Psoriasis vulgaris (PV) is a cutaneous inflammatory disorder stemming from abnormal, persistent activation of the interleukin-(IL-)23/Th17 axis. Pustular psoriasis (PP) is a clinicopathological variant of psoriasis, histopathologically defined by the predominance of intraepidermal collections of neutrophils. Although PP pathogenesis is thought to largely follow that of (PV), recent evidences point to a more central role for IL-1, IL-36, and IL-6 in the development of PP. We review the role of IL-6 in the pathogenesis of PV and PP, focusing on its cross-talk with cytokines of the IL-23/Th17 axis. Clinical inhibitors of IL-6 signaling, including tocilizumab, have shown significant effectiveness in the treatment of several inflammatory rheumatic diseases, including rheumatoid arthritis and juvenile idiopathic arthritis; accordingly, anti-IL-6 agents may potentially represent future promising therapies for the treatment of PP.

1. Introduction
Psoriasis is an immune-mediated cutaneous disease with an estimated prevalence of approximately 2% in the European and North American population [1, 2]. The most common clinical presentation of psoriasis, namely, psoriasis vulgaris (PV), is defined by multiple erythematous plaques, histologically characterized by (1) epidermal acanthosis, hyperkeratosis, and parakeratosis; (2) dilated capillary network in the papillary dermis; (3) a mixed inflammatory infiltrate including polymorphonuclear cells, as well as intraepidermal collections of neutrophils [3]. Epidermal clusters of neutrophils have been given eponymous names such as Munro’s microabscesses and Kogoj pustules [3]. Various evidences deriving from genetic studies, adoptive transfer models, and molecular evaluation of human samples point to a key pathogenetic role for T helper-1 (Th1)/Th17 cells and related cytokines (including TNF-alpha, IL-17, and IL-22), as well as for myeloid cell-derived cytokines such as IL-12 and IL-23 [1, 2, 4–8].

Pustular psoriasis (PP) is a clinicopathological variant of psoriasis distinguished by the following features: (1) clinically, presence of pustules on variably erythematous skin; (2) histopathologically, predominance of intraepidermal collections of neutrophils [9–11]. Any biotpic sample presenting the histologic picture of PP should always undergo further investigations to rule out the eventuality of superficial dermatophytosis or Candida albicans infection, whose histopathologic features are often indistinguishable from those of PP [12, 13].

PP has been classified into generalized and localized forms [14]. Generalized PP is a life-threatening, systemic inflammatory condition characterized by repeated attacks of diffuse, erythematous, pustular rash associated with high-grade fever, general malaise, and frequent extracutaneous organ involvement; possible laboratory testing abnormalities include leukocytosis with left shift, increased erythrocyte sedimentation rate (ESR), or increased C-reactive protein (CRP) [14, 15]. Acute flare-ups of generalized PP may be triggered by pregnancy status, infection, or exposure to drugs [15]. Though generalized PP formally belongs to the psoriasis spectrum because of its frequent clinical association with PV and multiple similarities in molecular pathogenesis, it is debated whether it may represent a distinct clinicopathological entity [16, 17]. Another controversy is related to the classification of generalized PP alone or accompanied by PV.
as distinct subtypes with different etiologies [17]. Likewise, localized PP, which is often limited to palms and soles (i.e., palmoplantar pustulosis), has been regarded by several authors as a separate entity rather than a clinical variant of psoriasis [17, 18]. However, a close relationship between localized PP and PV is likely suggested by lack of significant epidemiologic differences, frequent coexistence in the same patients, and largely shared genetic background [18].

Conventional first-line therapies for PP include topical corticosteroids, phototherapy, acitretin, cyclosporine, and methotrexate [14, 16]. Because the use of therapeutics is often hampered by low efficacy and/or adverse effect profile, a need to develop novel therapeutic approaches for PP is arising [14]. Infliximab is actually recognized by many experts as a first-line treatment option for PP, especially in severe cases [14, 19, 20]. Nonetheless, paradoxical TNF-alpha inhibitor-induced PP is a newly occurrence, whose pathogenic mechanism is still relatively unclear [21, 22].

The pathogenic process underlying PP development is only partially shared with PV [16, 17]. The efficacy of TNF-alpha inhibitors in most patients with PP or PV points to a crucial role of TNF-alpha in their pathogenesis [14]. In addition to TNF-alpha, alternative signaling pathways relevant to PP include those mediated by IL-17 and the IL-1/IL-36 family [17, 23–25]. Furthermore, recent evidence seems to indicate IL-6 as a new druggable target for PP [23].

