

Clinical Trials With Recombinant Allergens – a Regulatory Perspective

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Similar to all other biotechnological products, recombinant allergen preparations are subjected to marketing authorisation by the European Medicines Agency (EMA) through the centralised procedure. For such products, the EU has established a framework of regulations, of which several would apply to allergens (reviewed in [1]), with the Note for Guidance CPMP/ICH/365/96 (Q6B) [2] regulating the test procedures and acceptance criteria for such products. Compared to conventional allergen extracts, in the future recombinant allergens may lead to better standardised products and bridging between similar recombinant products may be possible.

Regarding clinical trials in principle, the evaluation of safety and efficacy is not different between allergen extracts and recombinant allergen preparations and is laid down in the EMA “Guideline on the Development of Products for Specific Immunotherapy for the Treatment of Allergic Diseases” [3]. According to this guideline, the clinical development plan may be designed to support different claims: 1. Treatment of allergic symptoms; 2. Sustained effect under treatment; 3. Long term efficacy and disease modifying effect; 4. Curing allergy. These claims are presented in the indication and determine the clinical development package.

The assessment of the claims includes validity, reliability and clinical relevance of the study outcomes. Assessment of validity is related to the question whether it can be excluded that the observed effect is attributable to factors other than treatment. The least biased are studies based on a randomised double blind placebo controlled trial design provided there is adherence to the *priori* protocol/analysis plan. Due to a lack of assay sensitivity of clinical trials in allergic rhino-conjunctivitis with subjective primary endpoints (e.g. symptom scores) and high rate of unsuccessful trials where placebo does not separate from active treatment, two armed comparative non inferiority trials are no option in studies of allergic rhino-conjunctivitis. Reliability indicates whether the observed effect can be reasonably attributed to chance or not.

It depends on the data analysis plan, the significance of *p-values*, robustness of the results in sensitivity analyses, and multiplicity issues. Post hoc analyses may initiate further research, but can hardly be used for supporting claims. The assessment of clinical relevance depends on the definition of the primary endpoint, the magnitude of its effect, the definition and results of secondary endpoints, and external knowledge. The application of responder definitions as well as the evaluation of relationships between primary and secondary endpoints may be helpful in this context. It should be noted that clinical relevance does not guarantee statistical significance and that statistical significant results do not mean that they are clinically relevant.

To improve the informational value of clinical trials on specific immunotherapy the analyses needs to be enhanced. It is desirable to solve the problematic relationship between symptom and medication score by standardised and validated individual and combined scores. The clinical relevant effect should be defined and powered in the study protocol and not after the study. Moreover, an analysis of pollen exposure days only may enhance the significance of the results.

In the future, clinical development packages establishing sustained effect under treatment, disease modifying effect, or cure of allergy should be preferred. A higher importance for provocation test is anticipated, but in the near future the importance of biomarkers is still questionable. Individual exposure measurements may be taken into consideration and in summary there remains a strong need for placebo controlled comparative immunotherapy trials.

References

1. Lorenz AR, Lüttkopf D, Seitz R, Vieths S. The regulatory system in Europe with special emphasis on allergen products. *Int Arch Allergy Immunol* 2008; 147: 263–275.
2. Note for Guidance on Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products. EMEA, CPMP/ICH/365/96, 1999.
3. Guideline on the Clinical Development of Products for Specific Immunotherapy for the Treatment of Allergic Diseases. EMEA, CHMP/EWP/18504/2006, adopted by CHMP November 20, 2008.

Discussion

Frew: I think that was very clear about how we should be assessing immunotherapy. Can I challenge you about assessing recombinant materials because it seems to me that we have here two separate issues. The first is: if we make a cocktail of recombinant materials to replace the existing extracts so that we try and mimic standard grass pollen extract, then clearly it has to go through the same regulatory frame work as this, we have the same group of patients that we would have for a conventional immunotherapy trial. The challenge is if we want to move on and do something which is more specific to individual patients and if we believe that tailoring the vaccine will be a more efficient way of doing this. and create greater efficacy, we will have a great difficulty. It will not be a single vaccine – what you are testing is a concept that is making up a mixture – and testing it according to the patients' individual antibody profile that you will have a better thing. I cannot imagine how you would get this sort of process to apply to that type of trial.

