

EDITORIAL

A position paper on drug allergy – pinpointing problems rather than suggesting solutions

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A position paper is an essay presenting an opinion about an issue, typically that of the author or another person or group. Such papers are also used by large organizations to publicize their official statements and recommendations. Position papers in academia permit discussion on emerging topics without the experimentation and original research accompanying or preceding an academic paper. Commonly, a document of this nature will substantiate the opinions or positions put forward, with evidence from an extensive objective discussion of the subject.

The diagnostic and treatment modalities deployed in the evaluation of drug allergy/hypersensitivity reactions (DHRs) by members of the World Allergy Organization are quite heterogeneous (1). The diagnosis of DHRs is primarily based on a detailed clinical history (2) and *in vivo* procedures, such as skin tests (3) and drug provocation tests (4), as well as *in vitro* tests. Whereas guidelines for the first three columns for this purpose were published already several years ago, generally accepted recommendations for the fourth are still missing. A variety of *in vitro* tests, including some to characterize the active phase of a reaction (5) and tests and procedures to identify the culprit drug (6, 7), have been published and recommended in specific position papers (8) and are performed in daily practice. However, no more than a handful of these can be given a grade B recommendation or above, mainly because of the absence of well-controlled studies.

Thus, the European Network on Drug Allergy and the Drug Interest Group of the EAACI have organized a task force to provide data and recommendations regarding the existing *in vitro* methods for the diagnosis of DHR. The outcome is presented as a position paper in this issue (9). Several tests to characterize the active phase of the reaction, such as determination of tryptase, histamine and its metabolites, as well as cell analyses in skin biopsies and peripheral blood, are reported on extensively. Even greater attention is given to tests for the identification of the culprit drug, ranging from specific IgE determination to cellular tests, including mediator release such as histamine and leukotrienes, basophil activation tests, HLA allele determination, lymphocyte transformation tests, ELISpot, cell marker definition, and cytokine release. All of these are listed and critically evaluated, and the results presented in detail.

An extensive literature search revealed a number of studies that pretend to prove or disprove beta-lactam allergy (10), acetylsalicylic acid intolerance (11), and many others, by applying such tests. However, the critical comparison of positive, negative and mixed results has led to contradictory propositions.

The overall conclusions of the task forces work are brief and disillusioned. To quote the authors: the attempt to reach a diagnosis is complex, time-consuming, expensive, and not risk-free. As regards the majority of the current *in vitro* methods, only few of them show enough evidence for at least a grade B recommendation.

So why perform these tests? The resulting recommendations seem to contradict the aim of a position paper. The reader does not learn how to correctly diagnose DHRs in daily practice. Instead, the reader gets to know that the experts have identified several important unmet needs which should be addressed first: which patient to test, for what reaction, which drug, which test to apply, at which laboratory, etc. The final message, it appears, is that the grades of recommendation given in the position paper are rather low. Therefore, one might conclude that the experts should first spend their time developing reliable tests before writing an extensive position paper on a topic that does not permit specific recommendations at the present time.

Before reliable tests will be developed, detailed history-taking remains the basis, skin testing the *in vivo* testing approach, and provocation testing the gold standard (4). Notably, even this approach is not as ideal as it is postulated to be. And currently marketed *in vitro* tests seem to be overestimated in regard of their validity; new tests for drug hypersensitivity diagnosis are most welcome although not really foreseeable in the near future. But a critical position paper such as the current one (9) may well serve as a potent promotor of this delicate and essential task.

When the experts in the field acknowledge the paucity of well-controlled studies and assert that much of the information on the subject is derived from small studies with few case numbers, the resulting conclusion is simple: Do not complain, just start performing large studies with well-defined patients and reproducible procedures. This is undoubtedly the need of the hour if we wish to publish position papers or guidelines for nonexperts who will gladly welcome the data.

So why publish a position paper now that tells us more what not to do instead of what to do? First, this paper does inform the nonexpert in detail on the few capacities and the many limitations of *in vitro* testing methods regarding DHRs currently in common use. And it should motivate the experts to urgently develop *in vitro* test methods that better reflect the degree and the relevance of the sensitization status of patients suffering from suspected drug hypersensitivity. The concluding list of *identified unmet needs, which should be addressed in the future* is most important: The experts thereby have defined our homework. And we have a concise survey

of the existing *in vitro* tests in hand, their capacities, and also their many limitations.

Conflict of interest

None.

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