Editorial

Statin Allergy: An Evidence-Based Approach

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Statins inhibit 3-hydroxy-3-methylglutaryl-coenzyme a reductase, a key enzyme in cholesterol biosynthesis, resulting in a dose-dependent reduction in plasma levels of low-density lipoprotein cholesterol. Statins are by far the most widely used class of lipid-lowering drugs, taken by millions of patients every day, for many years. And statins appear to be remarkably safe.[1] Severe adverse effects are rare, and the benefits associated with the reduction in cardiovascular events outweigh the increase in incidence of diabetes.[2] Allergic reactions are not even mentioned in respected textbooks.[2]

In this issue of the journal, Ogai et al[3] describe a reaction in a 59-year-old man with coronary artery disease and hyperlipidemia. Thirty minutes after the first dose of simvastatin, taken at home, he reported by phone to have developed a sensation of numbness and tingling of the distal extremities and face, progressing to generalized urticaria, angioedema of the lips and tongue, and throat tightness. No specific treatment was necessary, and the symptoms resolved spontaneously. No other new medications were administered around the time of this reaction. Nobody witnessed the intake of simvastatin, the symptoms, or the information given by the patients via phone call.

An allergy to simvastatin was assumed, but no skin testing, *in vitro* testing, or provocation testing with this drug was performed. Instead, after a negative skin test result with the structurally quite different synthetic statin rosuvastatin, the patient was admitted to an intensive care unit and underwent a 3-dose challenge to rosuvastatin, which he tolerated well. The authors concluded that their case provides evidence supporting challenge to a different type of statin drug as a safe therapeutic alternative to desensitization in patients with immediate-type reactions and a clear indication for statin therapy. And they propose an algorithmic approach to the evaluation of patients with presumed IgE-mediated statin allergy. This algorithm starts with the indication of "known IgE-mediated reaction to statin." Here, the problem of this publication, that mirrors daily-life experience, begins!

The authors did not try to prove an IgE-mediated reaction to the suspected statin, simvastatin. They have based their diagnosis solely on a telephone report given by the patient. When drug allergy is suspected, the first thought should be to prove or disprove the suspicion.[4] Misclassification based solely on history without further testing may affect treatment options, result in adverse consequences, and lead to the use of more-expensive or less-effective drugs, in contrast to patients who had undergone a complete drug allergy workup.

The authors performed a 3-dose challenge with an alternative drug in an intensive care unit. Why did they not first perform a skin test and, if the result was negative, a provocation test with the original preparation in a normal ward, or in a well-equipped office? We would have done that. There are no standardized skin test concentrations given in the literature[5] for simvastatin, but the same is stated by the authors to be true for rosuvastatin, yet they performed skin tests to rosuvastain. And the same is again true for the provocation test—daily practice in an experienced institution![6]

In the recently published international consensus on drug allergy,[7] key points regarding drug-hypersensitivity-reaction (DHR) diagnosis can be summarized as follows:

1. A definitive diagnosis of a DHR is in many cases required to institute proper preventive measures; however, the authors of the present report did not even try.
2. Misclassification based on the DHR history alone may have consequences on individual treatment choices and be more detrimental for the patients than a complete drug allergy workup. This seems particularly relevant regarding this case: the full workup would have been easy, but the consequences minor. Whether the patient receives simvastatin or rosuvastatin should not make a major difference, except regarding the price, because rosuvastatin is more costly.
3. The clinical tools allowing a definitive diagnosis include a thorough clinical history, standardized skin tests, reliable *in vitro tests*, and drug provocation tests. As noted above, the authors did not perform any objective diagnostic tests but based their diagnosis on a nonverifiable phone call.
4. When properly performed in specialized centers, a reliable diagnosis is often possible and safe alternative medication can be administered. Because diagnostic procedures were not performed in this case, the necessity for an alternative medication was thus not proven.
5. Screening subjects without a history of allergic drug reactions is not recommended. This key point is valid but not relevant in this case.

In their article,[3] the authors present a simple and convincing algorithm for patients suffering from IgE-mediated reactions to statins (Figure 1 in their article). There is however one major problem—they did not substantiate their procedure in a patient proven to be suffering from an IgE-mediated reaction. A definitive diagnosis is essential, if at all possible, before labeling someone as allergic. Admittedly, acute urticaria after intake of simvastatin may occur, despite being rare, and seems to be quite indicative for an allergic mechanism. But IgE-mediated reactions typically do not occur after the first intake of a drug, such as in this reported case. And if this happens, it is unique and should be

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investigated, not taken for granted based solely on the patient's description via phone call.

The algorithm presented by the authors has face validity, and the suggested framework for evaluation seems reasonable. However, for the reasons described, their presented patient does not prove the value of the suggested approach. This will require its application to patients with more objective evidence of a statin allergy.

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