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Review Article

Anti-cytokine therapy in the treatment of psoriasis

Erine A. Kupetsky, Alicia R. Mathers, Laura K. Ferris *

Department of Dermatology, University of Pittsburgh School of Medicine, Pittsburgh, PA 3601 Fifth Avenue, 5th Floor, Pittsburgh, PA 15213, United States

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ABSTRACT

Psoriasis is a chronic, inflammatory skin disease with many associated co-morbidities including diabetes, hypertension, obesity, psoriatic arthritis, and cardiovascular disease. It has long been known that psoriasis is a T cell-mediate disease and recent findings further demonstrate the important roles of the Th17 and Th22 arms of the immune system in the pathogenesis of psoriasis. Our understanding of this disease has progressed greatly and agents that target the cytokines involved in disease activity are under development or currently being used to treat psoriasis. A comprehensive review of the literature for cytokine-targeted therapies, their safety concerns, and efficacy in psoriasis are discussed here.

1. Introduction

Psoriasis vulgaris is a chronic sometimes debilitating, disease characterized by thick, red, scaling plaques on the skin (Fig. 1). This clinical appearance is the result of premature keratinocyte cornification and increased keratinocyte proliferation in response to inflammatory and angiogenic stimuli in the skin. Psoriasis is a strongly T cell mediated disease and advances in knowledge of the immunologic basis of psoriasis have allowed the development of several targeted therapies for psoriasis.

2. Clinical background

Psoriasis affects up to 3% of the world's population [1] and current estimates put the prevalence of psoriasis in the United States at about 7.5 million cases [2]. Psoriasis can occur at any age, however there is a bimodal peak in incidence in early adulthood (age 18–25) and in later adulthood (age 50–55) [3]. Both genders tend to be equally affected and psoriasis is seen across multiple ethnic and racial backgrounds. Psoriasis is responsible for significant health care costs, estimated to be $649.6 million annually in the United States [4].

In addition to involvement of the skin, patients with psoriasis often suffer from other medical co-morbities. Approximately 20–35% of patients with psoriasis have inflammatory joint involvement, or psoriatic arthritis which can vary greatly in severity from mildly tender or stiff joints to a mutilating arthritis that renders small joints in the hands nonfunctional [3]. Patients with psoriasis have been found to have higher rates of obesity, type 2 diabetes, cardiovascular disease, depression, lymphoma, and inflammatory bowel disease than the general population [5]. All of these comorbid conditions, like psoriasis, are associated with an increase in inflammatory cytokine expression.

Any anatomic area can be affected by psoriasis, however extensor surfaces, i.e. the elbow and knee areas, tend to be preferentially involved with discrete areas, or plaques, of psoriasis. It is not clear if this is due to differential keratin expression, or an increase in trauma to these areas, or to some other factor. Psoriasis severity can vary widely and there are several ways to rate disease severity. For clinical purposes, severity is often judged based upon the body surface area (BSA) involved with psoriasis and is classified as mild (<5% BSA), moderate (5–10%), or severe (>10%) disease. However, the BSA measurement does not take into account plaque characteristics such as the degree of redness (erythema), thickness (induration), or scaling. Thus, for the purposes of evaluating psoriasis severity in the context of a clinical trial the psoriasis area and severity index (PASI) is used. The PASI is a clinically-validated tool that takes into consideration BSA, erythema, induration, and scaling. The PASI is scored on a scale of 0–72, with a higher score representing an increased severity. Clinical trials in psoriasis generally measure the percent improvement in PASI score before vs. after an intervention. A PASI75 response represents a 75% or greater reduction in the PASI score post-treatment. The percent of patients achieving a PASI75 response is a common primary endpoint in clinical trials of potential psoriasis therapies. In clinical trials psoriasis severity may also be measured using the less quantitative

* Corresponding author. Tel.: +1 412 647 4200; fax: +1 412 647 4832.
E-mail addresses: kupetskye@upmc.edu (E.A. Kupetsky), Alicia@pitt.edu (A.R. Mathers), ferrislk@upmc.edu (L.K. Ferris).

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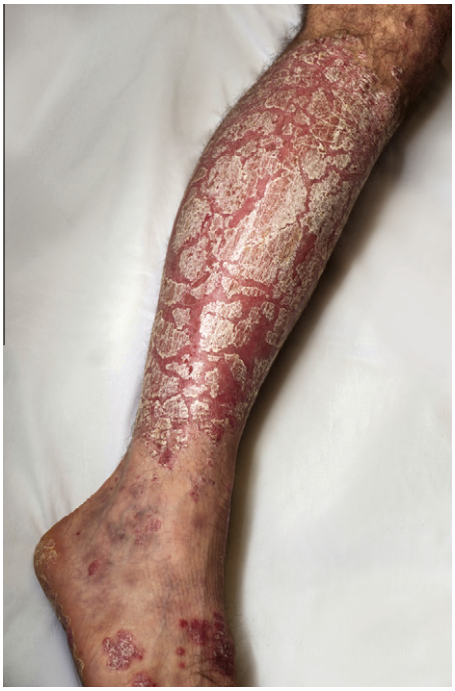

Fig. 1. Cytokines involved in the pathogenesis of psoriasis.

physician's global assessment (PGA), a 6-point scale ranging from 0 (clear) to 5 (very severe).

