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Editorial

Enthesitis and seronegative arthritis induced by Dupilumab: how relevant are these adverse events?

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1. INTRODUCTION

Autoimmune diseases constitute one of the groups of chronic illnesses with the highest burden of disease worldwide, impacting quality of life and organic functionality [1]. These diseases arise due to numerous risk factors, such as genetic and epigenetic factors, as well as

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environmental factors, which trigger a loss of immunological tolerance, leading to an immune response against an antigen from a tissue or organ system [1, 2]. Autoimmunity and autoimmune conditions related to drug consumption are also frequently reported causes [2]. Moreover, they can pose a significant challenge in the medical approach to certain diseases, depending on the severity and mode of onset of autoimmunity, as well as the availability of a therapeutic arsenal for treating the underlying disease. For example, atopic dermatitis (AD) is a commonly encountered dermatopathy in dermatology [2, 3]. Dupilumab, an IL-4/IL-13 receptor blocker, is a biological drug approved for use in moderate to severe AD [3]. However, it has been associated with certain adverse effects that could hinder its implementation in certain cases [3-5]. How relevant is this situation in the management of AD?

At the end of the year 2022, Bridgewood et al [4] conducted a systematic analysis using the global pharmacovigilance database of the World Health Organization to determine the clinical patterns and frequency of autoimmune disorders linked to the occurrence of type 2 helper T-cell-mediated adverse reactions and associated autoimmunity due to the administration of Dupilumab. It was identified that, up to that date, 37,848 adverse events related to Dupilumab had been reported, with the skin, eyes, and musculoskeletal system being the most frequently affected organs. It was determined that enthesitis (OR 12.6; 95% CI: 6.54–24.47), seronegative arthritis (OR 9.6; 95% CI: 3.07–30.07), iridocyclitis (OR 3.7; 95% CI: 1.88–7.55), and psoriasis (OR 1.4; 95% CI: 1.29–1.70) were, in descending order, the conditions most frequently associated with the occurrence of adverse events. Through the identification of specific pathways linked to the occurrence of these reactions, such as the FG fibroblast receptor (FGFR2) pathway and certain microRNAs, the authors concluded that this drug does not protect against immunomediated humoral disorders but dynamically biases other pathways for AD control [4].

Through basic research experimental trials, it has been proposed that the IL-4/IL-13 axis plays a certain role in interacting with the genesis of enthesitis, linked to the IL-23/IL-17 axis [5]. The expression and/or attenuation of IL-4 and IL-13 are related to the presence of T cells and other proinflammatory molecules. Thus, although imprecise, there is a potential causal association between clinical observations and histological and immunohistochemical findings of autoimmune manifestations [5].

Sleep disorders are also frequently observed adverse events in these types of reports, with a considerably high probability of occurrence compared to control groups (up to 15 times more likely to experience sleep deficits) [6]. Among the described case series focused on addressing these reactions, it is noted that it takes just over a year to achieve complete recovery from autoimmune manifestations, for which the use of corticosteroids and antimetabolites is necessary [7]. Therefore, depending on the underlying syndromic presentation and the health phenotype of the affected individual, the occurrence of these reactions and the need for implementing this treatment regimen can have significant implications [7].

The presence of polymorphisms is an important variable to consider in the risk of developing these adverse reactions [5, 6]. Therefore, it is imperative to advance in the implementation of precision medicine, utilizing pharmacogenomic tools and drug susceptibility assessments. Currently, much is unknown about variants with a significant impact on a mixed-race population that could determine the efficacy and safety of these drugs [8]. Based on the above, various authors worldwide have prioritized the establishment of an open-access bank, along with massive prevalence studies, to provide relevant information regarding genetic and pharmacological susceptibility to autoimmunity [9, 10]. Thus, although enthesitis and seronegative arthritis are not fatal conditions, they influence certain health outcomes such as quality of life and morbidity, depending on the health context of the individual affected. Consequently, alternative options for managing AD may be preferred in cases where pharmacogenomic susceptibility analyses are not available.

2. CONFLICT OF INTERESTS

The authors have no conflict of interest to declare. The authors declared that this study has received no financial support.

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