Psoriasis is a frequent inflammatory skin disease. Fundamental research on the pathogenesis of psoriasis has substantially increased our understanding of skin immunology, which has helped to introduce innovative and highly effective therapies. Psoriasis is a largely T lymphocyte-mediated disease in which activation of innate immune cells and pathogenic T cells result in skin inflammation and hyperproliferation of keratinocytes. B cells have thus far largely been neglected regarding their role for the pathogenesis of psoriasis. However, recent data shed light on their role in inflammatory skin diseases. Interestingly, interleukin (IL)-10-producing regulatory B cells have been assumed to ameliorate psoriasis. In this review, we will discuss the development of disease, pathogenicity, and current developments in therapeutic options. We describe different roles of T cells, B cells, and cytokines for the immunopathology and disease course of psoriasis.

Psoriasis is a frequent inflammatory skin disease. Fundamental research on the pathogenesis of psoriasis has substantially increased our understanding of skin immunology, which has helped to introduce innovative and highly effective therapies. Psoriasis is a largely T lymphocyte-mediated disease in which activation of innate immune cells and pathogenic T cells result in skin inflammation and hyperproliferation of keratinocytes. B cells have thus far largely been neglected regarding their role for the pathogenesis of psoriasis. However, recent data shed light on their role in inflammatory skin diseases. Interestingly, interleukin (IL)-10-producing regulatory B cells have been assumed to ameliorate psoriasis. In this review, we will discuss the development of disease, pathogenicity, and current developments in therapeutic options. We describe different roles of T cells, B cells, and cytokines for the immunopathology and disease course of psoriasis.

Psoriasis is an immune-mediated inflammatory disease with autoimmune pathogenic traits that affects the skin and joints. The worldwide prevalence of psoriasis is 2 to 3%, which tends to be lower in some regions of Asia and Africa but higher in Scandinavian populations [1-3]. Known environmental triggers and associations include streptococcal infections, physical trauma (e.g., tattoos, surgical incisions), certain medications (such as antidepressants, antihypertensive drugs, anti-cytokine therapy), smoking, as well as alcohol abuse, respectively [4-6]. Psoriasis is characterized by the excessive proliferation and aberrant differentiation of keratinocytes resulting clinically in erythematous scaly plaques of variable sizes. Psoriasis was initially believed to be a variant of leprosy until 1841 when von Hebra [7] identified it as a separate disease entity. Psoriasis patients typically have demarcated chronic erythematous plaques covered by silver white scales mainly on the knees, elbows, scalp, umbilicus, and lumbar region [8]. The disease is often associated with psoriatic arthritis,
metabolic syndrome, cardiovascular problems, diabetes mellitus, and other comorbidities. Psoriasis patients have a higher risk for chronic inflammatory bowel disease and chronic kidney disorders. Moreover, the prevalence of depression, anxiety, and suicidality is increased [6,9]. Taken together, different factors contribute to the development of psoriasis causing adverse effects on patients’ quality of life and disease burden.

PATHOGENESIS

Psoriasis is a complex genetic disorder that is triggered by various risk factors involving a variety of processes such as inflammation, antigen presentation, cell signaling, and transcriptional regulation [10]. The hallmark of psoriasis is sustained inflammation leading to uncontrolled keratinocyte proliferation and dysfunctional differentiation (Figure 1). Psoriatic plaque formation is believed to be a combination of inflammation in epidermal layers resulting from interaction of keratinocytes with many different cell types in the skin. Histological studies often show dramatic alterations in psoriatic skin characterized by profound thickening of the epidermis (acanthosis), hyperkeratosis and parakeratosis. In “metaanalyses” of transcriptomes of lesional versus non-lesional psoriatic skin by cDNA microarrays transcripts more than 1000 genes were found to be differently expressed [11,12]. There is a genetic predisposition to psoriasis, and many psoriasis susceptibility (PSORS) loci have been identified that appear to be involved in the pathogenesis of the disease. In one of the latest meta-analyses of genome-wide association studies, 15 new loci were identified, which increased the number of PSORS loci in European patients to 36. Among those are several loci that code for components of the NFκB signal transduction cascade such as REL, NFKBIZ (encoding IkB-zeta), NFKBIA (encoding IkBa), TRAF6, CARD14, and ILF3 [13,14]. The latter is an RNA-binding protein affecting the transcription factor Nuclear factor of activated T cells (NFAT) expression. These genome-wide studies display the complexity of gene expression alterations during psoriasis development. Among a variety of risk factors promoting the development of psoriasis, HLA-C*06:02 is a predominant risk gene. T cell hybridoma studies with a unique T-cell receptor (Vx3S1/Vβ13S1) have shown that T cells detect the melanocyte-derived autoantigen ADAMTS-like protein 5 in a HLA-C∗06:02-restricted manner [15]. Several reports have also suggested an
important role of the nervous system for the pathogenesis of psoriasis. The latter appears to be co-responsible for the symmetric plaque distribution on the body and interactions between immunomodulatory networks and peripheral sensory nerves have been described [16-18]. Clinical data also suggest that the surgical denervation of psoriatic lesions or local anesthesia not only diminish the local sensation but also leads to reduced regional inflammation [18]. In this context, emotional stress may be also linked to the onset and/or exacerbation of psoriasis [19].

Basic research using human and mouse data has illustrated the pivotal role of the immune system in psoriasis development. Traditionally, psoriasis is considered as a T cell-controlled systemic inflammatory disease modulated by genetic susceptibility along with environmental factors. The massive infiltration of lymphocytes, macrophages, and neutrophils into the skin is a hallmark of psoriatic lesions. In this respect, is clear that the disturbance of the innate and adaptive cutaneous immune responses along with non-immune cells lead to development and sustainment of psoriatic inflammation [20,21]. The pathogenesis of psoriasis is commonly acknowledged with two phases, (i) the initiation phase and (ii) the maintenance of the pathological state phase.

**KERATINOCYTES AND INNATE IMMUNITY CELLS IN THE SKIN**

The skin is the largest, multi-layered organ of the body comprising multiple cell types [22]. In psoriasis there is an intense crosstalk between innate immune cells (e.g. dendritic cells (DCs), macrophages, neutrophils), adaptive immune cells (B and T cells) and resident skin cells (e.g. keratinocytes, melanocytes, and endothelial cells). These interactions appear to amplify and sustain chronic inflammation.

DCs, being professional antigen-presenting cells (APCs), play a major role in the initial stages of disease. Though DC activation in psoriasis is not entirely clear, proposed mechanisms involve recognition of released antimicrobial peptides (LL37, S100 proteins, and β-defensins) by keratinocytes in response to injury. These peptides (mainly LL37) are overexpressed in psoriatic skin [23] and bind to DNA of damaged cells. Such binding may result in activation of plasmacytoid DCs to produce IFNα in psoriatic plaques. IFNα leads to maturation/activation of myeloid DCs. These activated DCs are transformed into APCs to interact with naïve T cells and start producing high amounts of TNF-α, IL-23, IL-12, and IL-6. Those cytokines activate cascades of inflammatory responses by promoting keratinocyte proliferation and recruitment of neutrophils to sites of inflammation. Keratinocytes perpetuate the inflammatory milieu via production of antimicrobial peptides, secretion of cytokines (IL-6, IL-1β, and TNF-α) and chemokines (e.g. CCL20, CXCL5, CXCL8, CXCL9, CXCL10) [24]. Abundant accumulation of neutrophils in psoriatic lesions is a typical feature of psoriasis. Neutrophil granules are accumulated by IL-36, which is mainly secreted by keratinocytes and dendritic cells in the skin [25,26]. IL-36 is expressed in three isoforms (i.e. IL-36α, β, and γ), all of them belonging to the IL-1 family. After binding to its receptor IL-36Rα, IL-36 promotes transcription of various inflammatory mediators through activation of NF kappa B. On the other side, IL-36 also interacts with other inflammatory cytokines like IL-17 thereby increasing inflammation. Genetic mutations/polymorphisms in genes regulating IL-36 cause uncontrolled inflammation as well as excessive neutrophil accumulation at sites of inflammation [10]. Interestingly, there is evidence that neutrophil depletion significantly relieves patients who did not respond to conventional therapeutic approaches [15,27].

