Research Strategy: Vincent Charlon

Designing trials for allergy product development

According to the European Academy of Allergy and Clinical Immunology (EAACI), allergy is the most common chronic disease in Europe. Up to 20% of allergy patients struggle daily with the fear of a possible asthma attack, anaphylactic shock, or even death from an allergic reaction. In a 2012 position paper published by the EAACI[1], Papadopoulos and colleagues cite the need for researchers and developers to better understand the causes and natural history of the disease, and to bring better treatments to patients. The allergy field took a big step forward in 2006 when the first sublingual tablet allergy immunotherapy was approved in Europe, followed in 2014 by the first US approval. However progress in developing better treatments has stalled.

In this article, we review recent developments in the field and highlight some of the regulatory challenges facing developers, especially in the design of clinical trials.

Currently the only disease-modifying treatments for allergies are allergen specific immunotherapies (AITs) which are allergy shots or sublingual treatments consisting of doses of allergens designed to induce immune tolerance. These treatments have been administered to patients for more than 100 years[2]. In Europe, two to three million patients with allergies receive AIT each year, with an equivalent number in the US. Yet current AIT treatments require three years of therapy and, as a consequence, eligible patients are reluctant to accept treatment. Those who do show low rates of compliance: 50% of AIT patients discontinue sublingual or subcutaneous AIT treatment within the first year and up to 80% never reach three years of treatment[3].

Papadopoulos and colleagues[1] have proposed that the treatment modality should evolve towards efficient short course but long-lasting treatments. This would involve studying the mechanisms of tolerance induction and identifying better adjuvants to promote tolerance induction after short course treatments.

However in recent years, several trials with promising short-course innovations have failed. It is an open question as to whether this is the result of regulatory requirements, particularly in the design of allergy immunotherapy trials, or other reasons such as shortcomings in the products themselves.

Regulatory requirements are recent

Until 2006 and the European approval of Grazax, all marketed AIT treatments were named patient products and didn't require regulatory approval. This changed with the development of the first fixed-dose treatments. The development of sublingual tablets started in the late nineties and led to the approval in Europe and the US of the first AIT products using evidence-based medicine and internationally accepted quality standards. These programmes led regulators to define guidelines for the development of novel AIT products. An example is the European Medicines Agency's 2008 guideline on the clinical development of treatments for allergic diseases[4].

Today, the clinical registration trials for AIT in Europe and the US against respiratory allergies are required to demonstrate efficacy in conditions of natural allergen exposure, using a combined symptom and medication score (CSMS). The allergy symptoms and the use of allergy medications are captured daily by the patients on a hand-held device. The data are automatically transmitted to a central database and analysed at the end of the trial during a predefined period of allergen exposure (e.g. during the entire pollen season, or during the peak pollen season).

Until the mid 2000s, no benchmarks were available to compare the new trials using a CSMS with the untested marketed subcutaneous or sublingual AIT treatments. In addition, the initial CSMSs were developed independently and calculated differently by individual companies. As a consequence, they were not easily comparable between trials or between allergy indications. Nevertheless a threshold of a minimum 20% improvement in the CSMS was generally considered to be clinically relevant and remains today the targeted minimum benefit to be demonstrated, at least in Europe.

The US Food and Drug Administration is not using a 20% threshold but requires that the lower limit of the 95% confidence interval of the difference from placebo be at least 10%, which leads to a similar range of minimum efficacy. The publication of recommendations by the EAACI for a standardised CSMS has recently enabled the comparison of results between different trials.

Strategies for designing clinical trials

In order to meet the new regulatory requirements, AIT companies have developed design strategies to account for the specificities of AIT trials. Several extract-based sublingual tablets have successfully been shown to provide a more than 20% treatment benefit vs placebo with strong statistical significance: e.g. HAL Allergy Group in birch allergy, Stallergenes Greer Plc and ALK-Abelló in grass allergy and ALK-Abelló in ragweed allergies. More recently, ALK-Abelló was also able to register a sublingual tablet, Mitizax/Acarizax, to treat house dust mite allergy, an indication where a less than 20% benefit was considered acceptable by regulators.

