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Immunobiologics in the treatment of psoriasis

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Abstract

The pathogenesis of various inflammatory cutaneous diseases such as psoriasis, atopic dermatitis and mycosis fungoides relies greatly on the abnormal function of T cells. Fundamental knowledge of the role of T cells in the cutaneous immune response has led to the development and production of biologic molecules designed to block T cell function at various steps, specifically activation (i.e. alefacept, efalizumab), trafficking into inflamed skin (i.e. efalizumab) and effector function under cytokine control (i.e. etanercept, infliximab, adalimumab, and anti-IL-12 antibody). We review the immune abnormalities and the role of T cells in psoriasis, and the recent biologic therapies, which share the common mission to hinder T cell activity in inflammatory diseases. An advantage from the preciseness of these biologic therapies is the potential limit of non-specific and potentially devastating organ toxicity, which commonly plagues other systemic therapies.

Keywords

T cell; TNF-alpha; Psoriasis; Inflammation; Biologics; Skin disease

Introduction

Substantive advances have been made in understanding how T cells contribute to a variety of cutaneous inflammatory diseases, including psoriasis, mycosis fungoides and atopic dermatitis. Extensive research has shown that the responses of T cells are abnormal in these diseases [1]. When activated and stimulated in response to skin-infiltrating antigens that are processed and displayed by antigen presenting cells (APCs), skin CD4⁺ T cells induce tissue damage by perpetuating inflammation. When this process is deregulated, there is abnormal immune homeostasis, leading to subsequent clinical pathology. The basis for the activation of abnormal T cells is not fully clear and remains the subject of intense research. However, the advances thus far in understanding the molecular and cellular mechanisms in T cell activation and migration have led to the development of therapeutic agents that inhibit the function of these abnormal T cells as a strategy for controlling disease manifestations [2].

These highly specific biologic molecules show that normalizing the immune response or inhibiting an abnormal immune response can be achieved by modulating the function of T cells, which can dramatically impact on the course of chronic inflammatory diseases. Taking advantage of this strategy, numerous biologics have been developed and are available for the

treatment of rheumatoid arthritis, the disease that serves as a model for understanding the effectiveness of these immune modifying drugs [3]. Since cutaneous inflammatory diseases share numerous underlying abnormalities in T cells with rheumatoid arthritis, these drugs have been translated for use in skin diseases.

The goal of this review is to provide evidence for a relationship between T cells and psoriasis and to discuss several biologic therapies that target T cells to treat psoriasis.

Psoriasis and T cells

The immune response requires the precise orchestration of events to activate a specific subset of cells to eliminate a particular pathogen. However, aberrant regulation of the immune response can be reflected clinically in cutaneous disease, such as psoriasis. Although the mechanism is unclear, abnormally activated T cells elaborate cytokines inappropriately, perpetuating inflammation, which, in turn, can lead to tissue damage manifesting clinically as psoriasis.

Initially thought to be a disease characterized by defects in keratinocytes leading to epidermal hyperplasia [4], psoriasis has now been shown to largely involve the abnormal activity of T cells. This observation has been supported both from therapeutic trials involving drugs inhibiting T cells such as cyclosporine [5], and animal models [6,7]. Murine models utilizing xenografts have demonstrated the critical involvement of T cells in the development of psoriasis. Recently, grafts of asymptomatic pre-psoriatic human skin onto AGR129 mice, which were deficient in T and B cells, developed psoriatic lesions, due to increases in the T cell population that was sparked by the presence of tumor necrosis factor (TNF)- α [7]. TNF- α produced by keratinocytes, activated T cells, macrophages and dendritic cells (DCs) plays a central role in the pathogenesis of psoriasis due to its ability to stimulate and propagate widespread immunological activity by targeting various cells in the skin, such as endothelial cells, keratinocytes and dendritic cells. TNF- α induces keratinocytes to express at least 70 genes, ranging from chemokines to other cytokines [8]. Circulating leukocytes can enter the skin due to the TNF- α -mediated increase in expression in dermal endothelial adhesion molecules such as E-selectin and intercellular adhesion molecule-1 (ICAM-1) [9]. In addition, under the influence of TNF- α , macrophages generate cytokines and chemokines and DCs undergo maturation in preparation to present antigens to T cells. The subsequent recruitment of inflammatory cells can amplify the inflammatory response by generating TNF- α . UV exposure can also induce TNF- α expression in human skin, with maximal mRNA expression seen at 6 h of irradiation [10]. Another cytokine in T_H1 T cells, interferon (IFN)- γ , also promotes the expression of the transcription factor, signal transducer and activator of transcription 1 (STAT1). STAT1 can trigger the expression of multiple inflammatory genes seen in psoriasis [11].

The actual trigger that leads to psoriatic plaques remains unknown, but it is postulated that it could be due to pathogen-activated danger signals, internal agents such as heat-shock proteins, and medications [12]. This triggering stimulus leads to the activation of DCs in the dermis. As antigen presenting cells (APCs), these DCs serve as the sentinels of the cutaneous immune response because they monitor for pathogen invasion, internalize

microbes, degrade them for presentation at the DC cell surface and migrate to lymph nodes to notify the proper T cell of the presence of its cognate antigen [13].