2. Psoriasis Pathogenesis: Current Concepts

2.1. The IL-23/Th17 Axis in the Pathogenesis of Psoriasis. A distinct lineage of IL-23-responsive CD4+ T cells secreting IL-17A and IL-17F and expressing the lineage-specific transcription factor RORC has been recently identified as Th17 cells [1, 5, 26–28]. Additional effector cytokines produced by Th17 cells include IL-21 and IL-22, as well as other non-Th17-specific cytokines, such as IL-6 [29–31]. Cytokine requirements for inducing Th17 differentiation are similar in mice and humans [26, 32]. Naive CD4+ T-cell activation in the presence of both TGF-beta and IL-6 is key to priming the initial differentiation into Th17 cells [2, 27]. TGF-beta also exerts an indirect action through suppression of T-bet-dependent Th1 differentiation [2, 26]. IL-6-dependent STAT3 activation plays an essential role in Th17 differentiation by initially inducing the transcription of RORC, IL17, and IL23R genes and later promoting the expansion of differentiated and memory Th17 cells [26, 32]. However, TGF-beta and IL-6-driven Th17 cells are weakly functional without further exposure to IL-23; the latter cytokine is crucial for differentiation into effector cells, lineage stabilization, and full maturation to inflammatory Th17 cells [2, 5, 27, 28, 33].

Psoriasis skin lesions are the result of complex interactions between dendritic cells (DCs), keratinocytes, and Th1/Th17 lymphocytes [30, 34, 35]. Recent pathogenic models of psoriasis emphasized the role of IL-23/Th17 axis [1, 2, 5, 36]. IL-23 production by inflammatory DCs and activated keratinocytes stimulates Th17 cells within the dermis to release proinflammatory mediators such as IL-17 and IL-22 that, in turn, activate resident tissue cells, particularly keratinocytes [33, 35]. Psoriatic plaques harbor higher levels of IL-23p19 and IL-12/23p40 than those of IL-12p35 [1, 27]; polymorphisms in IL12/23p40 and IL23R genes are associated with increased risk of developing psoriasis, and injection of recombinant IL-23 into healthy skin results in inflammatory changes with histologic features of psoriasis [5, 30]. According to this evidence, the pathogenic relevance of IL-23 has been also confirmed by the high efficacy of both anti-IL-12/IL-23p40 monoclonal antibodies (i.e., ustekinumab) and IL-23p19 neutralizing agents (i.e., tildrakizumab) [8, 27, 33, 37, 38].

IL-17A (simply known as IL-17) belongs to the IL-17 cytokine family, which includes six members (from IL-17A to IL-17F) [1, 2]. IL-17A shows similar pleiotropic effects acting on a wide range of nonimmune cells, resulting in the induction of different proinflammatory cytokines, chemokines, antimicrobial peptides, nitric oxide, and matrix metalloproteinases [1, 2, 30, 34]. IL-17 is able to induce IL-6, IL-8, and CXCL5 in human skin keratinocytes, indirectly promoting the differentiation, activation, and migration of neutrophils [5, 34, 35]. Biopctic samples from PV plaques show elevated levels of IL-17 in parallel with increased expression of IL-23 and IL-22, while serum levels of IL-17 are correlated to psoriasis severity [2, 6, 30, 39]. IL-22 is another key downstream cytokine in the IL-23/Th17 axis, being upregulated in psoriatic skin as compared to normal skin [5, 29, 40, 41]; IL-22 mediates keratinocyte hyperplasia via STAT3 activation, leading to psoriasisiform hyperplasia. In the absence of IL-22, severity of both IL-23-mediated and imiquimod-induced psoriasis-like dermatitis in corresponding mouse models is markedly reduced [40, 42, 43].