Macrophages (MPs) derive from monocytes and represent tissue-resident phagocytic and antigen-presenting cells. There is manifold evidence that MPs contribute to inflammatory processes in psoriasis. Elevated numbers of MPs are found in psoriatic lesions [28]. MPs are an important source of TNF-α, a key mediator in chronic inflammation [29]. Additionally, it was shown that IFN-γ can activate the expression of proinflammatory cytokines such as CXCL9 [28] assigning them a role as target as well as acting cells in psoriasis.

In the emerging field of the innate immune system lymphoid cells without antigen-specific receptors, innate lymphoid cells (ILC), contribute to antimicrobial defense and balance between pro- and anti-inflammatory factors. Among the three different subtypes ILC3 appear to be most important in psoriasis due to their ability to produce IL-22 and IL-17A [30]. ILC3 are present in the blood and skin of affected patients to a greater extent than in healthy individuals [30]. Moreover, their number in the peripheral blood and in the affected skin decrease with disease remission indicating a negative correlation between cell number and disease activity. In a mouse model in which psoriasis-like skin lesions are induced by imiquimod, ILC3 – besides γδ T cells – were the major source of IL-17 and IL-22 rather than Th17 cells [30]. This suggests a so far underestimated role of ILC3 in the pathogenesis of psoriasis and requires further investigation.

**T CELLS**

T cells play a central role in defense against different pathogens and tumors. Successful treatment of psoriasis patients with cyclosporine A (CsA) has highlighted the
crucial role of T cells in its pathophysiology [31]. CsA treatment leads to T cell suppression [32]. T cell signaling is a highly organized process in recognizing antigens presented by APCs in the skin. Psoriasis pathogenesis involves crucial interplay between T cells (CD8\(^+\), Th1, autoreactive T cells, Th17, and Th22) and dermal DCs [33,34]. Cytokines IL-12 and IL-23 released by dermal DCs promote Th1, Th17, and Th22 responses. These helper T cells stimulate epidermal hyperproliferation and alter epidermal differentiation leading to their decreased helper T cells stimulate epidermal hyperproliferation and alter epidermal differentiation leading to their decreased apoptosis [35,36]. The role of CD4\(^+\) T cells in psoriasis was convincingly shown by transferring human skin transplants to immunodeficient SCID mice followed by injection of autologous CD4\(^+\) T cells from psoriasis patients that resulted in psoriasis development [37]. Th1-type CD4\(^+\) T cells producing high levels of IFN-γ and TNF-α are important players in triggering psoriasis [6].

Tissue residential T cells (T\(_{\text{RM}}\)) provide a pivotal role in local protection from environmental dangers challenging body surfaces. T\(_{\text{RM}}\) induce antimicrobial, inflammatory, and cytotoxic tissue responses. IL-17 and IL-22 producing T\(_{\text{RM}}\) are enriched in active and resolved psoriatic lesions, thereby influencing the onset and maintenance of a psoriatic plaque [38,39]. Skin sensations and some form of itch are transmitted by sensory fibers that express TRPV1 (The transient receptor potential cation channel subfamily V member 1) cation channels. These fibers co-express the sodium channel Nav1.8. It has been shown recently that these receptors interact with dermal dendritic cells, thereby regulating the IL-17/IL-23 pathway and hence controlling immune responses [40]. Skin inflammation is strongly diminished in IL-17 receptor-deficient mice suggesting a vital role of IL-17 in the generation of psoriasis-like lesions in mice [41]. While Th17 cells are a main source of IL-17 production, other cells including natural killer cells, myeloid cells, γδ T cells, lymphoid-tissue inducer-like cells, and invariant natural killer T cells have also been reported to release IL-17 [42-44]. Increased expression in lesional skin [45] and higher IL-17 serum levels are typical features of psoriasis [46]. Although Th17 and other IL-17-producing cells protect the epidermal barrier against bacterial and fungal infections, when overproduced, they contribute to chronic inflammation and autoimmune diseases [47]. The successful therapeutic application of antibodies against IL-17 and the IL-17 receptor underpins the importance of Th17 cells concealing that IL-17 works as “driving force” in the generation and maintenance of psoriasis [48-51]. However, after deciphering that IL-23 derived from DCs promotes Th17 development it became obvious that the IL-23/Th17 axis plays a major role for the development of psoriasis [52]. Therefore, inhibition of IL-23 is an alternative approach to control the production of IL-17 [46]. Other T cell subsets involved in the pathophysiology of psoriasis include dermal γδ T cells that are capable of producing IL-17A independent of IL-23 stimulation [53].

**B CELLS**

B cells contribute to innate and adaptive immune responses by antibody production and antigen presentation. B cells play an essential role in the protection against different infectious and inflammatory diseases. They are generally believed to be a positive regulator of the pathogenesis of various inflammatory diseases by producing autoantibodies and providing T cell help. B cell depletion by anti-CD20 mAbs (e.g., Rituximab) studies have shown promising effects in treating different autoimmune diseases [54-56]. However, regulatory roles of B cells have been discovered in the past few decades. Such B cell subsets have been collectively named regulatory B cells (B\(_{\text{reg}}\)). In 1996, Wolf et al. reported compelling data of adverse disease affects from mice deficient for B cells after inducing experimental autoimmune encephalomyelitis (EAE) [57]. Using an intestinal inflammation model, Mizoguchi et al. [58] showed that the CD1d\(^{hi}\) B cell subset protects from inflammation mainly by IL-10 production. Similarly, Fillatreau et al. showed that IL-10 produced by B cells plays a vital role in ameliorating inflammatory autoimmunity [59]. B\(_{\text{reg}}\) exert an immunosuppressive function by secreting IL-10 that plays an important role in dampening various inflammatory and allergic diseases [59-62].

B\(_{\text{reg}}\) do not appear to be a distinct B cell lineage but rather a differentiated stage of different B cell subsets. It remains to be clarified which factors initiate the development or maturation of B cells into a B\(_{\text{reg}}\) phenotype. Several subsets of B\(_{\text{reg}}\) have been identified in mice and humans. In mice, B cell subsets including CD5\(^+\) B1a and CD5\(^-\) B1a are found in peritoneal and pleural cavities. The well characterized murine B\(_{\text{reg}}\) population is defined by CD5\(^-\)CD1d\(^{hi}\) surface expression. Other B cell subsets with IL-10-mediated regulatory functions are marginal zone (MZ) B cells (CD19\(^+\)CD21\(^+\)CD23\(^-\)CD24\(^-\)IgM\(^-\)IgD\(^-\) CD1d\(^{hi}\)), precursors of MZ B cells and CD138\(^-\) plasma cells [63-66]. In humans, an IL-10-producing CD19\(^+\)CD38\(^-\)CD24\(^-\) immature transitional B cell subset is commonly defined as B\(_{\text{reg}}\). The other defined populations include CD19\(^+\)CD24\(^+\)CD38\(^-\)CD1d\(^{hi}\) and CD19\(^+\)CD24\(^+\)CD27\(^-\) B cell subsets [67-70]. The immunosuppressive function of B\(_{\text{reg}}\) critically depends on intrinsic Toll-like receptor (TLR) signaling. TLR agonists induce IL-10 secretion by naïve B cells ex vivo [60].

