Allergy Asthma Immunol Res. 2021 Mar;13(2):171-172
https://doi.org/10.4168/aair.2021.13.2.171
pISSN 2092-7355·eISSN 2092-7363

Allergy, Asthma & Immunology Research AAIR

Editorial

Clinical Characteristics of NSAID-induced Blended Reaction

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▸ See the article "Clinical Characteristics, Urinary Leukotriene E4 Levels, and Aspirin Desensitization Results in Patients With NSAID-Induced Blended Reactions" in volume 13 on page 229.

Received: Dec 17, 2020
Accepted: Dec 18, 2020

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Disclosure
There are no financial or other issues that might lead to conflict of interest.

Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) is the most common drug hypersensitivity. A recent study proposed the classification of NSAID hypersensitivity into 5 phenotypes: NSAID-exacerbated respiratory disease (NERD); NSAID-exacerbated cutaneous disease (NECD); NSAID-induced urticaria, angioedema, or anaphylaxis (NIUAA); single NSAID-induced urticaria, angioedema, or anaphylaxis (SNIUAA) and single-NSAID-induced delayed reactions (SNIDR).[1,2] NSAID hypersensitivity can also be classified as cross-reactive reactions or single NSAID-induced reactions. Cross-reactive NSAID hypersensitivity is often mediated by non-immune (*e.g.*, COX-1 inhibition) reactions caused by 2 or more NSANIDs with different chemical properties. Cross-reactive NSAID hypersensitivity is characterized by the overproduction of cysteine leukotriene (CysLT). In contrast, single-NSAID-induced reactions are mediated by immune responses (*e.g.*, immunoglobulin E or T-cell mediated).

More than 2 phenotypes of NSAID hypersensitivity have been described as NSAID-induced blended reactions (NIBR).[3,4] We have previously shown that 20% of NERD patients had a NIBR, NERD plus NECD/NSAID-induced urticaria, angioedema (NIUA). Compared to patients with NERD, those with NIBR had better clinical outcomes and lower eosinophil counts, and required lower medication requirements. These findings suggest that the clinicopathological characteristics of NERD differ from those of NIBR. The study in the current issue of *Allergy, Asthma & Immunology Research* analyzed the clinical characteristics and urinary leukotriene E4 (LTE4) levels in a Thai patient cohort with NSAID hypersensitivity.[5] The prevalence of NIBR among patients with NSAID hypersensitivity was higher (33.3%) than the prevalence reported in previous studies.[3,4] Some NIBR patients presented with NIUA plus upper airway and eye symptoms; facial angioedema around the periorbital area was the most common symptom of NIUA. Although these findings are similar to findings in southern Europeans and Latin Americans, different symptoms are reported in patients of northern European descent and in Korean patients.[3,6] Acetylsalicylic acid (ASA) desensitization alleviated skin rash, urticaria, and nasal and airway symptoms, indicating that NIBR classification is necessary for patients with NSAID hypersensitivity.

Increased CysLT levels with reduced PGE2 levels (before or after ASA/NSAID provocation testing) are the key findings in patients with NERD; therefore, urinary LTE4 level is the most reliable biomarker for distinguishing NERD patients from NSAID-tolerant asthmatic patients.[7-9] However, the increased level of urinary LTE4 before or after the ASA provocation test is not a consistent finding in patients with other forms of NSAID hypersensitivity except

those with NERD. Klaewsongkram *et al.*[5] reported that, in contrast to patients with other types of NIBR, patients with cross-reactive types of NIBR (NERD plus NIUA/NECD) exhibited increased urinary LTE4 levels after oral provocation tests. There is one study showing a significant increase in urinary LTE4 levels (up to 150 pg/mg creatinine) after ASA provocation test in patients with NIUA or NECD[10]; these levels were lower than those of NERD patients of this study (500–1,000 pg/mg creatinine).[5] These findings suggest that the urinary LTE4 level is not a reliable biomarker of NIUAA or NECD and that further studies are needed to establish more accurate NIBR classification guidelines.

In conclusion, NIBR needs to be distinguished from common NSAID hypersensitivity reactions (NECD/NIUA or NERD) as it has different underlying mechanisms and clinical outcomes.

ACKNOWLEDGEMENTS

This study was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health & Welfare, Republic of Korea (H116C0992).

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