A significant increase in IL-17 expression has been detected in lesional skin of PP, despite the absence of any significant increase in IL-12/IL-23 levels [44]; this is strikingly different from PV, where increased IL-17 levels are typically mirrored by analogous changes in IL-12/IL-23 expression [7, 37, 43]. Accordingly, conventional Th17 may not be the main driver for increased IL-17 expression in PP, with neutrophils being a possible, alternative source of IL-17 [23, 44]. Indeed, the anti-IL-23 agent ustekinumab appears to be significantly less effective in the treatment of PP than that of PV [44–46]. Of note, the immunopathology of two well-known histologic mimics of PP, that is, superficial dermatophytosis and mucocutaneous Candida albicans infection, relies heavily on the production of IL-17, as suggested by mouse models and rare human patients with loss-of-function defects in the IL17 gene [47–50]. It is now clear that IL-17-dependent recruitment of neutrophils and secretion of antimicrobial peptides are crucial for cutaneous protection against dermatophytic infections and Candida albicans [47, 49–51]. Importantly, the cellular sources of IL-17 production in this setting are not limited to conventional CD4+ T cells, as several components of the innate immunity (gamma/delta T cells, mast cells, and neutrophils) appear to be capable of immediate IL-17 secretion prior to the contribution of IL-23-dependent Th17 adaptive immunity [42, 48–52].

2.2. IL-36 and Pustular Psoriasis. Pathogenic IL36RN gene mutations have been identified in familiar and sporadic cases of PP, either generalized or localized [25, 53, 54]; IL36RN
encodes the IL-36 receptor antagonist (IL-36Ra), a soluble mediator that antagonizes the proinflammatory activity of IL-36 cytokines (IL-36-alpha, IL-36-beta, and IL-36-gamma) through binding IL-36R (IL-1Rl2) and inhibiting IL-36-dependent activation of NF-kappaB signaling [25, 55–57].

Several authors have detected elevated expression of keratinocyte-derived IL-36 cytokines in psoriatic lesional skin, as a result of keratinocyte stimulation by IL-17, IL-22, and TNF-alpha [58–60]. Primary epidermal IL-36 over-expression in transgenic mouse models results in PV-like phenotype histopathologically characterized by acanthosis, hyperkeratosis, and mixed inflammatory infiltration with predominance of neutrophils [55, 59]; further crossing with IL36RN knock-out strain augments IL-36 signaling leading to increased neutrophil infiltration and a histopathological picture more akin to classic PP [25, 55, 61]. Furthermore, loss of IL-36R signaling successfully counteracts development of imiquimod-induced psoriasisform dermatitis, pointing to a crucial role of IL-36 ligands in the proinflammatory activity of the IL-23/Th17 axis [61, 62]. Indeed, IL-36R signaling is relevant for the expansion of IL-17-producing T helper cells [25, 55].

IL-36 cytokines may exert a direct effect on immune cells [55]; activation of IL-36R, which is expressed constitutively on DCs, CD4+ T cells, and macrophages, promotes maturation of monocyte-derived DCs and induction of several cytokines, including IL-1, IL-6, IL-23, TNF-alpha, and IFN-gamma [59, 61, 63]. In addition, keratinocytes in psoriasis as well as synovocytes in RA are capable of responding to direct IL-36 ligand stimulation with production of IL-6, IL-8, and antimicrobial peptides, which cooperate with IL-17A and TNF-alpha promoting neutrophil activation and migration [1, 54, 56, 60].

Thus, IL-36 ligands not only act as effector cytokines of the IL23/Th17 axis, but also induce several proinflammatory mediators (including IL-6, IL-8, and IL-23) that reinforce the Th17-driven inflammatory milieu [25, 59, 60, 63]. The cross-talk between IL-36 ligands and Th17 mediators establishes a positive feedback loop involving keratinocytes, DCs, macrophages, and Th17 [60, 61]; as a consequence, activation of T cells is enhanced, recruitment of immune cells in psoriatic lesions is augmented, and the IL-23/Th17 axis is reinforced [55, 60]. In keeping, elevation of IL-36R ligands in psoriatic plaques is closely correlated with increased levels of TNF-alpha, IL-17, and IL-22, confirming the existence of a proinflammatory, self-reinforcing gene expression loop [56, 59].

Pathogenetic IL36RN mutations associated with PP abolish the antagonistic effect of IL-36Ra, enhancing the IL-36-dependent production of IL-1, IL-6, and IL-8 [25, 54]. Indeed, patients with IL36RN-dependent genetic predisposition to PP have been treated effectively with anakinra, an IL-1 antagonist [64]. Nonetheless, so far no specific data regarding effectiveness of IL-6 inhibitors in IL36RN-dependent PP are available. Overall, recessive IL36RN mutations are associated with increased risk of PP alone, but not PV [57, 65–67]; both phenotypic variance and incomplete penetrance have been observed, supporting the notion that IL36RN mutations are able to induce manifest disease only in the presence of specific environmental factors and/or further genetic defects at a second disease locus [25, 53, 65]. All genetic follow-up studies of PP patients have found evidence of genetic heterogeneity, proving that IL36RN mutations account for only a minority of sporadic PP cases [25, 57, 66].