Compared to the number of investigations on the role of T lymphocytes in psoriasis, there are only a few reports studying B lymphocytes in this disease. Currently, the role of B cells – in particular of B\(_{\text{reg}}\) – for the
development and/or maintenance of psoriasis in humans is unclear. This is in part due to the rare appearance of B cells in lesional psoriatic skin. Depletion of B cells by the anti-CD20 mAb rituximab in patients suffering from other autoimmune diseases or lymphomas resulted in the development of psoriatic skin lesions in individual cases [71,72]. The use of genetically altered mice which lack B cells and mainly IL-10-producing B cells showed that defective B cell development results in chronic inflammation [61,73]. Previously, it had been shown that B cells have the capacity to ameliorate the severity of autoimmune diseases [61,74,75]. B cells are decreased in patients with psoriasis [76]. Recently, a study was published on the suppression of imiquimod (a TLR7 agonist)-induced, psoriasis-like skin inflammation by B cells [77]. We showed previously that mice bearing B cells deficient for the transcription factor “nuclear factor of activated T cells” (NFATc1) harbored more B cells and ameliorated disease symptoms [78,79], it might be assumed that B cells play a vital role in driving diseases through various mechanisms. These skin-associated B cells are involved in skin homeostasis as well as in regulating the repair of the wounded skin and the cutaneous microbiome [80]. B cells are key effector cells and secrete inflammatory cytokines like IL-6, IL-4, GM-CSF, and IFN-γ [81]. Such effector functions have also been shown by skin-resident B cells in a recent study where inflamed mouse skin was shown to harbor increased numbers of IL-6-producing B cells in a scleroderma mouse model. Blocking IL-6 but not IL-10 led to reduced inflammatory symptoms of the disease [82]. These data indicate various functional properties of B cells in the skin and refer to a potential window of opportunity for selectively targeting distinct B cell subsets to treat skin diseases (Figure 1).

**CYTOKINES**

**IL-1**: IL-1 is a key mediator of inflammatory responses to bacterial and viral infections but also to injury [83]. The IL-1 family consists of multiple members such as IL-α and IL-β that are produced by macrophages, monocytes, and other cell types. These peptides are recognized by the IL-1 receptor type 1 (IL-1R) and its accessory protein (IL-1RAcP), which subsequently activate a complex network of intracellular signaling (including MyD88 and Interleukin-1 receptor-associated kinases, IRAKs) [84]. This finally leads to the induction of transcription factors such as NFkB resulting in inflammatory immune responses.

IL-1β is known to play a critical role in psoriasis. Elevated mRNA levels can be found in lesional skin compared to healthy skin and the same is true in an imiquimod-induced mouse model of psoriasis [85]. It induces T cell proliferation and enhances IL-17 production [85], thereby fueling inflammatory processes in psoriasis.

IL-1-targeting therapies such as the IL-1-receptor antagonist anakinra, however, have failed to improve chronic plaque psoriasis, but showed efficacy in some patients with generalized pustular psoriasis [86]. Recently, some molecules upstream from IL-1 were discovered to play a possible role in psoriasis, i.e., the inflammasome components NLRP1 and NLRP3, which are involved in the control of IL-1β maturation [87].

**IL-23**: IL-23 is an important cytokine in anti-bacterial and anti-fungal immune defense. It is a heterodimeric molecule composed of two subunits, p19 and p40, the latter of which is shared with IL-12 [88]. Diverse cell types produce IL-23 including macrophages and DCs. It binds to a receptor complex consisting of IL-23R and IL-12Rβ1 and leads to the activation of transcription factors including STAT-3 [89,90]. IL-23 is a key regulator of the Th17-driven pathogenesis of psoriasis [91] even though it cannot activate naïve T cells alone since these cells do not express the corresponding receptors [92]. IL-6, IL-1, and TGFβ promote differentiation of CD4 cells into Th17 cells via the transcription factor RORγt [89,93], which can be stimulated by IL-23 to produce proinflammatory cytokines including IL-17 and TNFα [89,94]. IL-23 is overexpressed in human psoriatic skin [95] and injection of IL-23 into the skin of wild-type mice can cause psoriasis-like lesions [96]. Its crucial role for the molecular pathogenesis of psoriasis led to the development of anti-IL-23 mAbs, which showed excellent efficacy in the treatment of psoriasis [94].

**IL-17**: The IL-17 family consists of 6 members, IL-17A, B, C, D, E, and F, amongst which IL-17A and IL-17F are the most similar while sharing about 50% of their sequence [97]. The main source of IL-17 are Th17 cells deriving from CD4 T cells [91], but also neutrophils, mast cells, NK cells, macrophages, and B cells are capable of producing this cytokine [98]. Hetero- or homodimers of IL-17A and IL-17F bind to the receptors consisting of the subunits IL-17RA and IL-17RC, while the receptor for IL-17E is formed by IL-17RA and IL-17RB and the one for IL-17C by IL-17RA and IL-17RE [97]. IL-17RA and IL-17RC are expressed by epithelial cells, fibroblasts, and different immune cells [97,99]. IL-17 induces the expression of proinflammatory molecules, e.g. IL-1β, IL-6, GM-CSF, G-CSF, and TNF-α in fibroblasts and macrophages. The latter also secrete chemokines such as CXCL9 and CXCL10 [99,100]. Epithelial cells are stimulated to secrete antimicrobial peptides and CCL20 [99,101]; secreted chemokines lead to the recruitment
and skin invasion of neutrophils. Thus, IL-17 plays an important role in the defense of bacterial and fungal infections at the epithelial barrier [99,102].

The proinflammatory impact of IL-17 on the immune system may cause autoimmunity as this has been shown for different diseases including rheumatoid arthritis, inflammatory bowel disease, and psoriasis [103-105]. Furthermore, IL-17 supports inflammatory processes in lifestyle-associated metabolic disorders like hepatic steatosis and arteriosclerosis [106,107]. IL-17 antagonists are not only effective in treating psoriasis, but may also contribute to improvement of frequent comorbidities [108,109].

**IL-22:** IL-22 is part of the IL-10 cytokine family, even so in some ways it differs from other members of this group. Its active form is a monomer as which it binds to its receptor composed of heterodimeric subunits, IL-22R1 and IL-10R2 [110,111]. These receptors are found on non-hematopoietic cells, i.e. epithelial cells and fibroblasts in diverse tissues [110]. Intracellular signaling of the IL-22 receptor is driven via phosphorylation of STAT3 as well as STAT1 and STAT5 [112]. Additionally, IL-22 activates the p38 and ERK MAPK pathways [112]. Cells producing IL-22 include CD4 (Th1, Th17, and Th22 cells) and CD8 lymphocytes, innate lymphoid cells and NK cells [110,111]. Also some non-lymphoid cells like macrophages and fibroblasts are capable of synthesizing IL-22 [111]. Crucial for IL-22 production are the transcription factor RORyt, IL-23, and the aryl hydrocarbon receptor (AhR), since CD4+ cells secrete IL-22 only when this receptor is present [113,114].

Imbalances in IL-22 secretion and signaling have been observed in various autoimmune diseases [114]. In psoriatic lesional skin IL-22 expression was found to be increased and serum levels are correlating with disease activity [115]. IL-22 induces keratinocyte migration and hinders their differentiation leading to epidermal thickening and scaling [90,115]. Additionally, it induces the secretion of chemokines and antimicrobial peptides promoting neutrophil invasion and inflammation. Therefore, IL-22 was considered a potential target for psoriasis treatment [13]. Phase I trials with IL-22 inhibitors, however, had to be discontinued due to lack of efficacy [86].

**IL-12:** IL-12 was initially named natural killer-cell-stimulating factor because it was discovered in transformed B cells activating NK cells and T cells [116]. It exists as a heterodimer consisting of a p35 and a p40 unit [116,117], the latter of which is shared with IL-23. DCs, macrophages, and neutrophils produce IL-12. Two subunits, IL-12Rβ1 and IL-12Rβ2, form its receptor, which is mainly found on T cells and NK cells. Binding of IL-12 to the receptor activates the JAK/STAT pathway [117].

IL-12 plays an important role in Th1 responses and in the induction of IFN-γ [117]. Since IL-12 increases IFN-γ and TNF-α, which are key molecules in psoriasis pathogenesis, IL-22 was also expected to be crucial. However, an increased expression of the IL-12 p35 subunit in psoriatic skin could not be detected [118]. It is now known that successfully targeting the p40 subunit in psoriasis treatment exert its effects via inhibition of IL-23 [94].

**IFN-γ:** Interferon-γ is a type 2 interferon and an important molecule in inflammatory responses and for the defense of viral and bacterial infections. The main source of IFN-γ are CD4+ and CD8+ lymphocytes and NK cells, but also APCs and B cells release this cytokine [119]. IFN-γ secretion is driven by IL-12 and IL-18. When APCs sense pathogenic patterns, IL-12 and chemokines like macrophage inflammatory protein (MIP)-1α are released that attract NK cells, which, in turn, are triggered to produce IFN-γ by the secreted IL-12 [120]. The IFN-γ receptor consists of two IFNGR1 chains, where the ligand binds and two IFNGR2 chains responsible for signal transduction leading to an activation of the JAK/STAT signaling pathway [120]. IFN-γ enhances antigen processing and presentation and drives CD4 cells towards a Th1 response.

