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Uncovering new potential culprits in drug allergy: non-vitamin K oral anticoagulants

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New anticoagulant drugs (Non-vitamin K Oral AntiCoagulants, NOACs) have massively entered the pharmaceutical market and are increasingly being prescribed as an alternative to vitamin K antagonists in the prevention and treatment of thromboembolism and in the prevention of stroke in atrial fibrillation (1,2). Predominantly skin adverse reactions were mentioned as side effects since the first clinical trials and isolated case reports have recently shed light on the possible role of these drugs in the induction of a specific immune-mediated response (3-7).

The present issue of *European Annals of Allergy and Clinical Immunology* focuses on emerging drug hypersensitivity reactions to NOACs as a novel chapter of drug hypersensitivity reactions (DHR) and for which a correct diagnostic approach has to be proposed and shared by allergists.

The article from Cortellini et al. (8) addresses the problem of performing a correct diagnosis in delayed reactions, assuming that the pathological mechanism is mediated by T lymphocytes (type IV DHR). The Authors report a case of delayed skin hypersensitivity reaction to factor Xa inhibitor edoxaban, in which the diagnosis was confirmed by epicutaneous tests, starting from the identification of a non-irritant concentration for edoxaban and all other NOACs. They also provide evidences of a good accuracy of this type of *in vivo* test especially at a late reading. Furthermore they highlight the possibility of cross-reactivity between different NOACs and suggest that warfarin may be tolerated as an alternative drug.

This work has prompted a more extensive review of the literature in order to better understand and classify adverse drug reactions to NOACs and to identify the most common types of DHR.

Carli et al. (9) reviewed published reports of hypersensitivity reactions to these drugs, which show a predominance of

delayed type III and IV reactions (both mild and severe), in particular for dabigatran and rivaroxaban, the earliest introduced drugs. Secondly, published papers confirm the previous suggestion by Cortellini et al. (8) that patients who reacted to NOACs, could afterwards tolerate warfarin and moreover that switching to low molecular weight heparins (LMWH) was found to be safe. A number of reported observations also leads to the hypothesis that rivaroxaban would not cross-react with other factor Xa inhibitors. The review (9) also stresses the importance of safety in dealing with a patient with a probable hypersensitivity reaction to a NOAC. As anticoagulation effect must be maintained, a multidisciplinary management in a hospital setting should be mandatory while performing diagnostic tests. Regarding the diagnostic work-up, the Authors (9) point at the unmet needs of both identifying standard techniques for prick and intradermal tests and adapting available *in vitro* tests (e.g. anti-drug antibodies, basophil activation test, lymphocyte transformation test) in relevant reactions. They also propose patch tests as first diagnostic step in mild/moderate delayed reactions, as previously described by Cortellini et al. (8), performing late readings and subsequently starting a very slow oral challenge with an alternative NOAC which resulted negative to patch tests.

Taken together the two papers on NOACs published in this issue of *European Annals of Allergy and Clinical Immunology* highlight the importance of raising clinicians' awareness on the risk of immune-mediated reactions to novel anticoagulant drugs, which might still be underestimated. Due to the complexity of dealing with patients often receiving multiple medications and suffering from cardiovascular diseases or prothrombotic conditions, a multidisciplinary approach is always recommended. Diagnostic strat-

egies are still at an early stage for this new chapter of drug allergy but a first tool for the evaluation of delayed reactions was provided: patch tests are easily available in the clinical practice. Nevertheless, more clinical and laboratory research is needed to go beyond the current probability scores and obtain a general consensus on standardized techniques in all types of DHR to novel anticoagulants.

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