3. IL-6 Signaling and Pustular Psoriasis

3.1. IL-6 Signaling and Selective IL-6 Inhibition. IL-6, a pleiotropic, proinflammatory cytokine, is the archetypal member of the gp130-related cytokine family, which also includes IL-11, IL-27, OSM, CNTF, CT-1, LIF, and CLC [68, 69]. IL-6 exerts its activity through interaction with a receptor complex composed of the nonsignaling alpha subunit IL-6R (CD126) and the common, ubiquitously expressed, beta subunit gp130 (CD130), resulting in immediate activation of receptor-associated kinases (JAK1/JAK2 and TYK2) and subsequent regulation of STAT1/STAT3 and SHP2-MAPK signaling pathways (Figure 1) [68, 70, 71]. The IL-6R subunit functions in vivo as both a conventional membrane-bound receptor, expressed on the surface of hepatocytes and certain inflammatory cells, and a soluble form (sIL-6R) which forms active IL-6/sIL-6R complexes (IL-6 transsignaling) [72, 73]; this property is unique to IL-6 among currently known cytokines [68–70].

In addition to being a major stimulus for the synthesis of acute-phase proteins, IL-6 promotes differentiation of B cells into mature plasma cells as well as T-cell differentiation and activation [69, 72]. Importantly, recent evidence demonstrated that IL-6 exerts a positive influence in initiating Th17 cell development, whereas it inhibits TGF-beta-dependent differentiation of regulatory T cells [32, 74]. IL-6 is also a downstream target gene of IL-17 signaling in nonimmune cells such as keratinocytes and fibroblasts [35, 72, 75]; this positive IL-6/IL-17 loop plays a key role in proinflammatory interactions between the immune system and nonimmune tissues [32, 76]. Additionally, IL-6 exerts a significant influence on myeloid precursor cells and circulating neutrophils [69, 77–79]: IL-6 promotes differentiation from myeloid progenitors to neutrophils as well as neutrophilia [80]. Furthermore, IL-6 secretion results in secondary production of chemokines such as IL-8 and MCP-1 by mononuclear cells/macrophages as well as expression of ICAM-1 and other adhesion molecules on endothelial cells, leading to enhanced neutrophil migration [75, 77, 79]. Last, mature neutrophils respond to IL-6 via membrane-bound IL-6R, releasing proinflammatory cytokines such as IL-23 and IL-17 and establishing a Th17-polarizing positive feedback loop [32, 76].

Transgenic IL6-KO mouse models are characterized by a unique resistance to several inflammatory conditions such as experimental autoimmune arthritis or encephalomyelitis [69, 70]; accordingly, IL-6 plays a central role in the pathological activity of several autoimmune diseases, including rheumatoid arthritis, juvenile idiopathic arthritis, adult onset Still's disease, systemic lupus erythematosus, Takayasu's arteritis, and inflammatory bowel disease [69, 72, 75]. As a consequence, IL-6 has gained attention as an attractive therapeutic target.
Figure 1: IL-6 signalling pathways. In classical signalling (red star), cells expressing membranous IL-6R are responsive to IL-6; in transsignalling (yellow star), cells lacking IL-6R are activated by IL-6/sIL-6R complexes (sIL-6R is generated by proteolytic shedding from IL-6R via ADAM10 and ADAM17 or by mRNA alternative splicing). Cellular events initiated by IL-6/IL-6R activity include activation of JAK, MEKs-ERKs, and PI3K/Akt kinases, resulting in changes in nuclear gene expression. IL-6: interleukin 6; sIL-6R: soluble interleukin 6 receptor.
Figure 2: IL-17/IL-6 axis in the pathogenesis of pustular psoriasis. Both innate (gamma/delta T cells, neutrophils, and macrophages) and adaptive (Th17 cells) immunities contribute to cutaneous IL-17 production. Macrophages, conventional DCs, and slan-DCs respond to IL-17 by releasing IL-6, which in turn plays a key role in neutrophils recruitment and pustules formation; additional IL-6-dependent effects include reinforcement of Th1/Th17 inflammatory cytokines production, facilitation of IL-22-mediated epidermal hyperplasia, and naive CD4+ T cells differentiation into Th17. Activated keratinocytes amplify the IL-17/IL-6 axis by producing IL-6, recruiting Th17 cells through CCL20, and inducing neutrophils chemotaxis via IL-8 and MCP-1. DCs: dendritic cells; IL: interleukin; KCs: keratinocytes; M/Ms: monocytes/macrophages; PMNs: neutrophils; Th17: T helper 17 cells.