IFN-γ can be found in psoriatic lesions. Serum levels are higher in affected patients than in healthy controls and appear to correlate with disease activity [52,121,122]. It promotes IL-1 and IL-23 production by APCs driving a Th17 response [123]. Interestingly, patients with a higher decrease of IFN-γ serum levels showed longer remission periods as compared to patients with less reduction of blood levels [52]. However, anti-IFN-γ therapy failed to show efficacy in improving psoriatic lesions [124].

**TNF-α:** TNF-α is an important proinflammatory cytokine in acute and chronic inflammation, has anti-tumor-activity and helps defending infections [125]. TNF-α is synthesized membrane-bound and is released by matrix metalloproteinases in its soluble form [126]. Many different cell types produce TNF-α including macrophages, monocytes, lymphocytes, and keratinocytes. TNF receptors are expressed on every nucleated cell, and there are two main isoforms: TNFR1 or TNFR2 [125]. TNFα induces CD4 cell proliferation, production of different chemokines and cytokines such as IL-1, but also promotes apoptosis in different cell types.

TNF-α is known as a critical player in different autoimmune disease such as Crohn’s disease, rheumatoid arthritis, and ankylosing spondylitis [29]. Serum levels of TNF-α may correlate with disease activity [127] and TNF-α inhibitors have been proven to be effective in the treatment of plaque psoriasis.
Table 1. Biologics approved for the treatment of plaque psoriasis and/or psoriatic arthritis.

| Name              | Structure                                      | Indication              | Approval state            | PASI75\(^1\)       | PASI90\(^1\)       | Approval state for PsA | Specifics                                                                 |
|-------------------|-----------------------------------------------|-------------------------|---------------------------|--------------------|--------------------|------------------------|--------------------------------------------------------------------------|
| **TNF antagonists** |                                               |                         |                           |                    |                    |                        |                                                                          |
| Infliximab        | chimeric human/murine mAb                     | adult psoriasis         | FDA, EMA                  | 80-87% at week 10  | 57-58% at week 10  | yes                    | i.v. every 8 weeks, CI: patients with NYHA III/IV                       |
| Etanercept        | soluble TNFR2: IgG1Fc human fusion protein    | adult psoriasis,       | FDA, EMA                  | 44-56% at week 24  | 21-32% at week 24  | FDA/EMA: yes, but     | s.c. weekly or twice weekly, CI: patients with NYHA III/IV              |
|                   |                                               | EMA (≥6 yrs of age)     |                           |                    |                    | adults only            |                                                                          |
| Adalimumab        | human mAb                                     | adult psoriasis,       | FDA, EMA                  | 71-78% at week 16  | 45-51% at week 16  | EMA: yes, but adults  | s.c. biweekly, CI: patients with NYHA III/IV                             |
|                   |                                               | EMA: children (≥4 yrs of age) |                           |                    |                    | only FDA: no           |                                                                          |
| Golimumab         | human mAb                                     | adult PsA only [146]    | FDA, EMA                  | n.a.               | n.a.               | yes                    | s.c. monthly, CI: patients with NYHA III/IV                              |
| Certolizumab      | humanized Fab-fragment, Polyethylene glycol-conjugated | adult psoriasis     | FDA, EMA                  | 67-81% at week 16  | 36-53% at week 16  | yes                    | may be used in pregnancy, s.c. biweekly or every 4 weeks, CI: patients with NYHA III/IV |
| **IL-17 antagonists** |                                               |                         |                           |                    |                    |                        |                                                                          |
| Secukinumab       | human mAb                                     | adult psoriasis         | FDA, EMA                  | 77-82% at week 12  | 54-59% at week 12  | yes                    | s.c. every 4 weeks, caution in patients with IBD                        |
| Ixekizumab        | humanized mAb                                 | adult psoriasis         | FDA, EMA                  | 89% at week 12     | 70% at week 12     | yes                    | s.c. every 4 weeks, caution in patients with IBD                        |
| Brodalumab        | human mAb                                     | adult psoriasis         | FDA, EMA                  | 80-92% at week 12  | 69-74% at week 12  | no                     | s.c. every 2 weeks, CI: active Crohn's disease. Caution in patients with depression |
| **IL-12/IL-23 antagonists** |                                               |                         |                           |                    |                    |                        |                                                                          |
| Ustekinumab       | human mAb                                     | adult psoriasis FDA/EMA: adolescent patients (≥12 yrs) | FDA, EMA                  | 67% at week 12     | 42% at week 12     | yes                    | s.c. every 12 weeks                                                    |
| **IL-23 antagonists** |                                               |                         |                           |                    |                    |                        |                                                                          |
| Guselkumab        | human mAb                                     | adult psoriasis         | FDA, EMA                  | 86-91% at week 16  | 70-73% at week 16  | no                     | s.c. bimonthly                                                        |
| Tildrakumab       | humanized mAb                                 | adult psoriasis         | FDA, EMA                  | 61-64% at week 12  | 35-39% at week 12  | no                     | s.c. every 12 weeks                                                    |
| Risankizumab      | humanized mAb                                 | adult psoriasis         | FDA, EMA                  | 87-89% at week 12  | 75% at week 16     | no                     | s.c. every 12 weeks                                                    |

\(^1\)under administration of approved dose; mAb, monoclonal antibody; PsA, psoriasis arthritis; FDA, Food and Drug Administration; EMA, European Medicines Agency; TNF, tumor necrosis factor; TNF-R2, TNF receptor 2; n.a., not applicable; IBD, inflammatory bowels disease; s.c., subcutaneous; i.v., intravenous; CI, contraindication.
There is a multitude of substances to treat psoriasis – from topical treatments and immunosuppressive agents to biologics. In the recent years many newly developed biologics have been approved by the Federal Drug Agency (FDA) and the European Medicines Agency (EMA) (see overview in Table 1). Patients with moderate to severe plaque psoriasis clearly benefit from their high efficacy.

**TNF-α inhibitors**: TNF-α inhibitors were the first biologics approved for the treatment of moderate to severe psoriasis. There are at the moment three approved monoclonal antibodies, *i.e.* infliximab, adalimumab, and certolizumab (the latter being a Fcg antibody fragment), as well as one fusion protein consisting of the recombinant TNF-α receptor 2 and the Fc fragment of IgG1 (etanercept) [128]. Infliximab has been proven to be most effective among this group of psoriasis therapies, followed by adalimumab and etanercept. Infliximab showed a decrease in the psoriasis area and severity index (PASI) of at least 75% (*i.e.* PASI75) in 80% of treated patients at treatment week 10 [129].

It is well known that TNF-α inhibitors are associated with the risk of reactivation of latent tuberculosis infection. Tuberculosis (TB) associated with TNF-α inhibitors, in contrast to classical TB, is more likely to be disseminated, atypical, extrapulmonary, and life-threatening [130]. Therefore, TB testing is mandatory in patients prior to starting therapy.

Despite of their efficacy in psoriasis there is evidence that TNF-α inhibitors may occasionally elicit new manifestations or worsening of psoriasis as paradoxical effect [131]. This is independent of the underlying disease and can resolve after termination of treatment [132]. More investigations are needed to fully understand the underlying mechanisms.

Up to now, there is no evidence of teratogenicity of TNF-α inhibitors. However, it is recommended to restrict the use of these drugs to the first two trimesters [133]. Since certolizumab is a pegylated Fcg fragment, it cannot be diaplacentally transported, so its use during the whole pregnancy is possible [134].

