Editorial

Nonimmediate drug allergy: Diagnostic benefit of skin testing and practical approach

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Adverse drug reactions assumed to be due to a drug allergy are a frequent problem in clinical practice. Information obtained from history alone is often not sufficient to make a diagnosis or to identify the culprit drug in patients who are frequently exposed to many different drugs. In these situations allergists often use drug skin tests with the incriminated drug or drugs to confirm or exclude a drug allergy, to identify the culprit drug, or both. Although there is some knowledge on how to apply and interpret skin test results for the diagnosis of immediate-type allergy to beta-lactams,[1] there are few data about skin tests for nonimmediate-type allergy, which in many areas of the world is more frequent.

In this issue Romano et al[2] report the results of a thorough allergologic diagnostic workup including skin and provocations tests in patients with a history of nonimmediate hypersensitivity to cephalosporins. The letter provides interesting and important scientific data on the diagnosis of this condition. It also illustrates common problems of diagnostic tests for nonimmediate drug hypersensitivity reactions as follows.

There is currently no established gold standard for the diagnosis of a delayed-type allergy. Romano et al[2] used weekly challenges with first one hundredth and then one tenth and finally one single therapeutic daily dose. However, it is well documented that some nonimmediate reactions appear only after a treatment of several days at full therapeutic dosage.[3] Furthermore, cofactors, such as concomitant viral infections, are considered important, and these are normally not present during challenge tests. Thus only a positive test result is conclusive, and even challenge tests are not an unequivocal gold standard. The authors discuss this issue briefly and imply that their challenge was appropriate at least for the detection of moderate-to-strong sensitization and allergy. This is a reasonable hypothesis. A long-term follow-up of the tested patients with therapeutic re-exposure during diseases might further substantiate this hypothesis.

Sensitivity and specificity can only be measured if one knows the true-positive and true-negative values of a test result. Let us first address sensitivity. It requires not only the detection of patients with drug hypersensitivity in spite of negative skin test results (false-negative results) but also the number of patients with positive skin test results who really have drug hypersensitivity (true-positive results). Assessment of the number of subjects with true-positive results (eg, challenge tests) is problematic for several reasons. As outlined above, there is no established test procedure for challenge tests; the optimal test procedure and accuracy are unknown, and guidelines make it obsolete to use challenge tests in patients with severe drug hypersensitivity. Moreover, drug hypersensitivity is an iatrogenic disease, and particular care should be taken to avoid further harm (*primum non nocere*!). Challenge tests in subjects with positive skin test results might provoke a long-lasting reaction. With the exception of 1 patient, such challenges were consequently not performed in the study by Romano et al,[2] and thus they do not comment on test sensitivity.

In many publications addressing skin tests for the diagnosis of drug hypersensitivity, the lack of knowledge of the number of true-positive results has been bypassed by reporting the negative predictive value. The negative predictive value (or negative posttest probability) stands for the probability that a patient with a negative test result has no allergy. Under the assumption that the performed challenge was an appropriate gold standard, the negative predictive value in the study by Romano et al[2] can be calculated as being very low as follows: Negative predictive value = False-negative results/(False-negative results + True-negative results).

However, the predictive value is not only dependent on test accuracy but also on the pretest probability. Pretest probability stands for the probability that a patient has an allergy before testing. It is influenced *inter alia* by patient selection and is practically never known in patients who undergo skin tests for the diagnosis of drug allergy either in studies or in the doctor's office. A low negative predictive value might be entirely due to a very low pretest probability. The predictive value is hence inappropriate to characterize the test accuracy of skin tests in patients with drug allergy and might even be misleading.

How can one circumvent this obstacle? Romano et al[2] made sure that the specificity of their test was excellent: they used skin test concentrations that were proved to be nonirritating in 30 control subjects, 20 of whom had tolerated at least 1 of these aminocephalosporins. Therefore we can expect that most or all of the 6 positive test results are true-positive results. This assumption allows the sensitivity to be estimated as follows: Sensitivity = Number of true-positive results/(Number of true-positive results + Number of false-negative results).

In their study the authors were able to check negative skin test results by means of provocation in 86 of 98 patients. Except for 1 patient (with a doubtful intradermal test result), all provocations were tolerated without any hypersensitivity reaction. The number of observed false-negative results was 1, and we can estimate

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sensitivity as 86% (6/[6 + 1], assuming that all patients who did not accept a provocation had true-negative results) or as at least 32% (6/[6 + 1 + 12], assuming that all patients who did not accept a provocation had false-negative results). This is better than has been described in children with nonimmediate-type penicillin allergy.[4,5]

What does this mean for the practitioner who is faced with patients with possible nonimmediate drug allergic reactions outside the realm of scientific studies? First, there is neither a reliable single diagnostic tool nor a validated evidence-based procedure available for the diagnosis of nonimmediate drug allergy. It would certainly be helpful if a solid history would more often be available, with a well-documented sequence of exposure and symptoms. The medical community has to become aware of this problem, and guidelines need to be established.

Second, intradermal skin tests with late reading might be useful. If they are performed in concentrations proved to be nonirritant, a high specificity (and also a good positive likelihood ratio) can be assumed. In patients with a suggestive clinical pattern and history, a positive test result is thus a strong corroboration of the diagnosis of a drug allergy. In these situations the causative drug should be avoided, further investigations are redundant, and a challenge test would put the patient in unnecessary jeopardy.

Third, the situation is more complicated if the history is suggestive but the skin test result is negative. According to the data currently available, the sensitivity (and also negative likelihood ratio) of skin tests is only moderate, and thus a negative skin test result does not exclude the diagnosis of a nonimmediate drug allergy. In the case of an immediate reaction, many authors recommend a further investigation by using challenge tests. However, for nonimmediate reactions, challenge tests are much more problematic. In particular, it is not clear for how long one should challenge, such as 1, 3, or 7 days or with weekly incremental single doses, as in the study by Romano et al.[2] One should keep in mind that a diagnosis is a means for optimal further management and not an end in itself. Avoiding further use of the incriminated drug without performing a challenge test might be a pragmatic and widely used approach, especially if the incriminated drug is easy to replace. When the incriminated drug (or drug class) is difficult to replace and there is an urgent need for this treatment, a stepwise (graded) challenge might be an option, hoping to eliminate those reactions that are due to strong sensitizations. Altogether, the situation is not yet satisfying, and improvements in *in vivo* and *in vitro* evaluations of these reactions are urgently needed.

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