Figure 2: IL-17/IL-6 axis in the pathogenesis of pustular psoriasis. Both innate (gamma/delta T cells, neutrophils, and macrophages) and adaptive (Th17 cells) immunities contribute to cutaneous IL-17 production. Macrophages, conventional DCs, and slan-DCs respond to IL-17 by releasing IL-6, which in turn plays a key role in neutrophils recruitment and pustules formation; additional IL-6-dependent effects include reinforcement of Th1/Th17 inflammatory cytokines production, facilitation of IL-22-mediated epidermal hyperplasia, and naive CD4+ T cells differentiation into Th17. Activated keratinocytes amplify the IL-17/IL-6 axis by producing IL-6, recruiting Th17 cells through CCL20, and inducing neutrophils chemotaxis via IL-8 and MCP-1. DCs: dendritic cells; IL: interleukin; KCs: keratinocytes; M/Ms: monocytes/macrophages; PMNs: neutrophils; Th17: T helper 17 cells.

Activation of STAT3 in keratinocytes [71, 97, 98]. Increased activation of STAT3 (pSTAT3) has been detected in lesional skin of psoriatic patients [98]; several cytokines upregulated in psoriasis, including IL-6, IL-20, and IL-22, signal through STAT3 activation [71, 98]. STAT3 phosphorylation influences the expression of genes controlling keratinocyte survival and proliferation through interactions with other transcription factors such as NF-kappaB [96, 99]. STAT3 activation has a key role in the psoriasis-associated IL-23 signaling cascade [71, 97, 99]. Accordingly, JAK inhibition is being assessed as a novel therapeutic strategy for treatment of psoriasis. Importantly, IL-6 produced by DCs, macrophages, T cells, and keratinocytes further augments the IL-6-rich microenvironment in psoriatic plaque, resulting in the robust induction of pSTAT3 in effector and memory Th17 cells [76]. Persistent pSTAT3 signaling in T cells is required for initial Th17 differentiation and promotion of Th17 cytokines production, unleashes unrestrained activation of effector T cells, and prevents suppressive activity of T regulatory cells [76]. Additionally, IL-6-mediated pSTAT3 signaling is capable of enhancing keratinocyte growth and proliferation, promoting psoriasis epidermal hyperplasia [96, 98]; IL-6 signaling on keratinocytes also induces chemoattractant proteins via AP-1 downstream activation [97].

IL-6 is a key mediator of IL-23/Th17-driven cutaneous inflammation [37, 94]. IL-23-induced dermal inflammation in psoriasis mouse models relies on T cells and IL-6 [96]. In IL-6-deficient mice, intradermal injections of IL-23 lead to increased IL-22 production compared with WT mice, but this response is not sufficient for effective dermal inflammation and epidermal hyperplasia [96]. This finding seems to be secondary to insufficient expression of IL-22R1A in the absence of IL-6. The increased level of IL-6 in the skin of imiquimod-treated IL17RA-del mice compared with treated WT skin confirms the role of IL-6 in disease development in the absence of IL-17 signaling [41]. Accordingly, imiquimod is thought to indirectly activate the preexisting IL-17-producing T cells, which are capable of secreting other cytokines such as IL-6 that drive development of psoriasiform dermatitis independent of IL-17 [41, 43].

3.3. IL-6 and Pustular Psoriasis. Recent evidence points to an unexpected, central role of IL-6 in driving the abnormal recruitment of neutrophils into lesional skin of PP [23]; accordingly, IL-6 would be the key downstream mediator acting together with IL-17 to induce excessive skin infiltration by neutrophils resulting in intraepidermal pustules typical of PP (Figure 2) [23]. Importantly, IL-6 could be a novel, attractive target for the treatment of PP, in the light of the current availability of biologic agents safely and effectively antagonizing IL-6.