**IL-12/23 inhibitors**: Among this group of drugs, one substance (ustekinumab) targets the p40 subunit and therefore both IL-12 and IL-23. The monoclonal antibodies guselkumab, tildrakizumab and risankizumab target exclusively the p19 subunit of IL-23 [128]. The latter have been proven to be more effective than ustekinumab suggesting that neutralizing p19 leads to a more potent inhibition of IL-23 [135]. Compared to TNF antagonists, IL-23 blockade shows a higher efficacy while the safety profile remained similar [136]. All the antibodies directly targeting IL-23 have first line approval in adult patients with moderate to severe plaque psoriasis. Ustekinumab is approved as second-line therapeutic by the EMA but as first-line treatment by the FDA. Moreover, it is approved by FDA and EMA for therapy in children beginning from the age of 12 [128].

Similar to the TNF-α inhibitors TB screening has to be performed prior to initiating therapy. In general, no significant safety issues were observed during clinical trials, most frequent adverse events were upper respiratory tract infections [137]. Thus, IL-23 and IL12/IL-23 inhibitors are a good therapeutic option treating chronic plaque psoriasis.

**IL-17 inhibitors**: Three monoclonal antibodies targeting IL-17 signaling are approved for the first-line therapy of moderate to severe plaques psoriasis in adults, namely secukinumab and ixekizumab, which inhibit IL-17A, and brodalumab that blocks the IL-17 receptor A. Considering their similar mode of action, all three antibodies show comparable efficacy in psoriasis, which has been proven to be higher than the efficacy of ustekinumab [128].

Due to some cases of suicidal ideation and completed suicides among patients treated with brodalumab, special care must be taken in patients with psychiatric comorbidities like depression [128], which is quite common among psoriatic patients [138].

Other relevant side effects mainly manifest as infections, especially mucocutaneous *Candida* infections [139]. As for the other biologics, TB testing is mandatory before initiation of psoriasis.

Recently, some biosimilars of effective biologics have become available for TNF-α inhibition. Studies showed that there are no significant differences with respect to efficacy and safety [140].

**CONCLUSIONS**

T lymphocytes unequivocally play a crucial role for the development of psoriasis, however, not all aspects of the disease can be exclusively explained by the mode of action of T lymphocytes. Different cytokines and the cellular contribution of other cells including (but not limited to) DCs, neutrophils, macrophages, keratinocytes, and B cells refer to a more complex cascade of events that finally results into the development of psoriasis. Despite the identification of early players in triggering this disease, the exact sequence of events during initiation and propagation of the psoriasis cascade remains largely unknown. Deciphering the role of regulatory immune cells (*e.g.* Bregs) may contribute to a better understanding of the pathogenesis and to a further improvement of our therapeutic strategies controlling psoriasis.
Acknowledgments. The authors acknowledge the funding support of their research by grants of the Interdisziplinäres Zentrum für Klinische Forschung (IZKF) Würzburg (FG, KM, and AK) and the Deutsche Forschungsgemeinschaft (DFG; SE469/24-1, GO811/5-1, KE1343/2-1).

REFERENCES

1. Parisi R, Symmons DP, Griffiths CE, Ashcroft DM; Identification and Management of Psoriasis and Associated Comorbidity (IMPACT) project team. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Invest Dermatol. 2013 Feb;133(2):377–85.

2. Gibbs S. Skin disease and socioeconomic conditions in rural Africa: Tanzania. Int J Dermatol. 1996 Sep;35(9):633–9.

3. Danielsen K, Olsen AO, Wilsgaard T, Furberg AS. Is the prevalence of psoriasis increasing? A 30-year follow-up of a population-based cohort. Br J Dermatol. 2013 Jun;168(6):1303–10.

4. Raychaudhuri SP, Jiang WY, Raychaudhuri SK. Revisiting the Koebner phenomenon: role of NGF and its receptor system in the pathogenesis of psoriasis. Am J Pathol. 2008 Apr;172(4):961–71.

5. Abel EA, DiCicco LM, Orenberg EK, Fraki JE, Farber EM. Drugs in exacerbation of psoriasis. J Am Acad Dermatol. 1986 Nov;15(5 Pt 1):1007–22.

6. Perera GK, Di Meglio P, Nestle FO. Psoriasis. Annu Rev Pathol. 2012;7(1):385–422.

7. Schön MP, Boehncke WH. Psoriasis. N Engl J Med. 2005 May;352(18):1899–912.

8. Owen CM, Chalmers RJ, O’Sullivan T, Griffiths CE. Antistreptococcal interventions for guttate and chronic plaque psoriasis. Cochrane Database Syst Rev. 2000;(2):CD001976.

9. Nestle FO, Kaplan DH, Barker J. Psoriasis. N Engl J Med. 2009 Jul;361(5):496–509.

10. Muhr P, Zeitvogel J, Heitland I, Werfel T, Wittmann M. Expression of interleukin (IL)-1 family members upon stimulation with IL-17 differs in keratinocytes derived from patients with psoriasis and healthy donors. Br J Dermatol. 2011 Jul;165(1):189–93.

11. Tian S, Krueger JG, Li K, Jabbari A, Brodmerkel C, Lowes MA, et al. Meta-analysis derived (MAD) transcriptome of psoriasis defines the “core” pathogenesis of disease. PLoS One. 2012;7(9):e44274.

12. Suárez-Fariñas M, Li K, Fuentes-Duculan J, Hayden K, Brodmerkel C, Krueger JG. Expanding the psoriasis disease profile: interrogation of the skin and serum of patients with moderate-to-severe psoriasis. J Invest Dermatol. 2012 Nov;132(11):2552–64.

13. Tsai LC, Spain SL, Knight J, Ellingham E, Stuart PE, Capon F, et al.; Collaborative Association Study of Psoriasis (CASp); Genetic Analysis of Psoriasis Consortium; Psoriasis Association Genetics Extension; Wellcome Trust Case Control Consortium 2. Identification of 15 new psoriasis susceptibility loci highlights the role of innate immunity. Nat Genet. 2012 Dec;44(12):1341–8.

14. Tsai LC, Spain SL, Ellingham E, Stuart PE, Capon F, Knight J, et al. Enhanced meta-analysis and replication studies identify five new psoriasis susceptibility loci. Nat Commun. 2015 May;6(1):7001.

15. Arakawa A, Siewert K, Stöhr J, Besgen P, Kim SM, Rühl G, et al. Melanocyte antigen 2 triggers autoimmunity in human psoriasis. J Exp Med. 2015 Dec;212(13):2203–12.

16. Ostrowski SM, Belkadi A, Loyd CM, Diaconu D, Ward NL. Cutaneous denervation of psoriasiform mouse skin improves acanthosis and inflammation in a sensory neuropeptide-dependent manner. J Invest Dermatol. 2011 Jul;131(7):1530–8.

17. Farber EM, Nickoloff BJ, Recht B, Fraki JE. Stress, symmetry, and psoriasis: possible role of neuropeptides. J Am Acad Dermatol. 1986 Feb;14(2 Pt 1):305–11.

18. Farber EM, Lamigan SW, Boer J. The role of cutaneous sensory nerves in the maintenance of psoriasis. Int J Dermatol. 1990 Jul-Aug;29(6):418–20.

19. Seville RH. Psoriasis and stress. Br J Dermatol. 1977 Sep;79(3):297–302.

20. Harden JL, Krueger JG, Bowcock AM. The immunogenetics of Psoriasis: A comprehensive review. J Autoimmun. 2015 Nov;64:66–73.

21. Rendon A, Schäkel K. Psoriasis pathogenesis and treatment. Int J Mol Sci. 2019 Mar;20(6):E1475.

22. Vidal Yucha SE, Tamamoto KA, Kaplan DL. The importance of the neuro-immuno-cutaneous system on human skin equivalent design. Cell Prolif. 2019 Nov;52(6):e12677.

23. Morizane S, Gallo RL. Antimicrobial peptides in the pathogenesis of psoriasis. J Dermatol. 2012 Mar;39(3):225–30.

24. Rauschenberger T, Schmitt V, Azeem M, Klein-Hessling S, Murti K, Grün F, et al. T cells control chemokine secretion by keratinocytes. Front Immunol. 2019 Aug;10:1917.

25. Chiang CC, Cheng WJ, Korinek M, Lin CY, Hwang TL. Neutrophils in Psoriasis. Front Immunol. 2019 Oct;10:2376.

26. Schön MP. Adaptive and innate immunity in psoriasis and other inflammatory disorders. Front Immunol. 2019 Jul;10:1764.

