German) to receive either high-dose grass pollen drops SLIT (AllerSlit, Allergopharma) or placebo daily for one pre-/co-seasonal period. They found that the reduction of the median area under the curve about symptoms was 20% higher in the treated group than in the placebo group (37% vs. 17%, $p=0.012$).

We did not find another relevant DB through a Pubmed research up to May 6th, 2015, using as key words = ”sublingual grass pollen immunotherapy” and as limits = ”randomised controlled trials, all child, last five years”.

Is the SLIT complementary to the pharmacological treatment or is it an alternative?

We found six PB RCTs evaluating the efficacy of grass pollen drop SLIT vs. placebo for paediatric AR: three of them showed an advantage in terms of symptoms improvements and three did not. However, since different AIT products from different brands were used, according to Bachert et al. it should be advisable to consider separately the results of the different studies. Going back to our patient, the most fitting study to refer to is the one from Wahn et al.: their cohort is numerically large and pollen concentration in Germany is more or less the same as in Lazio (where our patient lives). It is true that pollen concentrations frequently change even in the same place and that there are other several variables to take into account but it is also necessary to make a choice, identifying only some parameters on which to base our decision. Nevertheless, we could also decide to not consider all these variants (e.g. pollen concentration, different brands of products) but just explain to GS and his family that the reduction of symptoms he can obtain through the grass pollen drop SLIT may vary between 20% and 42% according to the brand chosen. However, GS already has the same result with the mometasone furoate nasal spray therapy (that lasts half the time comparing to the drop SLIT), confirming what is already described in literature. The data on the equivalent symptomatic efficacy of AIT and nasal steroids do not derive from a direct comparison - except in one case - , but from retrospective studies on SCIT or tablet SLIT efficacy in the treatment of seasonal AR. Therefore, according to these reviews, the AIT could be a symptomatic alternative to drug therapy.

But could the drop SLIT be synergic with the steroid nasal spray therapy? May they together produce a greater effect? There are not many studies on this topic. If we focus, as previously said, on the DB RCT, there are only two studies on the drop SLIT in the childhood: Pajno et al. study on the Parietaria drop SLIT and the one from Pham Ti et al. on the Dermatophagoides drop SLIT. In both studies, the SLIT did not show a significant synergic effect neither in the reduction of symptoms nor in the reduction of the drug dose. Anyway, we have to take into account that none of these studies perfectly fits with the GS condition, since he has a grass pollen allergy.
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The preventive effect of SLIT

Another important question was about the preventive effect of drop SLIT towards a potential worsening of GS symptoms, for example in the prevention of the onset of persistent asthma. At the moment there are no DB RCT demonstrating this possible advantage. Some data should awfully derive from the GAP study, which is expected to end in the 2015 but that focuses on tablet SLIT, not useful in our case.

Adverse effects and economic costs

Adverse effects of both drop SLIT and nasal mometasone furoate are rare and usually mild.

Focusing on the cost of these therapies, in Italy (and in particularly in Lazio, where GS lives) a three-month treatment with mometasone nasal steroid spray (which is the most expensive steroid nasal spray) costs more or less 55 Euros whilst a six months drop SLIT treatment costs at least 370 Euros.

Our answer to the patient’s questions

We have previously imagined some questions that GS and his family could have asked us before taking a decision. Taking into account his economic condition and the good results of the steroid nasal spray therapy, we exclusively considered the drop SLIT and we tried to give our answers only on the basis of DB RCTs.

- Will GS heal from his rhinitis through the SLIT? No one knows, there are not certain data on it.
- Will the SLIT prevent a worsening of his allergic symp- toms, for example of his asthma? No one knows, there are not certain data on it.
- Will the SLIT reduce the symptoms? If yes, more or less than the steroid spray? The effect may probably be, in the best case, more or less the same as mometasone furoate nasal spray.
- Does the SLIT have collateral effects? If yes, more or less than the steroid spray? In both cases, adverse effects are rare and mild.
- Is the SLIT administration more or less disturbing than the steroid spray? It depends on the patient’s preferences; for sure the SLIT treatment last longer.
- Is the SLIT more expensive than the steroid spray? It is at least six times more expensive.

Conclusion

In this specific case, we would not suggest the AIT, drop SLIT in particular, to GS: according to the results of DB RCTs, there are no clear advantages if compared to the mometasone nasal spray and it is significantly more expensive. The economic condition of GS and his family plays an important role in this clinical decision; such a cost for the family is acceptable only if there is clear and well documented evidence of SLIT superiority over mometasone therapy, deriving from absolutely reliable studies (DB RCT) on children with grass pollen AR. However, a less clear advantage, for example from studies methodologically less valid, could be enough in the case of a richer family, where the impact of the cost and the risk of a possible ineffectiveness of this approach would be lower.

At the moment this is our behaviour, but we know that in the next years there will probably be an improvement in AIT therapy; it is possible that new generation AIT will be more successful (even in preventing a worsening of allergic symptoms) and/or cheaper. In this case, even our answers to GC question may be different.

Conflict of interest

None.

References


