

Multiple Nonsteroidal Anti-Inflammatory Drug-Induced Cutaneous Disease: Relevance, Natural Evolution and Relationship with Atopy

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Dear Editors,

The recent study by Asero [1] in the February issue of *International Archives of Allergy and Immunology* adds important information to the study of hypersensitivity reactions (HRs) to nonsteroidal anti-inflammatory drugs (NSAIDs), particularly those with skin involvement. In recent years, a considerable effort has been made by the ENDA (European Network for Drug Allergy) group of the European Academy of Allergy and Clinical Immunology in order to establish a consensus on this topic. As a new classification of NSAIDs hypersensitivity has been proposed, we will use the new nomenclature here [2]. Thus, we will refer to the chronic spontaneous urticaria (CSU) that exacerbates with NSAID intake as NSAID-exacerbated cutaneous disease (NECD), whereas urticaria/angioedema induced by multiple NSAIDs in subjects without a history of CSU is defined as NSAID-induced urticaria/angioedema (NIUA) [2]. Both phenotypes belong to the group of nonimmunologically mediated (cross intolerance) HRs to NSAIDs. There are several statements in Asero's article that we believe warrant further comment and clarification.

In the introduction, the author stated that NSAIDs are probably the second most frequent cause of HRs following beta-lactams, even though NSAIDs are the most highly consumed drugs worldwide. In our view, this statement is frequently used in publications without appropriate supporting references. Although few studies have been carried out on this topic, current evidence indicates that NSAIDs are the most frequent group of medicines triggering HRs [3, 4]. In the work by Messaad et al. [3], the highest percentage of positive challenges was found for aspirin and other NSAIDs and to a lesser extent for macrolides, quinolones and beta-lactams. In the work by Doña et al. [4], which includes the largest series of subjects suffering from HRs to drugs studied to date, the most frequently confirmed diagnosis was hypersensitivity to multiple NSAIDs (47.29%), followed by immediate reactions to beta-lactam (18.12%) and quinolone (6.8%) antibiotics. A recent multicenter study presented at the last meeting of the American Academy of Allergy, Asthma and Immunology including more than 700 cases from 11 countries showed that NSAIDs account-

ed for 55 and 60% of reactions in adults and children respectively, whereas beta-lactams were responsible for less than 20% of the reactions in both groups [5]. Moreover, recent works by Zambonino et al. [6, 7] showed that only 8% of patients with symptoms suggestive of beta-lactam hypersensitivity could be confirmed as such compared to 68% for NSAID-hypersensitive patients. Therefore, we believe that sufficient information is now available to state that NSAIDs are the drugs most frequently involved in HRs.

We also have some comments with regard to the natural history of NIUA. Asero [1] found that 20% of patients with NIUA developed CSU over time. However, no control group was used, and thus we do not know the baseline rate for developing CSU in the general population. Recent work by our group has shown that after following up a large series of patients over a period of 12 years, the risk of developing CSU in the course of NIUA was similar to those of a negative control group of healthy individuals and a group of patients suffering from selective urticaria induced by NSAIDs, now known as SNIUA [8]. We believe that

these control groups are necessary to verify whether the association of CSU with NSAIDs is significant or not.

Our final comment concerns the atopy-related data presented by Asero [1]. A similar prevalence of atopy can be found for both NIUA and NECD patients, and the value is lower than those found in other studies. In a recent study from our group, the preva-

lence of atopy in NIUA was found to be 60% compared to 40% for controls [9]. In the work of Asero, the prevalence of atopy in the general population was not provided, therefore, the relevance of atopy for the two NSAID-hypersensitive groups studied cannot be put into context. Our data highlighting the high prevalence of atopy in patients with HRs to NSAIDs are in line with other

studies [10–12]. In general, other studies have also supported the role of atopy in chronic urticaria [13, 14]. In our experience, atopy (defined as the percentage of positive skin prick test results to inhalant allergens) is present in around 25% of CSU patients [unpubl. data]. Whether atopy is highly prevalent in NECD remains to be verified and requires further study.

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