27. Ikeda S, Takahashi H, Suga Y, Eto H, Etoh T, Okuma K, et al. Therapeutic depletion of myeloid lineage leukocytes in patients with generalized pustular psoriasis indicates a major role for neutrophils in the immunopathogenesis of psoriasis. J Am Acad Dermatol. 2013 Apr;68(4):609–17.

28. Lorthois I, Asselineau D, Seyler N, Pouliot R. Contribution of in vivo and organotypic 3d models to understanding the role of macrophages and neutrophils in the pathogenesis of psoriasis. Mediators Inflamm. 2017;2017:7215072.

29. Desplat-Jégo S, Buryk L, Puterman C. Targeting TNF and its family members in autoimmune/inflammatory disease. Mediators Inflamm. 2014;2014:628748.

30. Ebbo M, Crinier A, Vély F, Vivier E. In innate lymphoid cells: major players in inflammatory diseases. Nat Rev Immunol. 2017 Nov;17(11):665–78.

31. Mueller W, Herrmann B. Cyclosporin A for psoriasis. N Engl J Med. 1979 Sep;301(10):555.

32. Rebora A. Cyclosporine A in psoriasis. Clin Dermatol. 1991 Oct-Dec;9(4):515–22.

33. Casciano F, Pigatto PD, Secchiero P, Gambari R, Reali E. T cell hierarchy in the pathogenesis of psoriasis and associated cardiovascular comorbidities. Front Immunol.
new actor in IFN-driven systemic autoimmune diseases. Eur J Immunol. 2012 Sep;42(9):2274–84.
49. Abdallah MA, Abdel-Hamid MF, Kobt AM, Mabrouk EA. Serum interferon-gamma is a psoriasis severity and prognostic marker. Cutis. 2009 Sep;84(3):163–8.
50. Benhadjou F, Mintoff D, Del Marmol V. Psoriasis: keratinocytes or immune cells - which is the trigger? Dermatology. 2019;235(2):91–100.
51. Edwards JC, Leandro MJ, Cambridge G. B-lymphocyte depletion therapy in rheumatoid arthritis and other autoimmune disorders. Biochem Soc Trans. 2002 Aug;30(4):824–8.
52. Leandro MJ, Edwards JC, Cambridge G, Ehrenstein MR, Isenberg DA. An open study of B lymphocyte depletion in systemic lupus erythematosus. Arthritis Rheum. 2002 Oct;46(10):2673–7.
53. Muhammad K, Roll P, Einsele H, Dörner T, Tony HP. Delayed acquisition of somatic hypermutations in repertoire IGD+CD27+ memory B cell receptors after rituximab treatment. Arthritis Rheum. 2009 Aug;60(8):2284–93.
54. Wolf SD, Dittel BN, Hardardottir F, Janeway CA Jr. Experimental autoimmune encephalomyelitis induction in genetically B cell-deficient mice. J Exp Med. 1996 Dec;184(6):2271–8.
55. Mizoguchi A, Mizoguchi E, Takeda T, Blumberg RS, Bhan AK. Chronic intestinal inflammatory condition generates IL-10-producing regulatory B cell subset characterized by CD1d upregulation. Immunity. 2002 Feb;16(2):219–30.
56. Fillatreau S, Sweenie CH, McGahey MJ, Gray D, Anderton SM. B cells regulate autoimmunity by provision of IL-10. Nat Immunol. 2002 Oct;3(10):944–50.
57. Alrefai H, Muhammad K, Rudolf R, Pham DA, Klein-Hessel S, Patra AK, et al. NFATc1 supports imiquimod-induced skin inflammation by suppressing IL-10 synthesis in B cells. Nat Commun. 2016 May;7(1):11724.
58. Yanaba K, Bouaziz JD, Haas KM, Poe JC, Fujimoto M, Tedder TF. A regulatory B cell subset with a unique CD1dhiCD5+ phenotype controls T cell-dependent inflammatory responses. Immunity. 2008 May;28(5):639–50.
59. Katz SI, Parker D, Turk JL. B-cell suppression of delayed hypersensitivity reactions. Nature. 1974 Oct;251(5475):550–1.
60. Rosser EC, Mauri C. Regulatory B cells: origin, phenotype, and function. Immunity. 2015 Apr;42(4):607–12.
61. Bouaziz JD, Yanaba K, Tedder TF. Regulatory B cells as inhibitors of immune responses and inflammation. Immuno Rev. 2008 Aug;224(1):201–14.
62. Lykken JM, Candando KM, Tedder TF. Regulatory B10 cell development and function. Int Immunol. 2015 Oct;27(10):471–7.
63. Matsumoto M, Baba A, Yokota T, Nishikawa H, Ohkawa Y, Kayama H, et al. Interleukin-10-producing plasmablasts exert regulatory function in autoimmune inflammation. Immunity. 2014 Dec;41(6):1040–51.
64. Mota I, Martins C, Borrego LM. Regulatory B cells and Allergy: uncovering the link. J Investig Allergol Clin Immunol. 2017:0.
65. Lykken JM, Candando KM, Tedder TF. B10 cell regulation of health and disease. Immunol Rev. 2014 May;259(1):259–72.
69. Blair PA, Noreha LY, Flores-Borja F, Rawlings DJ, Isenberg DA, Ehrenstein MR, et al. CD19(+)CD24(hi) CD38(hi) B cells exhibit regulatory capacity in healthy individuals but are functionally impaired in systemic lupus erythematosus patients. Immunity. 2010 Jan;32(1):129–40.

70. Iwata Y, Matsushita T, Horikawa M, Dillilo DJ, Yanaka K, Venturi GM, et al. Characterization of a rare IL-10-dependent B-cell subset in humans that parallels mouse regulatory B10 cells. Blood. 2011 Jan;117(2):530–41.

71. Dass S, Vital EM, Emery P. Development of psoriasis after B cell depletion with rituximab. Arthritis Rheum. 2007 Aug;56(8):2715–8.

72. Mielse F, Schneider-Obermeyer J, Dörner T. Onset of psoriasis with psoriatic arthropathy during rituximab treatment of non-Hodgkin lymphoma. Ann Rheum Dis. 2008 Jul;67(7):1056–7.

73. Fjelbye J, Antvorskov JC, Buschard K, Issazadeh-Navikas S, Engkilde K. CD1d knockout mice exhibit aggravated contact hypersensitivity responses due to reduced interleukin-10 production predominantly by regulatory B cells. Exp Dermatol. 2015 Nov;24(11):853–6.

74. Yanaba K, Yoshizaki A, Asano Y, Kadono T, Tedder TF. Regulatory B cells inhibit EAE initiation in mice while other B cells promote disease progression. J Clin Invest. 2008 Oct;118(10):3420–30.

75. Matsushita T, Yanaka K, Bouaziz JD, Fujimoto M, Tedder TF. Regulatory B cells inhibit EAE initiation in mice while other B cells promote disease progression. J Clin Invest. 2008 Oct;118(10):3420–30.

76. Kahlert K, Grän F, Muhammad K, Benoit S, Serfling E, Mielke F, Schneider-Obermeyer J, Dörner T. Onset of psoriasis with psoriatic arthropathy during rituximab treatment of non-Hodgkin lymphoma. Ann Rheum Dis. 2008 Jul;67(7):1056–7.

77. Yanaba K, Yoshizaki A, Asano Y, Kadono T, Tedder TF, Sato S. IL-10-producing regulatory B10 cells inhibit intestinal injury in a mouse model. Am J Pathol. 2011 Feb;178(2):735–43.

78. Asadullah K, Sterry W, Stephanek K, Jasulaitis D, Leopold M, Audring H, et al. IL-10 is a key cytokine in psoriasis. Proof of principle by IL-10 therapy: a new therapeutic approach. J Clin Invest. 1998 Feb;101(4):783–94.

79. Weiss E, Mamalak AJ, La Morgia S, Wang B, Feliciani C, Tulli A, et al. The role of interleukin 10 in the pathogenesis and potential treatment of skin diseases. J Am Acad Dermatol. 2004 May;50(5):657–75.