3. Cytokines in the pathogenesis of psoriasis

Psoriasis arises from an imbalance in both innate (TNF-α and IL-17) and adaptive (IL-23/Th17) immune responses [6–11]. Following an environmental trigger one of the earliest events that occur in the initiation phase of psoriasis is the release of several innate inflammatory cytokines, including IL-1β, IL-6, and TNF-α. TNF-α is secreted by keratinocytes, inflammatory dendritic cells (DCs), mast cells, macrophages, and effector T cells [12–14]. Genomewide association studies have implicated the TNF-α pathway (*TNIP1, TNFAIP3*) in psoriasis susceptibility [15]. TNF-α maintains a critical role in psoriasis, in part, by initiating Langerhans cell (LC) migration via the down-regulation of e-cadherin, the cell surface molecule that mediates the attachment between LCs and keratinocytes [16]. TNF-α is also involved in the induction of NF-κB leading to cell survival, proliferation, and transcription of anti-apoptotic factors along with the induction of angiogenic VEGF [17]. These NF-κB-dependent effects help to mediate the epidermal hyperplasia and the increased vascularization observed in psoriatic lesions. Additional down-stream inflammatory mediators induced by the presence of TNF-α include IL-1β and iNOS, along with chemokines, including IL-8, CCL20, CXCL12, CCL21, CCL2, CCL5, and CCL4 [13,18–20]. Together these factors further enhance DC activation and migration, T lymphocyte recruitment, and neutrophil recruitment and microabscess formation. Moreover, TNF-α and IL-17 cooperate in the pathogenesis of psoriasis, as evidenced by the effect of TNF-α antagonism on IL-17 signaling and in their synergistic effect on the production of inflammatory cytokines by keratinocytes [21,22].

Following activation via TNF-α and IL-1β, cutaneous DCs migrate to the skin draining lymph nodes where they have the capacity to promote T cell activation and Th17 differentiation. Th17 differentiation is dependent on DC-secreted IL-6, IL-1β, and low levels of TGF-β1 [23–29]. IL-6 is particularly important in the development of psoriasis for its capacity to initiate Th17 responses and block regulatory T cell functions [30]. Furthermore, Th17 immunity is amplified by IL-21 and IL-15 and terminally differentiated by DC-secreted IL-23 [28,29,31–36]. Upon differentiation, Th17 cells home to the inflamed cutaneous tissues where they enact their effector roles relevant to psoriasis, including the induction of chronic inflammation and tissue damage, neutrophil maturation and chemotaxis, Th1 cell chemotaxis, and keratinocyte proliferation and epidermal hyperplasia. These functions are conferred in part by secreting IL-17, IL-17F, IL-22, TNF-α, IL-8, CXCL1, CXCL10, CXCL2, and CCL20 [6,26,27,31,37–39]. Of note, in addition to the prominent Th17 cells, there are also several innate sources of IL-17 in psoriatic lesions including neutrophils, mast cells, innate lymphoid cells, and $\gamma\delta$ T cells [40–42].

The IL-17 family of cytokines is made up of six isoforms of IL-17 (IL-17 A-F), with IL-17A and IL-17F being primarily expressed in T cells and mediating the IL-17 effects in psoriasis. Also, IL-17A and IL-17F are able to form an active IL-17A/F heterodimer. IL-17 cytokines bind to a family of IL-17 receptors (IL-17RA-RE), which are able to multimerize as well, modulating affinity for different IL-17 subunits. IL-17A binds to a heterodimer of two or more subunits of IL-17RA and one subunit of IL-17C. IL-17F binds to IL-17RA with low affinity and to IL-17RC with much higher affinity. IL-17RA and IL-17RC are necessary for the biologic activity of IL-17A/F heterodimers [43].

Prior to the discovery of Th17 responses psoriasis was believed to be mediated by the IL-12/Th1 pathway. This theory was largely dependent on the observed expression of IL-12 in psoriatic lesions and the clinical efficacy of IL-12p40 neutralization [44,45]. However, it was later determined that IL-23 also shares the IL-12p40 subunit and that the IL-23/Th17 pathway has a critical role in psoriasis pathogenesis [21,40,46,47]. IL-23 is a key cytokine involved in psoriasis pathogenesis via (1) expansion and activation of Th17 cells, (2) the induction of IL-22 and acanthosis of the epidermis, (3) the conversion of regulatory T cells (Tregs) into IL-17 producers, and (4) adjuvant activity that directly stimulates DCs to present self-peptides [15,39,48–51]. Interestingly, the IL-23R is also increased in psoriatic lesions on dermal and epidermal dendritic cells, likely leading to positive feedback mechanisms that potentiate the observed inflammatory response in psoriatic lesions [48]. Further support for a role of IL-23 in psoriasis pathogenesis comes from the demonstration that cutaneous injection of IL-23 in a murine model induces psoriasiform lesions and genetic association studies have identified the IL-23 signaling pathway as a susceptibility loci [52]. The pathways are illustrated in Fig. 2.

4. Targeting cytokines to treat psoriasis

Mild psoriasis can be treated using topical therapies; primarily topical steroids, tar preparations, and ultraviolet light therapy. Systemic therapies are often needed, however, and can be divided into biologic therapy (molecules, usually monoclonal antibodies, which target a particular cytokine or receptor) and non-biologic therapy (other oral agents with various molecular targets). The cytokine pathways targeted in psoriasis therapies are illustrated in Fig. 3. Table 1 also summarizes these agents and their targets (cytokine or pathway).

4.1. Non-biologic systemic therapies for psoriasis

4.1.1. Cyclosporine

Cyclosporine A (CsA) is a systemic immunosuppressive drug that was developed to prevent rejection in organ transplant patients but was incidentally found to greatly improve the coexisting psoriasis in a few transplant patients afflicted with the disease.

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