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Editorial

Phenotypes In Immunological Occupational Asthma: What You See Is Not What You Get

Fenotipos en asma ocupacional inmunologico: lo que se ve no es lo que hay

Occupational asthma (OA) is the most common work-related respiratory disease in developed countries[1] and is defined as asthma that is caused by agents present in the affected individual's workplace and not outside it. It is divided into immunological OA (IOA) and irritant-induced OA.[2] The diagnosis of irritant-induced OA is usually straightforward and based on the clinical history, but this is not the case for IOA, in which to differentiate it from work-exacerbated asthma (WEA), it is often necessary to perform a specific inhalation challenge.[3] Both entities (OA and WEA) form what is referred to as work-related asthma.[4]

Unlike common asthma, IOA has traditionally been divided, based on the mechanisms of action of the different causative agents, into IgE-mediated and non-IgE-mediated IOA. In general, high molecular weight (HMW) agents, essentially proteins, cause IOA via an IgE-mediated mechanism, while low molecular weight (LMW) agents, essentially chemical agents, do so by mechanisms that are not yet fully understood.[5] Also, since IOA was first described, it has been apparent that the clinical phenotype differs according to whether the asthma is caused by HMW or LMW agents and therefore whether or not it is IgE-mediated. IOA caused by HMW agents appears to have a shorter latency period between exposure and onset of symptoms, is usually associated with rhinitis, conjunctivitis and/or dermatitis, the symptoms usually occur soon after exposure to the agent, and on inhalation challenge there is usually an early or dual reaction. In contrast, in IOA caused by LMW agents, the latency period is usually longer, the symptoms occur later and may even occur when the patient is outside of the workplace and on inhalation challenge they are usually observed as a late reaction.[6]

Currently, with the new concepts of personalised, precision medicine, until there is a better understanding of the pathophysiological mechanisms that could provide reliable biomarkers to guide appropriate treatment, in the field of asthma in general and OA in particular, there is increasing use of the inflammatory phenotype as the (most likely) best marker of the underlying pathophysiological mechanisms. Therefore, in the specific case of IOA, at the end of the 1990s and the beginning of the 2000s, several studies, mostly carried out in Canada, demonstrated that patients with IOA had a significant increase in sputum and blood eosinophils when at work compared with periods outside the workplace.[7] However, in the context of the specific inhalation challenge (SIC), there was an increase in median sputum eosinophil and neutrophil numbers in subjects with positive SIC responses independently of whether they were exposed to HMW or LMW agents.[8] It was also observed that in patients with IOA due to isocyanates there was a significant correlation between the maximum percentage decrease in FEV1 after exposure to 1 ppb and the increase in sputum neutrophils.[9] On this background of some doubt as to whether there was always an eosinophilic response independently of the agent of if an eosinophilic response may occur with a HMW agent or a neutrophilic response with a LMW agent, Prince et al.[10] demonstrated that either an eosinophilic or a neutrophilic response could occur in the context of the SIC independently of whether the asthma was caused by a HMW or LMW agent. Similar results were also found by Sanchez-Vidaurre et al.[11] Most of these studies were conducted in a single centre and one of their main limitations was the low number of patients that were ultimately included.

Recently, 15 centres from 11 European countries decided to generate a cohort of patients with a confirmed diagnosis of IOA, based on the SIC, with the aim of being able to study all of these factors in a larger number of patients. Analysing 1180 patients with IOA, 635 (53.8%) secondary to HMW and 544 (46.2%) due to LMW agents, we were indeed able to demonstrate that there was a clear difference in clinical phenotype between the two populations, without observed differences at the inflammatory level. While subjects with IOA due to HMW agents, and therefore driven by an IgE-dependent mechanism, had a higher incidence of rhinitis, conjunctivitis, atopy, early response on SIC and a greater tendency to chronic airflow limitation, patients with IOA induced by LMW agents had more chest tightness, more expectoration, late response on SIC and more exacerbations. Although the peripheral blood eosinophil count was higher when the asthma was caused by HMW agents, the sputum results showed no differences for the two different types of agent. Independently of whether the asthma was caused by HMW or LMW agents, the percentage of eosinophils and neutrophils was similar, as were the observed increases in both cells after SIC.[12]

The interpretation is clear: what you see is not always what you get, at least in terms of the inflammatory response. Patients with IOA caused by HMW agents, with a clinical phenotype that is clearly distinct and in whom there is undoubtedly an IgE-mediated mechanism, can have an eosinophilic or a neutrophilic inflammatory response. This variability in inflammatory response is more understandable in cases of IOA caused by LMW agents in which, as

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mentioned above, the mechanisms that produce this asthma are not fully understood. Undoubtedly, evidence that the same pathophysiological pathway can result in distinct inflammatory responses opens new avenues for future clinical research that should bring us closer to the ultimate goal of finding biomarkers that allow us to deliver precision treatment to these patients.

Conflicts of interest

Xavier Muñoz has received fees as a speaker, scientific advisor or participant of clinical studies from (in alphabetical order): AstraZeneca, Boehringer Ingelheim, Chiesi, Faes, GlaxoSmithKline, Menarini, Mundifarma, Novartis, and Teva.

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