80. Debes GF, McGgettigan SE. Skin-associated b cells in health and inflammation. J Immunol. 2019 Mar;202(6):1659–66.

81. Shen P, Fillatreau S. Suppressive functions of B cells in infectious diseases. Int Immunol. 2015 Oct;27(10):513–9.

82. Matsushita T, Kobayashi T, Mizumaki K, Kano M, Sawada T, Tennichi M, et al. BAFF inhibition attenuates fibrosis in scleroderma by modulating the regulatory and effector B cell balance. Sci Adv. 2018 Jul;4(7):eaas9944.

83. Dinarello CA. Biology of interleukin 1. FASEB J. 1988 Feb;2(2):108–15.

84. Jensen LE. Targeting the IL-1 family members in skin inflammation. Curr Opin Investig Drugs. 2010 Nov;11(11):1211–20.

85. Cai Y, Xue F, Quan C, Qu M, Liu N, Zhang Y, et al. A critical role of the il-1beta-il-1r signaling pathway in skin inflammation and psoriasis pathogenesis. J Invest Dermatol. 2019 Jan;139(1):146–56.

86. Tsai YC, Tsai TF. Anti-interleukin and interleukin therapies for psoriasis: current evidence and clinical usefulness. Ther Adv Musculoskelet Dis. 2017 Nov;9(11):277–94.

87. Su F, Xia Y, Huang M, Zhang L, Chen L. Expression of nlp3r in psoriasis is associated with enhancement of interleukin-1beta and caspase-1. Med Sci Monit. 2018 Nov;24:7909–13.

88. Oppmann B, Lesley R, Blom B, Timans JC, Xu Y, Hunte B, et al. Novel p19 protein engages IL-12p40 to form a cytokine, IL-23, with biological activities similar as well as distinct from IL-12. Immunity. 2000 Nov;13(5):715–25.

89. Girolomoni G, Stroh R, Puig L, Bachelez H, Barker J, Boehncke WH, et al. The role of IL-23 and the IL-23/TH17 immune axis in the pathogenesis and treatment of psoriasis. J Eur Acad Dermatol Venereol. 2017 Oct;31(10):1616–26.

90. Chiricozzi A, Romanelli P, Volpe E, Borsellino G, Romanelli M. Scanning the immunopathogenesis of psoriasis. Int J Mol Sci. 2018 Jan;19(1):E179.

91. Aggarwal S, Ghilardi N, Xie MH, de Sauvage FJ, Gurney AL. Interleukin-23 promotes a distinct CD4 T cell activation state characterized by the production of interleukin-17. J Biol Chem. 2003 Jan;278(3):1910–4.

92. Stritesky GL, Yeh N, Kaplan MH. IL-23 promotes maintenance but not commitment to the Th17 lineage. J Immunol. 2008 Nov;181(9):5948–55.

93. Teng MW, Bowman EP, McElwee JJ, Smyth MJ, Casanova JL, Cooper AM, et al. IL-12 and IL-23 cytokines: from discovery to targeted therapies for immune-mediated inflammatory diseases. Nat Med. 2015 Jul;21(7):719–29.

94. Fotiadou C, Lazaridou E, Sotiriou E, Ioannides D. Targeting IL-23 in psoriasis: current perspectives. Psoriasis (Auckl). 2018 Jan;8:1–5.

95. Lee E, Trepicchio WL, Oestreicher JL, Pittman D, Wang F, Chianmanelli M. Interleukin-23 promotes a distinct CD4 T cell activation state characterized by the production of interleukin-17. J Biol Chem. 2003 Jan;278(3):1910–4.

96. Chiricozzi A, Romanelli P, Volpe E, Borsellino G, Romanelli M. Scanning the immunopathogenesis of psoriasis. Int J Mol Sci. 2018 Jan;19(1):E179.

97. Aggarwal S, Ghilardi N, Xie MH, de Sauvage FJ, Gurney AL. Interleukin-23 promotes a distinct CD4 T cell activation state characterized by the production of interleukin-17. J Biol Chem. 2003 Jan;278(3):1910–4.

98. Fotiadou C, Lazaridou E, Sotiriou E, Ioannides D. Targeting IL-23 in psoriasis: current perspectives. Psoriasis (Auckl). 2018 Jan;8:1–5.

99. Veldhoen M. Interleukin 17 is a chief orchestrator of inflammation and psoriasis pathogenesis. J Invest Dermatol. 2019 Jan;139(1):146–56.

100. Korn T, Bettelli E, Oukka M, Kuchroo VK. IL-17 and Th17 cells. Annu Rev Immunol. 2009;27(1):485–517.

101. Kolls JK, McCray PB Jr, Chan YR. Cytokine-mediated regulation of antimicrobial proteins. Nat Rev Immunol. 2008 Nov;8(11):829–35.

102. Liévin-Le Moal V, Servin AL. The front line of enteric immunity. Nat Immunol. 2017 May;18(4):400–10.
host defense against unwelcome intrusion of harmful microorganisms: mucins, antimicrobial peptides, and microbiota. Clin Microbiol Rev. 2006 Apr;19(2):315–37.

103. Arican O, Aral M, Sasmaz S, Ciragil P. Serum levels of TNF-alpha, IFN-gamma, IL-6, IL-8, IL-12, IL-17, and IL-18 in patients with active psoriasis and correlation with disease severity. Mediators Inflamm. 2005 Oct;2005(5):273–9.

104. Cătană CS, Berindan Neagoe I, Cozma V, Magdaş C, Tăbăran F, Dumitraşcu DL. Contribution of the IL-17/IL-23 axis to the pathogenesis of inflammatory bowel disease. World J Gastroenterol. 2015 May;21(19):5823–30.

105. Kirkham BW, Kavanaugh A, Reich K. Interleukin-17A: a unique pathway in immune-mediated diseases: psoriasis, psoriatic arthritis and rheumatoid arthritis. Immunology. 2014 Feb;141(2):133–42.

106. Liuzzo G, Trotta F, Pedicino D. Interleukin-17 in atherosclerosis and cardiovascular disease: the good, the bad, and the unknown. Eur Heart J. 2013 Feb;34(8):556–9.

107. Tang Y, Bian Z, Zhao L, Liu Y, Liang S, Wang Q, et al. Interleukin-17 exacerbates hepatic steatosis and inflammation in non-alcoholic fatty liver disease. Clin Exp Immunol. 2011 Nov;166(2):281–90.

108. Grozdev I, Korman N, Tsankov N. Psoriasis as a systemic disease. Clin Dermatol. 2014 May-Jun;32(3):343–50.

109. Xu R, Tao A, Zhang S, Zhang M. Neutralization of interleukin-17 attenuates high fat diet-induced non-alcoholic fatty liver disease in mice. Acta Biochim Biophys Sin (Shanghai). 2013 Sep;45(9):726–33.

110. Dudakov JA, Hanash AM, van den Brink MR. Interleukin-22: immunobiology and pathology. Annu Rev Immunol. 2015;33(1):747–85.

111. Perusina Lanfranca M, Lin Y, Fang J, Zou W, Frankel T. Biological and pathological activities of interleukin-22. Mol Med (Berl). 2016 May;94(5):523–34.

112. Lejeune D, Dumoutier L, Constantinescu S, Caruntu C, Sarbu MI, Mitran CI, Mitran MI, et al. Advances in understanding the immunological pathways in psoriasis. Int J Mol Sci. 2019 Feb;20(3):E739.

113. Di Meglio P, Duarte JH. CD8 T Cells and IFN-γ emerge as critical players for psoriasis in a novel model of mouse psoriasisform skin inflammation. J Invest Dermatol. 2013 Apr;133(4):871–4.

114. Kryczek I, Bruce AT, Gudjonsson JE, Johnston A, Aphale A, Vatan L, et al. Induction of IL-17+ T cell trafficking and development by IFN-gamma: mechanism and pathological relevance in psoriasis. J Immunol. 2008 Oct;181(7):4733–41.

115. Harden JL, Johnson-Huang LM, Chamian MF, Lee E, Pearce T, Leonard CL, et al. Humanized anti-IFN-γ (HuZAF) in the treatment of psoriasis. J Allergy Clin Immunol. 2015 Feb;135(2):553–6.