The following are some clinical trial strategies that have been shown to be effective:

Enrolled patients must not only be sensitised but also symptomatic: Patients with allergies often have multiple sensitivities which do not always translate into clinical symptoms. Skin sensitivity (or serum IgE) against a specific allergen is therefore insufficient to select a patient for a trial. Most successful trials have screened patients first for sensitivity to the allergen and then through an allergen provocation test, to ensure that they do experience clinical symptoms when exposed to the allergen. A baseline

season of data collection or the history of allergy symptoms requiring medication during the previous annual season(s) may also be useful for this purpose although not as reliable as a direct provocation test. The natural history of the allergic disease is such that some patients may no longer be symptomatic even though they were during the season preceding the trial.

Accounting for variability and placebo effect: It is known that the improvement of patients receiving placebo may be significant in allergy trials. The allergic disease presentation is highly variable between patients, as is the response to treatment. The response may also be accompanied by a spontaneous resolution of symptoms in some patients. As in any pharmaceutical drug development, subject and disease variability must be accounted for in the calculation of the number of subjects necessary for the trial. Thus, the sample size of pivotal AIT trials must be at least 100-150 patients per treatment group. It is actually often closer to 200-300 patients per treatment group. An additional placebo effect can still be a challenge, particularly in perennial allergies where no clearly defined natural exposure season occurs. Having to ensure allergen exposure artificially for the purpose of the trial may in itself affect the placebo response in the trial. It has been hypothesised that the regular exposure to cats during a cat allergy field study may desensitise the patients recruited for the trial and thereby lead to an improvement in the placebo group which renders the treatment effect very difficult to detect.

Ensuring natural allergen exposure during the trial: Even with efficacious products, a sufficient number of patients, and in an indication with a well-defined natural allergen exposure season, some development trials have failed. Low natural allergen exposure during the year of the trial may be responsible for these results. This could occur because of low pollen levels or low allergen content in the pollen, both resulting from the weather conditions that year. Low exposure to the allergen in a trial results in fewer symptoms experienced in the placebo group and therefore creates difficult conditions for demonstrating the efficacy of the treatment. With pollen allergies, a good way of minimising the risk of a low exposure is to spread the study centres across various geographies because pollen exposure varies widely between countries in any given year and year-on-year. Having a spread of countries and centres will ensure that if the allergy season is low in a country or region, the treatment effect may still be detectable in the other centres. AIT trials usually include a secondary analysis of the primary endpoint excluding the quartile of centres with the lowest pollen exposure to test whether the trial results differ when this subgroup is excluded.

Selecting the right dose for the registration trials: A common challenge in the development of AIT products has been the method used for dose selection before going into the well-designed field trials. According to the 2008 EMA guideline, dose-finding for AIT products may be performed based on immunogenicity studies or using provocation tests. At the same time, the guideline points out that these endpoints cannot be used to establish the therapeutic dose because their predictability to real-life efficacy remains unclear. Nevertheless, for lack of a better option, innovative AIT companies continue to select the dose for Phase 3 based on immunogenicity or based on the treatment effect in a provocation test. Provocation tests may include ocular or nasal provocation tests or studies in environmental exposure chambers. These provocation tests are artificial by design and have not always correlated well to field-based efficacy. As a result, the definitive Phase 3 studies frequently include more than one dose from the dose-range identified as likely efficacious in Phase 2.

Why do recent trials fall short of expectations?

Most of the recent trials of new AIT products using the CSMS primary endpoint have failed to achieve the threshold of a more than 20% benefit vs placebo and/or reaching statistical significance. These include Anergis SA's trial in birch pollen allergy, Circassia Pharmaceuticals Plc's trials in cat allergy and house dust mite allergy and Biomay AG's trial in grass allergy.

The recent trials that have missed the mark on clinical relevance or statistical significance have been performed with new products, allergen fragments or synthetic peptides derived from selected allergens. The trials used short schedules with few pre-seasonal injections and may not have used the optimal route of administration or the right treatment schedule to induce tolerance to the allergen. The addition of an adjuvant or carrier to rapidly induce allergen tolerance may well be necessary to achieve the full potential of any short course AIT[2].

At Anergis, we continue to believe that the future of allergy treatment will be in short-course tolerance induction providing allergy symptom relief for several years. However further research is needed to identify the right mix of antigens, the right treatment schedule and the right adjuvants. With this clear goal in mind, we are currently studying the use of virus-like particles combined with a carefully selected toll-like receptor agonist as the most promising avenue of research.

References:

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