

Design of Clinical Trials With Patch Test Allergens in the Netherlands

Thomas Rustemeyer

Introduction

This presentation has tried to address the following subjects: 1. legal aspects, 2. test materials and methods, 3. selection and recruitment of volunteers, and 4. data collection, organization and analysis with respect to clinical trials with patch test allergens. Finally, several recent examples of principal study questions and designs were given.

1. Legal aspects

All human studies have to fulfill regulations defining rights and duties of all persons involved in these trials. Hereto, research protocols have to be written according to the rules of the respective research center(s). The required regulations can be obtained from the involved research boards. The protocols are then judged by, first, the scientific research board. This research board aims to strengthen fundamental and patient related research and to improve patient care. This board studies whether the proposal addresses a scientific resilient question, whether the given background information supports the research question, whether the suggested materials and methods are appropriate to answer the question, whether the size of the study population is sufficient (power assessment) and whether the study aims to publish the obtained results. Furthermore, this board judges on the amount of reimbursement of volunteers and ensures the correct insurance of participating volunteers. Upon their approval or, if necessary, after conducting required improvements and subsequent approval, the protocol will be forwarded to the central committee on research involving human subjects in the Netherlands. This is a national committee and guarantees the implementation of Dutch laws on research on human subjects. Furthermore, all research projects in the Netherlands are registered and regional medical ethical committees are monitored. In addition, the principal scientific and ethical aspects will be assessed. Upon the approval by this national board, protocols

can be submitted to the local ethical committee. They will assess potential ethical dilemmas according to Dutch law and, at our university, according to the policy of the VU university medical center based on its Christian background. These include issues such as privacy regulations, appropriate study budget, style and contents of patient invitation letter, informed consent form, notification letter to general practitioner and patient's study file.

2. Test materials and methods

In general, contact allergens are skin contact materials of our daily life and are chemically exactly defined. They can act as contact allergens due to their intrinsic capacity to mount specific T cell responses. They are not known to be toxic, teratogenic or mutagenic. Hence, the principal risk of participating volunteers in clinical studies (and in routine diagnostic procedures, however at a very low chance) is the iatrogenic sensitization during the controlled skin exposure. In order to minimize this risk, certain safety steps have to be followed. The test materials and concentration has to be determined on the basis of available human, animal and *in vitro* data. If insufficient solid information is available, test concentration studies have to be conducted first aiming at the identification of the highest non skin irritating concentration. Hereto, also new *ex vivo* skin explants models and *in vitro* skin culture models can be used. These models also facilitate the distinction of aero-allergens from contact allergens. In clinical trials, potential aero-allergens have to be administered with great care due to the imminent risk of life-threatening anaphylactic shocks. This is in sharp contrast to contact allergens lacking this danger. There are only few different test methods for contact allergens. These include open skin test, patch tests and use tests. If contact allergens can cause skin irritation open tests can be used. The mainly applied test method, however, is the patch test, which is also used in daily routine diagnostics. Tiny amounts of the test substance solved in appropriate vehicles are given on plastic or alumina chambers that are on a self-adhesive patch. These patches are applied on the upper back of the volunteers and have to stay in place between 24 to 48 hours. Upon removal test sites will be marked and skin test readings will be done directly, after 24 and sometimes even after 120 hours after patch test removal. If positive, little skin eczematous reactions are evoked, which will be scored according to the presence of distinct clinical signs. After few days, these mini-eczema reactions will vanish. Another skin test used in clinical studies of contact allergens is the use test. Hereby, consumer cosmetic products are used as intended and potential skin reactions are recorded after few days up to two weeks.

3. Recruitment of volunteers

Volunteers participating in clinical patch test studies can be recruited by advertisements. Hereby it is important to notice that the amount of reimbursements shall not appeal potential volunteers. When individuals are needed with a certain known condition, e.g. existence of known contact allergies, volunteers can be identified from electronic databases of the VU university medical center and other participating centers.

4. Data collection, organization and analysis

The appropriate preparation of clinical patch test studies takes in general 6 to 8 months. The conduction of the study can vary from few months up to few years. The final data collection, organization and analysis can take few months again. Hereto, an electronic database is used. This database is developed by a medical statistician and an ICT specialist who have translated the scientific questions into this electronic database that allows for extended statistical analysis.