116. Palladino MA, Bahjat FR, Theodorakis EA, Moldawer LL. Anti-TNF-alpha therapies: the next generation. Nat Rev Drug Discov. 2003 Sep;2(9):736–46.

117. Kriegler M, Perez C, DeFay K, Albert I, Lu SD. A novel form of TNF/cachectin is a cell surface cytotoxic transmembrane protein: ramifications for the complex physiology of TNF. Cell. 1988 Apr;53(1):45–53.

118. Sereifian B, Goksgur N, Bugdayci G, Polat M, Haydar Parlak A. Serum visfatin, adiponectin, and tumor necrosis factor alpha (tnf-alpha) levels in patients with psoriasis and their correlation with disease severity. Acta Dermatovenerol Croat. 2016 Apr;24(1):13–9.

119. Menter A, Strober BE, Kaplan DH, Kivelevitch D, Prater EF, Stoff B, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. J Am Acad Dermatol. 2019 Apr;80(4):1029–72.

120. Reich K, Burden AD, Eaton JN, Hawkins NS. Efficacy of biologics in the treatment of moderate to severe psoriasis: a comprehensive review of the literature. Acta Dermatovenerol Croat. 2016 Apr;24(1):13–9.

121. Ko JM, Gottlieb AB, Kerbleski JF. Induction and exacerbation of psoriasis with TNF-blockade therapy: a review and analysis of 127 cases. J Dermatolog Treat. 2009;20(2):100–8.
133. van der Woude CJ, Ardizzone S, Bengtson MB, Fiorino G, Fraser G, Katsanos K, et al.; European Crohn’s and Colitis Organization. The second European evidenced-based consensus on reproduction and pregnancy in inflammatory bowel disease. J Crohn’s Colitis. 2015 Feb;9(2):107–24.

134. Clowse ME, Wolf DC, Förger F, Cush JJ, Golembesky A, Shaughnessy L, et al. Pregnancy outcomes in subjects exposed to certolizumab pegol. J Rheumatol. 2015 Dec;42(12):2270–8.

135. Papp KA, Blauvelt A, Bukhalo M, Gooderham M, Krueger JG, Lacour JP, et al. Risankizumab versus ustekinumab for moderate-to-severe plaque psoriasis (IMMvent): a randomised, double-blind, active-comparator-controlled phase 3 trial. Lancet. 2019 Aug;394(10198):576–86.

136. Reich K, Gooderham M, Thaçi D, Crowley JJ, Ryan C, Krueger JG, et al. Risankizumab compared with adalimumab in patients with moderate-to-severe plaque psoriasis (IMMvent): a randomised, double-blind, active-comparator-controlled phase 3 trial. Lancet. 2017 Apr;376(16):1551–60.

137. Crowley JJ, Warren RB, Cather JC. Safety of selective IL-23p19 inhibitors for the treatment of psoriasis. J Eur Acad Dermatol Venereol. 2019 Sep;33(9):1676–84.

138. Cai Q, Teeple A, Wu B, Muser E. Prevalence and economic burden of comorbid anxiety and depression among patients with moderate-to-severe psoriasis. J Med Econ. 2019 Dec;22(12):1290–7.

139. Dávila-Seijo P, Dauden E, Descalzo MA, Carretero G, Carrascosa JM, Vanaclocha F, et al.; BIOBADADERM Study Group. Infections in moderate to severe psoriasis patients treated with biological drugs compared to classic systemic drugs: findings from the biobadaderm registry. J Invest Dermatol. 2017 Feb;137(2):313–21.

140. Puig L, López-Ferrer A. Biosimilars for the treatment of psoriasis. Expert Opin Biol Ther. 2019 Oct;19(10):993–1000.

141. Gottlieb AB, Evans R, Li S, Dooley LT, Guzzo CA, Baker D, et al. Infliximab induction therapy for patients with severe plaque-type psoriasis: a randomized, double-blind, placebo-controlled trial. J Am Acad Dermatol. 2004 Oct;51(4):534–42.

142. Reich K, Nestle FO, Papp K, Ortonne JP, Evans R, Guzzo C, et al.; EXPRESS study investigators. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. Lancet. 2005 Oct;366(9494):1367–74.

143. Gottlieb AB, Matheson RT, Lowe N, Krueger GG, Kang S, Goffe BS, et al. A randomized trial of etanercept as monotherapy for psoriasis. Arch Dermatol. 2003 Dec;139(12):1627–32.

144. Leonardi CL, Powers JL, Matheson RT, Goffe BS, Zitnik R, Wang A, et al.; Etanercept Psoriasis Study Group. Etanercept as monotherapy in patients with psoriasis. N Engl J Med. 2003 Nov;349(21):2014–22.

145. Menter A, Tyring SK, Gordon K, Kimball AB, Leonardi CL, Langley RG, et al. Adalimumab therapy for moderate to severe psoriasis: A randomized, controlled phase III trial. J Am Acad Dermatol. 2008 Jan;58(1):106–15.

146. Saurat JH, Stingl G, Dubertret L, Papp K, Langley RG, Ortonne JP, et al.; CHAMPION Study Investigators. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). Br J Dermatol. 2008 Mar;158(3):558–66.

147. Kavanaugh A, McIlmes I, Mease P, Krueger GG, Gladman D, Gomez-Reino J, et al. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. Arthritis Rheum. 2009 Apr;60(4):976–86.

148. Gottlieb AB, Blauvelt A, Thaci D, Leonardi CL, Poulin Y, Drew J, et al. Certolizumab pegol for the treatment of chronic plaque psoriasis: Results through 48 weeks from 2 phase 3, multicenter, randomized, double-blinded, placebo-controlled studies (CIMPASI-1 and CIMPASI-2). J Am Acad Dermatol. 2018;79(2):302–14 e6.

149. Langley RG, Elewski BE, Lebwohl M, Reich K, Griffiths CE, Papp K, et al.; ERASURE Study Group; FIXTURE Study Group. Secukinumab in plaque psoriasis—results of two phase 3 trials. N Engl J Med. 2014 Jul;371(4):326–38.

150. Papp KA, Leonardi CL, Blauvelt A, Reich K, Korman NJ, Ohtsuki M, et al. Ixekizumab treatment for psoriasis: integrated efficacy analysis of three double-blinded, controlled studies (UNCOVER-1, UNCOVER-2, UNCOVER-3). Br J Dermatol. 2018 Mar;178(3):674–81.

151. Papp KA, Reich K, Paul C, Blauvelt A, Baran W, Bolduc C, et al. A prospective phase III, randomized, double-blind, placebo-controlled study of brodalumab in patients with moderate-to-severe plaque psoriasis. Br J Dermatol. 2016 Aug;175(2):273–86.

152. McMichael A, Desai SR, Qureshi A, Rastogi S, Alexis AF. Efficacy and safety of brodalumab in patients with moderate-to-severe plaque psoriasis and skin of color: results from the pooled amagine-2/-3 randomized trials. Am J Clin Dermatol. 2019 Apr;20(2):267–76.

153. Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, et al.; PHOENIX 1 study investigators. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet. 2008 May;371(9625):1665–74.

154. Papp KA, Langley RG, Lebwohl M, Krueger GG, Szapary P, Yeilding N, et al.; PHOENIX 2 study investigators. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). Lancet. 2008 May;371(9625):1675–84.

155. Blauvelt A, Papp KA, Griffiths CE, Randazzo B, Wasfi Y, Shen YK, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. J Am Acad Dermatol. 2017 Mar;76(3):405–17.
anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: results from the phase iii, double-blind, placebo- and active comparator-controlled voyage 2 trial (vol 76, pg 418, 2017). J Am Acad Dermatol. 2017;76(6):1226.

157. Reich K, Papp KA, Blauvelt A, Tyring SK, Sinclair R, Thaçi D, et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials. Lancet. 2017 Jul;390(10091):276–88.

158. Gordon KB, Strober B, Lebwohl M, Augustin M, Blauvelt A, Poulin Y, et al. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. Lancet. 2018 Aug;392(10148):650–61.