Immunotherapy with fungal allergens. Can we consider it precision medicine?

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Dear Editor,

Health sciences are currently pursuing a path of precision medicine, which is characterized by individualized treatment for each patient based on genotypic, pathophysiological, and environmental characteristics. Allergen immunotherapy is one therapy type for which precision medicine is more feasible.

With the improvement of allergen extracts, we can now perform diagnosis and immunotherapy more effectively. We know that allergen immunotherapy depends on an accurate diagnosis of IgE-mediated hypersensitivity to ensure the specificity of treatment, as well as an extract that contains the exact allergens to which the patient is sensitized.

Thus, the efficacy of immunotherapy depends on the relevance of the allergen it involves. For example, what is the point of accurately diagnosing hypersensitivity to dog hair antigens and beginning immunotherapy with an extract containing precise and specific allergens if the patient is not exposed to dogs? Relevance is a fundamental factor for good immunotherapy practice.

Therefore, we ask: is recommending immunotherapy with fungal allergens precision medicine? Below we will discuss hypersensitivity, the extracts used in immunotherapy, and their relevance.

In fungal growth cultures, the type of protein expressed by the fungus is directly related to the culture medium in which it is grown and the point at which the fungus is extracted.[1] For example, *Aspergillus spp.* grown in Fava-Neto medium and extracted after 30 days of cultivation will express different proteins than those expressed by the same species grown in another culture medium and extracted after 40 days of cultivation. Since fungal allergens consist of proteins or peptides, the culture medium and the cultivation period will directly influence the type of allergens present in the extract.[1] This becomes significant when less precise extracts are used, such as extracts from a genus, e.g., *Aspergillus spp.*, rather than from isolated purified allergens. Furthermore, in addition to spores, hyphal fragments, which secret different proteins, can be allergenic. Therefore, if diagnosis is made using fungal extracts whose culture media or culture times differ from those used in immunotherapy, there may be a discrepancy between the diagnosed hypersensitivity and the extract used in immunotherapy.

Another problem related to fungal extracts is the endogenous concentration of proteolytic enzymes, which decreases the shelf life of the allergens. Thus, fungal extracts have a significantly shorter half-life than other extracts, such as pollen and dust mite.

Of the estimated 1-1.5 million different fungi species, only about 80,000 have been described. Of these, 112 species are considered allergen sources. Approximately 80 species of fungi have been linked to respiratory allergy. The genera *Alternaria*, *Cladosporium*, *Penicillium*, and *Aspergillus* are the most prevalent hypersensitizing fungi[2]. By 2017, an International Union of Immunological Societies subcommittee, which reports allergens to an international database, catalogued a total of 28 fungal genera as sources for 107 allergens.[2]

The effectiveness and efficiency of immunotherapy and allergy diagnosis depend on the standardization of fungal extracts. Standardization of fungal extracts is a limiting factor; *Alternaria alternata* is the only standardized extract available. Many studies have confirmed its efficacy and safety in allergen immunotherapy for patients with asthma or hypersensitive rhinitis. Other fungal extracts, such as *Aspergillus fumigatus*, *Cladosporium herbarum* and *Penicillium notatum*, are not supported by the same level of evidence due to poor standardization and a lack of studies.[3]

The European Academy of Allergology and Clinical Immunology does not recommend immunotherapy with fungal extracts for children due to a lack of evidence on its efficacy and safety.[4] However, the American Academy of Allergy, Asthma, and Immunology suggests that immunotherapy with fungal extracts may be effective. International consensus considers immunotherapy for fungi a possibility, but only if standardized extracts are used.[5]

Fungi and their mycotoxins can stimulate the formation of immune complexes (as in cases of pneumonitis), and it cannot be ruled out that immunotherapy with fungal extracts can trigger them.[6]

Regarding relevance, the risk of prescribing an immunotherapy that does not adequately address the patient's problem is considerable. Even with an accurate diagnosis of type I hypersensitivity and standardized extract, if exposure to the fungus is irrelevant, immunotherapy

should not be indicated, given that uncertainty about which fungus the patient is exposed to can result in inaccurate and inappropriate immunotherapy with fungal extracts. Furthermore, the patient may be exposed to different fungi in external and internal environments than those with positive results in the prick test. Depending on the region, patients may be exposed to different genera and species of fungi than those used in the prick tests, leading to dissociation between hypersensitivity diagnosis and the relevance of exposure.

Immunotherapy with fungal allergens involves many significant variables related to the type of allergen expressed in the extract, which can affect both diagnosis and treatment, in addition to the relevance of the patient's actual environment exposure and, most importantly, treatment safety. We believe that there is still much imprecision when it comes to immunotherapy with fungal allergens.

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