Elferink: We should be pragmatic, I agree on that. I can imagine, if you have three treatments, placebo, treatment A and treatment B that in treatment B you have your regular major allergens one, three, five and six. But in the second arm you have your individual patient-tailored therapy and it does not matter if one patient is treated in another way than another patient. So you have the proof of concept arm in the other one. I could imagine that would be a solution.

Cromwell: It is not a direct comment, it has nothing to do with recombinants either. In your concluding slides you mentioned you would like to see studies comparing immunotherapy, anti-symptomatic treatment, and placebo. What I think about that is that the only way this can work is if you deny your immunotherapy patients and your placebo patients anti-symptomatic medication. And I can imagine if that were the case we would have a problem getting ethical committee approval for such a study.

Elferink: Not necessarily. Your immunotherapy arm could be your standard therapy arm and you could have a placebo arm and take rescue medication as a primary endpoint.

Cromwell: But then the patient would be denied the routine anti-symptomatic medication, but only have the option to use rescue medication if it is necessary.

Leibold: My comment is in the same direction. You have heard through these two days that treating allergies is not an easy thing. And you hardly have really cured individual patients. So if you make a study now with an allergen and you claim you will cure the allergy, because you say we have enough symptomatic treatments – we do not need an additional one. Now we have a double question. First, the medication score is real significantly positive but the symptoms continue. So the patient is not cured, but needs less medication. Would that be a sufficient criterion to agree that this is on your line? And the second question is how many of the patients must have been cured, that means they have a continued symptom-free period, that you would accept such a study?

Elferink: To start with the first question. I think if you are at this level, you have done a great job because this is a very large hurdle, I agree on that. If you talk about cure it is a much larger hurdle, but it has some advantages. It is not a law what I am saying now, but personally I would say if you show me that with your therapy ten patients are cured that is marvelous and I do not need a randomized control trial with one hundred patients. Let us look at the first randomized control trial we ever had, I think it was an antibiotic in bacterial carditis. Nobody so far survived till then and then two patients survived. I cannot say it should be 10, 20 or 100 patients. But you have to consider that it had never been shown so it is very exceptional and it probably was not by chance. The other thing is what is better to register: a product with which one in a thousand patients is cured or a product where five hundred patients have a symptom reduction of 50%. That is the judgment we have to make and I cannot give an answer to that.

Pauli: A comment on provocation tests. Would you admit to base efficacy only on provocation tests, because you have many factors in provocation tests. First of all, in Allergology you have to elaborate allergens for inhalation to be sure that you have a modification. And there is variability of at least plus or minus one dose and second there is no good correlation between the sensitivity of nasal and bronchial provocation tests and the severity of the disease. I think it cannot be the main decision point.

Elferink: I would fully agree. If you cannot validate it for a clinical outcome it cannot be this easy, but it would be very helpful; that is one thing. It certainly leads to what you call supported evidence of efficacy if it shows an effect. I see a much larger problem in the clinical development plan and especially phase II studies. At the moment you see too much jumping directly to the phase III trial. There is a little bit known on the doses, a little bit on the responses of the patient and then you go for a phase III trial. The trials you showed here are small. I would say this is the kind of trials you need before you start a phase III trial. I think this phase III trial would be more successful nowadays and that is the place I see for pharmaceuticals.

Rüttgers: I like your idea of curing very much but being quite honest I am lacking the definition of cure in allergic patients taken the time course of the disease and the environmental impact of the disease. Could you give us an answer on that?

Elferink: Frankly speaking, I cannot. Cure is defined as the absence of symptoms. I admit it must be difficult to achieve, but perhaps in the next five years we might get answers.

Saxon: We should take a page from the oncologists. We generally achieve partial remissions, right, we do not get cures. A five-year cure, maybe, is a long-term cure in breast cancer, but most of us do not recognize cure in that sense. We can get good long-term partial remissions so that a medication decrease of 80% daily will make us happy.