Typical research questions addressed in patch test studies include issues such as analysis of the reactivity of a selected group of (exposed) individuals towards certain contact allergens and assessment of the reactivity of patients with known contact allergies to other (related) allergens.

Discussion

Robinson: These may be completely naïve questions concerning patch testing. Could you comment on the effect of the presence of IgE to the test allergen? If you are testing e.g. dust mites or mould or something like that. And could you also comment on the use of patch tests for non-skin-related diseases such as food allergy?

Rustemeyer: The first one: Definitely, you can have a kind of contact eczema due to house dust mite and dander and IgE reactions might also be involved. This has been nicely published by Werfel, for example. What is completely different is the pathomechanism where you have Langerhans cells bearing the specific IgE and this causes inflammation. But this is not involved in contact allergies in man. In mice you can have antibodies but not in men, they do not have a tail either. As for your second question, in fact we can use patch tests also for diagnosing drug allergies. This is not necessarily via skin contact; think about penicillin. Another good example is Abacavir, which is one of these anti-HIV drugs. Therefore, if you suspect an HIV-positive patient to be sensitized to Abacavir you have to perform patch tests. This is the gold standard for that and based on these patch test reactions it has been shown that Abacavir does have a certain genetic background of susceptibility.

Vieths: I have a question regarding the financial basis of your studies. You mentioned that some are funded by EU, but you performed a number of other studies. Were these sponsored by companies or by public money?

Rustemeyer: All three are true. We get some EU funding and of course we have national funds. In fact, we tried to avoid company-financed studies. We had been quite successful in raising national money.

Mäkinen-Kiljunen: This is rather a comment to the question asked before. The first reading is 48 hours after contact with the allergens. So the IgE response is not involved anymore. You can read, if you want, 20 minutes or so after applying the patches on the back; but after 48 hours, IgE has nothing to do with the reaction.

Robinson: I do not see how you can say that, it might have done at the initiation. That is important, too, the IgE will have something to do with the allergen presentation, I am sure.

Rustemeyer: Definitely. If we have very early reactions, it is probably immunoglobulin-mediated, it might be IgE. And for these patch tests we do not have positive reactions after a quarter of an hour, it takes hours to several days to develop, and still it is IgE-mediated. The allergens are kept in place and the inflammation goes on.

Geyer: I would like to comment on the special situation that we have in Germany. We have a very well-working network of departments of dermatology interested in contact allergy and we used to perform patch test studies on a large scale, say 1000 to 2000 patients, within a few months in 20 to 40, or even 50 collaborating centers. And since some time we face big problems in performing these tests, because, in contrast to the situation in the Netherlands, these patch test allergens are obviously regarded as drugs in Germany. And so you have to perform every study according to the Drug Legislation. This means that you have to do, e.g., a very extensive monitoring and you cannot finance this patch testing thousands of patients in say 20 to 40 centers because you do not find any sponsor for this. You know, you cannot earn much money with patch test substances. They are not very expensive to buy and you do hardly find any company that is interested in detecting contact allergens. So we are trapped. We have to perform studies according to the German Legislation, but we cannot finance it. For the last few years we did not perform any studies any more. Currently, this kind of clinical trials is dead in Germany. It is a very bad situation.

Vieths: Can I make a brief comment on the legal basis, because I was surprised about what you told us. It is not German Legislation but an EU directive, which clearly defines skin test allergens as medicines. So I was surprised that the definition in the Netherlands is different. Actually, I think that you would clearly demand that you perform those studies under “Good Clinical Practice” conditions.

Mari: I think it is important to stress that it is not the methodology that we use, but the compounds that we use that leads to these problems. So we could be in a very strange situation where extracts used for patch tests would not be considered drugs, whereas those used for skin testing – I mean IgE-mediated testing – would be considered drugs. I agree with you that they all should be considered drugs. I also would like to remind you that a patch test takes 48 hours. So we need to take care of the presence of other compounds, like endotoxins, in the extracts we are using; because they can stimulate the skin and thus produce false-positive results.

Rustemeyer: Right, but the test materials are mostly chemicals, they are really pure.

Mari: I am sorry. You are in an environment where everyone is thinking about extracts.

Rustemeyer: And then, in preparation for today, I have drawn information not only from our local medical ethical committee but also from the national one. And they really said it is indeed EU legislation, but it has been adapted or it has been changed somehow according to the national requirements.