IL-6 has been long known to favor neutrophil differentiation and activation both in vivo and in vitro [79, 80]. Positive correlations have been recorded between IL-6 serum levels and clinical severity of PP, as well as associated leukocytosis, ESR, and CRP levels [100, 101]. Clinical improvement of PP following tonsillectomy has been paralleled by reduction of serum IL-6 levels [102]; in keeping, in vitro exposure of tonsillar mononuclear cells to streptococcal antigens resulted in increased production of IL-6 [91, 103].
The K14-IL17A-ind/+ transgenic mouse represents an animal model of psoriasiform dermatitis characterized by deregulated, persistent overexpression of IL-17A in epidermal keratinocytes leading to prominent development of intraepidermal neutrophil microabscesses in addition to dermal T-cell infiltration, hyperkeratosis, and parakeratosis [23]. The immunopathogenesis observed in the K14-IL17A-ind/+ strain strongly supports a mechanism whereby IL-6 propagates IL-17-induced inflammation, as confirmed by the noticeable presence of IL-6Rα-expressing monocytes and neutrophils in the affected skin [23].

In this setting, the inflammatory cascade starts with epidermal IL-17A expression in the absence of IL-23 overexpression; similar conditions (i.e., a high IL-17A/IL-23 ratio) have been described as characteristic of biopitic samples of human PP compared to conventional PV (whereby IL-17A levels appear to follow those of IL-23). The persistent expression of IL-17A in basal keratinocytes seems to induce target cell to secrete significant amounts of IL-6, resulting in high levels of circulating IL-6 and sIL-6R/IL-6R heterodimers [23]; increased levels of local and systemic IL-6 influence IL-6Rα+ neutrophils and monocytes activity, leading to aberrant chemotaxis into lesional skin and formation of intraepidermal neutrophil microabscesses [23].

Importantly, administration of anti-IL-6 neutralizing antibody in K14-IL17A-ind/+ mice is sufficient to reduce and prevent the extent of leukocyte infiltration, leading to a sizeable decrease in cutaneous accumulation of myeloperoxidase+ CD11b+ cells, intraepidermal neutrophil microabscesses formation, and epidermal changes [23]. Hence, IL-6 seems to play a key role in the innate component of IL-17-driven PP-like dermatitis, and blockade of IL-6 activity may result in dramatic clinico-pathological improvements despite the persistent activation of the IL-17 signaling.

Interestingly, gene expression evaluation of psoriatic plaques in the initial 48 hours after anti-TNF-alpha infliximab administration revealed significant inhibition of slan-DC-derived IL-1β, TNF-alpha, IFN-gamma, IL-12, and IL-23 but not IL-6, suggesting that direct TNF-alpha blockade is less effective in targeting IL-6 production by inflammatory dermal DCs [95]. If IL-6 signaling was more relevant to PP development than to PV, such data would provide an explanation to clinical evidence that efficacy rates of TNF-alpha inhibitors in PP are lower as compared to PV [14].

4. Conclusions

So far, the experience with IL-6 inhibitors in psoriasis is limited, as other signaling pathways have been successfully investigated as therapeutic targets (i.e., TNF-alpha, IL-23, and IL-17) [8, 36, 38, 104]. Furthermore, paradoxical cases of biologic-induced psoriasiform dermatitis have been reported also for patients undergoing treatment with tocilizumab for RA [105, 106]. Tofacitinib and other Janus kinase inhibitors (targeting, among the others, also the IL-6R signaling pathway) are gaining significant attention as therapeutic options in psoriasis, but their efficacy in PP is still unclear [107, 108]. Only occasional patients with generalized PP, including paradoxical anti-TNF-induced cases, have been effectively treated with the anti-IL-6 agent tocilizumab [109, 110]. A larger amount of data exists with regard to the role of IL-1 antagonist anakinra in PP, especially in cases secondary to IL36RN mutations [24, 62, 64]. Nonetheless, it seems reasonable that IL-6 may play a crucial role as well as IL-1 independently from the persistent IL-36R activation in the epidermis [62]. If this evidence will be confirmed, agents neutralizing IL-1 and IL-6 may be effective in treating PP, similarly to juvenile idiopathic arthritis, which has been successfully treated with either anti-IL-1 agents or IL-6 inhibitors [82].

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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