Psoriasis and Its Clinical Implications

Subjects: Immunology

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Psoriasis is the result of uncontrolled keratinocyte proliferation, and its pathogenesis involves the dysregulation of the immune system. The interplay among cytokines released by dendritic, Th1, Th2, and Th17 cells leads to the phenotypical manifestations seen in psoriasis. Biological therapies target the cytokine-mediated pathogenesis of psoriasis and have improved patient quality of life.

Keywords: biologics ; IL-17 inhibitors ; IL-12/23 inhibitors ; IL-23/39 inhibitors ; IL-356RN ; JAK inhibitors ; plaque psoriasis ; pustular psoriasis ; TNF-α inhibitors

1. Introduction

Psoriasis is a chronic, systemic inflammatory skin disease that affects approximately 3% or 7.5 million people in the United States [1][2][3]. Worldwide, psoriasis has a prevalence of approximately 1.99% in East Asia, 1.92% in Western Europe, and 1.10% in high-income Southern Latin American countries [4]. Psoriasis occurs equally in both males and females and has a bimodal age of peak occurrence: between 20–30 and 60–70 [5][6]. The underlying pathogenesis of psoriasis results from an interplay between various genetic and environmental factors. Over 80 human leukocyte genes (HLA) are associated with psoriasis, and HLA-C*06:02 has the strongest association [2]. Environmental factors that can trigger psoriasis include trauma, drugs, infections, smoking, alcohol, and stress. In particular, certain drugs that can exacerbate psoriasis include antimalarials, bupropion, beta-blockers, calcium channel blockers, captopril, and fluoxetine [7]. Scratching, and other forms of trauma, are also associated with the onset of psoriasis, known formally as Koebner's phenomenon [3].

Psoriasis can be categorized into various subtypes based on clinical presentation and include psoriasis vulgaris or plaque psoriasis, inverse or flexural psoriasis, guttate psoriasis, pustular psoriasis, and erythrodermic psoriasis [1][2]. While psoriasis presents with cutaneous manifestations, it is also associated with other comorbidities. Systemic manifestations of psoriasis include psoriatic arthritis in the small and large joints, affecting 30% of patients with psoriasis, cardiovascular disease, such as myocardial infarctions, diabetes, depression, anxiety, certain malignancies, and obesity [1][8].

2. Current Insights

Psoriasis is a highly prevalent chronic, systemic inflammatory skin disease with variable clinical manifestations, and plaque psoriasis is the most prevalent type. The underlying molecular pathogenesis of psoriasis can be divided into an initiation and maintenance phase. The initiation phase is mediated by keratinocyte response to injury through the release of AMPs [1]. AMPs propagate the inflammatory pathway by their effect on dendritic cells. The main AMPs involved in psoriasis pathogenesis include LL37, β-defensins, and S100 proteins [1][9]. The TNF-α/IL-23/IL-17 axis mediates the maintenance phase. IL-17 in particular works via two mechanisms: an ACT1 dependent and ACT1 independent pathway [9]. The pathogenesis of pustular psoriasis is similar to the general pathogenesis of plaque psoriasis; however, it can involve a unique mutation in *IL356RRN* [10].

The type of psoriasis, its severity, associated comorbidities, and patient preferences should be taken into consideration when choosing treatment. There are currently four classes of biologics approved for the treatment of moderate to severe plaque psoriasis.

There are currently four FDA-approved TNF-α inhibitors: etanercept, infliximab, adalimumab, and certolizumab (and one additional one, golimumab, which is approved for psoriatic arthritis) [11]. According to data obtained from a recently completed meta-analysis, infliximab has the highest efficacy of the FDA-approved TNF-α inhibitors [12]. The adverse effects of TNF-α inhibitors are well documented. Particularly, adalimumab and infliximab have been associated with a higher risk for serious infections [13].

Ustekinumab is currently the only FDA-approved IL-12/IL-23 inhibitor and is a well-tolerated biologic [14]. In a Danish registry of 2161 patients, ustekinumab had the lowest risk for drug discontinuation and highest drug survival, when compared to TNF-α inhibitors [15].

There are currently three FDA-approved IL-17 inhibitors: secukinumab, ixekizumab, and brodalumab [16][17][18]. Bimekizumab is another IL-17 inhibitor currently undergoing phase III trials [19]. According to data from two network meta-analyses, brodalumab has the highest efficacy of the approved IL-17 drugs, but bimekizumab may be even more effective, especially for psoriatic arthritis [12][20]. According to safety data from a 2019 meta-analysis result, ixekizumab 80 mg/4 weeks has the highest short-term risk for adverse events, of the approved drugs [20].

There are currently three FDA-approved IL-23/IL-39 inhibitors: guselkumab, tildrakizumab, and risankizumab [11]. Mirikizumab, also an IL-23/IL-39 inhibitor, underwent phase III trials but was discontinued due to administrative purposes [21]. According to data from two network meta-analyses, risankizumab has the highest efficacy of the approved IL-23/IL-39 inhibitors [12][20]. Although IL-23/IL-39 inhibitors offer a tolerable safety profile with no black box warnings or contraindications, according to safety data from a 2019 meta-analysis, guselkumab 100 mg has the highest short-term risk for adverse events of the approved drugs [11][20].

Altogether, biological therapeutics offer a molecularly targeted approach for patients with plaque psoriasis. Although consideration should be taken into account for the specific contraindications and black box warnings for each medication, the overall safety profiles of biologics are favorable [22]. Generally, any specific biologic should be avoided in patients with a history of hypersensitivity to that medication [23]. Although there is scarce literature on the safety of biologics during pregnancy, secukinumab, brodalumab, risankizumab, tildrakizumab, and guselkumab have been found in breast milk in animal studies. Moreover, there is a possibility of spontaneous abortion and neonatal deaths according to animal studies, although there is no human data [24].

JAK inhibitors are also an emerging class of small molecule inhibitors, and oral tofacitinib is the most studied oral JAK inhibitor in psoriasis [25][26][27]. Although JAK inhibitors present a new small molecule inhibitor with efficacy in psoriasis, it is associated with numerous black box warnings, and careful consideration must be used when opting for these medications [11][28].

Biological therapies are efficacious in the treatment of psoriasis, have favorable adverse effect profiles, and improve patient quality of life. Compared to other treatment modalities, such as methotrexate and cyclosporine, the cost of treatment can be much higher [29][30][31]. However, the cost can be opaque. In the United States, insurers can contract with pharmaceutical companies and do not make the resulting costs public. In Europe, contracting occurs at the level of country-specific health plans, and they, too, may not make the price paid public.

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