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Review

Gene polymorphisms as predictors of response to biological therapies in psoriasis patients

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ABSTRACT

Psoriasis is a chronic inflammatory autoimmune skin disease, characterized by the formation of erythematous scaly plaques on the skin and joints. The therapies for psoriasis are mainly symptomatic and sometimes with poor response. Response among patients is very variable, especially with biological drugs (adalimumab, etarnecept, infliximab and ustekimumab). This variability may be partly explained by the effect of different genetic backgrounds. This has prompted the investigation of many genes, such as FCGR3A, HLA, IL17F, IL23R, PDE3A-SLCO1C1, TNFα and other associated genes, as potential candidates to predict response to the different biological drugs used for the treatment of psoriasis. In this article, we will review the influence of gene polymorphisms investigated to date on response to biological drugs in psoriasis patients.

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1. Introduction

Psoriasis is a chronic inflammatory autoimmune skin disease, characterized by the formation of erythematous scaly plaques on the skin and joints [1]. It may course accompanied by the emergence of other diseases, as cardiovascular disease, diabetes and/or arthritis [2,3].

Studies conducted in the United Kingdom, the United States and the Netherlands show that the incidence is approximately 80/100,000 per year in adults [4], being higher in men (85.5/100,000) than women (73.2/100,000) [5]. The prevalence of the disease worldwide is 2–3% [5].

The causes of the onset of the disease are currently unknown, although environmental and genetic factors are proposed to have an impact. Environmental factors that may be involved in the onset of the disease are: chronic infections, stress, low humidity in the environment, use of certain drugs such as β-blockers, lithium, antimalarial and interferon, consumption of snuff, alcohol and obesity [6,7]. Regarding genetic factors, there are DNA regions highly related to the pathology of psoriasis, mainly involving the adaptive immune system [8,9]. These regions include the human leukocyte antigen Cw6 (HLA-Cw6), interleukin 23 receptor (IL23R), interleukin 12B (IL12B), and variations in the tumor necrosis factor α (TNF-α) gene [9,10]. There are also genes involved in different pathways, as CARD14, TNIP1, REL and NFKB1A (associated to NF-Kβ), IL28RA, TYK2 (part of IFN signaling), RUNX3, IL13, TAGAP, ETS1, MBD2 (T-cell regulation), IFIH1, DDX8 and RNF114 (antiviral process), TNFAIP3, TRAF3IP2, IL23A, STAT3 (IL23 pathways), LCE (skin regulatory barrier) and PTTG1, MTHFR and CCDC129 [8]. Alterations in some of these genes can cause dysregulation of the immune system, thus causing susceptibility to this disease [11].

1.1. Pharmacotherapy of psoriasis

1.1.1. Assessment of severity of psoriasis

There are different parameters used to measure the severity of the disease, which are necessary to establish the correct treatment. Among them, BSA (Body Surface Area) indicates the body surface area affected, taking the palm as reference, which represents 1% of the body surface. According to this scale, it is considered mild disease when the BSA is <5%, moderate when it is between 5 and 10%, and severe when greater than 10% [12]. The most used parameter in clinical trials is the Psoriasis Area Severity Index (PASI), which evaluates erythema, induration and scaling in separate zones and establishes a relation with respect to the extent of the area affected. The scale ranges from 0 (no psoriasis) to 72 (severe psoriasis). This parameter is commonly used in terms of the percentage of improvement over baseline: PASI50 indicates the patient has improved by 50% over baseline and PASI75, PASI90 indicate 75% and 90% improvement, respectively [13]. According to BSA and PASI parameters, psoriasis is considered mild for PASI < 10, BSA < 10 values; and moderate to severe when PASI > 10, BSA > 10 [21].

The Dermatology Life Quality Index (DLQ1) is an indicator of the quality of life of patients, measured at the start and end of therapy, which assesses the health status. It ranges from 0 to 30, having a greater impact of disease on quality of life score when it is over 10 (itchy, sore painful, embarrassed because of the skin, social influence) [14]. To evaluate the severity of psoriatic arthritis, there are other parameters also used in rheumatoid arthritis, such as the Disease Activity Score 28 (DAS28) and the American College of Rheumatology and European League Against Rheumatism criteria (ACR/EULAR). In the case of DAS28, the severity of the disease in 28 joints of the body is measured and swelling and pain is observed, also including levels of C Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR) [15,16]. The ACR/EULAR classification criteria evaluate disease improvement based on number of swollen, tender joints, CRP levels and patient global assessment [17].

1.1.2. Drugs

Drugs administered in psoriasis are aimed at different pathways of the immune system, to block the inflammatory response. There are several lines of treatment, depending on the severity of the disease. The first line of treatment (BSA < 10, PASI < 10) is mainly based on topical and symptomatic therapy (corticosteroids, calcineurin inhibitors, ditrazol, topical retinoid vitamin D analogues). When the disease is more severe (BSA > 10, PASI > 10) systemic therapy (methotrexate, cyclosporine or acitetrina) or phototherapy (UV, UVB, PUVA) are recommended. Biological therapy is indicated when the disease becomes very serious (BSA > 10, PASI > 10 DQLI > 10), there is no response to previous treatments, or they are contraindicated [18].

Different types of biological drugs are used for the treatment of psoriasis: tumor necrosis factor inhibitors (anti-TNF), such as infliximab (IFX), adalimumab (ADA), and etanercept (ETN); interleukin blockers like ustekinumab (UTK) [19], secukinumab (SCK) [20], and the recently investigated ixekizumab (IXK) [21].

The anti-TNF drugs are recombinant human IgG1 antibody proteins, whose function is almost the same, the main difference among them is how they are synthetized. ADA is a protein obtained from recombinant DNA in mammalian cells, IFX is a chimeric protein derived from mouse, and ETN is a dimeric fusion protein whose extracellular portion is responsible for the recognition of TNF (ligand), and the transmembrane part corresponds to the immunoglobulin gamma-1 heavy chain constant region (IgG1-Fc) [22–24]. The main function of these drugs is to block TNF and thus their inflammatory activity.

Interleukin blockers are IgG1 monoclonal antibodies which have a different target: UTK is an inhibitor of interleukin-12 and interleukin-23; SCK and IXK inhibit interleukin 17 [25–27].

Other biological drugs whose pharmacogenetic facet is scarcely investigated are alefacept (AFT) and efalizumab (EFB). AFT is an inhibitor of CD4 and CD8 cells which interferes with their activation. EFB is an immunosuppressive recombinant humanized IgG1 kappa which can inhibit CD11 cells and was retired due to severe adverse reactions, mainly multifocal progressive encephalopathy, which resulted in 2 mortal cases [28,29].