Activation of T cells is dependent on at least two critical interactions between T cells with APCs. The first signal is from the T cell receptor (TCR) along with a co-receptor (either CD4 or CD8) binding to the appropriate peptide-major histocompatibility complex (MHC) on APCs. The second signal is via the attachment of B7, a co-stimulatory molecule on APCs, to CD28 on T cells. Without this second signal, a state of T cell unresponsiveness called anergy occurs, permitting antigen-specific tolerance [14]. The combination of both signals induces the production of interleukin (IL)-2, a cytokine promoting T cell proliferation [15]. Other co-stimulatory molecules besides CD28 and B7 can provide this second signal. The pairing of the integrin, lymphocyte function-associated antigen-1 (LFA-1) and ICAM-1 can also induce signal 2 [16].

The synergy of these two signals on the T cell membrane leads to the transformation of the T cell from a naïve to an activated phenotype. Naïve T cells, designated by the surface antigen CD45RA, have TCRs that have not previously engaged their cognate antigens, whereas activated T cells (CD45RO⁺) have achieved in finding matching antigens. Activated T cells are further subdivided by their specific capacity, either possessing a memory or an effector function. Two subclassifications of memory T cells exist, central memory and effector memory T cells. By expressing similar homing markers as naïve T cells (i.e. CC chemokine receptor 7 (CCR7)), central memory T cells follow a migration path similar to that of naïve T cells, entering secondary lymphoid organs to monitor for previously encountered antigens and organizing more rapid immune responses to a repeated insult. CCR7⁻ effector memory T cells are produced upon re-challenge of an antigen, and migrate to distal sites, such as psoriatic plaques, where they can induce inflammatory reactions via various effector functions (Fig. 1) [17].

In order to migrate into the skin from the circulating blood, T cells must undergo a series of sequential precise steps: rolling/tethering, integrin activation and firm adhesion to exit the vasculature. Thus, disruption of T cell trafficking may serve as an approach for the development of therapies that block T cell function. Cutaneous lymphocyte antigen (CLA), which is highly specific to skin-homing T cells [18], binds to E-selectin on endothelium, result in the rolling and tethering action of fast-flowing T cells. The interaction of the chemokine CCL17 with its receptor CCR4 on T cells alters the conformation of LFA-1, increasing its avidity for the endothelial ICAM-1 and inducing the firm arrest of T cells and their eventual extravasation into the skin (reviewed in [1]).

Upon activation of naïve T cells, it is now known that T cells undergo developmental differentiation to regulate the immune response. CD4⁺ effector T cells mature by polarization to a T_H1 or T_H2 phenotype. It has been well established that T_H1 and T_H2 cells are involved in two separate arms of acquired immunity, cell-mediated immunity or delayed type hypersensitivity for T_H1 and humoral immunity for T_H2, respectively [19,20]. Psoriasis appears to be largely mediated by T_H1 cells, given their cytokine profile with increased expression of IL-2 and IFN- γ [21]. Under the influence of IL-12 [22], IL-23 [23] and IL-27 [24], T_H1 differentiation is favored, promoting the production of various cytokines including

IFN- γ , granulocyte-macrophage colony-stimulating factor (GM-CSF) and TNF- α [25]. On the other hand, the presence of IL-4 will stimulate the differentiation of T_H2 cells, which manufacture a different pattern of cytokines including IL-4, IL-5, IL-10 and IL-13 (Fig. 1) [26].

A heterodimeric cytokine (p70) consisting of two subunits, p40 (heavy chain) and p35 (light chain), IL-12 induces a T_H1-mediated response by stimulating naïve T cells to differentiate into T_H1 cells. In conjunction with IL-18, IL-12 stimulates T_H1 cell production of IFN- γ , which, in turn, further enhances IL-12 secretion [27]. Produced by APCs, IL-12 has been implicated in the pathogenesis of psoriasis, with higher levels of the cytokine found in psoriatic skin versus normal controls [28,29]. In contrast, there was no significant difference in serum levels of IL-12 in normal control patients versus psoriasis patients [30]. As IL-12 contributes to development of psoriatic lesions by promoting the T_H1 pathway, bacterial superantigens such as staphylococcal enterotoxin B also up-regulate secretion of IL-12, which, in turn, increases the number of skin-homing T cells by inducing CLA expression [31]. As a member of the IL-12 family, IL-23 shares the same p40 subunit as IL-12 and contains a unique p19 subunit. IL-23 stimulates IFN- γ secretion and memory T_H1 cell production. It is thought that IFN- γ may help contribute to a self-propagating inflammatory cycle by stimulating production of IL-23 in keratinocytes and DCs. The presence of IL-23 is enhanced in keratinocytes and dermal APCs in psoriasis [32].

In addition, as IL-23 has been shown to promote IL-17 production from CD4⁺ T cells in mice, increased mRNA levels of IL-17 have been found in psoriatic lesions [33]. Produced by a distinctive class of CD4⁺ T cells, T_H17 cells [34], IL-17, with the help of IFN- γ , stimulates keratinocyte production of the pro-inflammatory cytokines IL-6 and IL-8, which are important in perpetuating inflammatory responses in the skin [33].

The role of T cells in the pathogenesis of psoriasis is hypothesized to be concentrated in three steps outlined earlier: T cell activation, T cell trafficking into the skin to reach sites of inflammatory foci and T cell effector function via cytokine secretion (Fig. 2) [2]. Thus, these are steps that are amendable for intervention, and biologic therapies have been designed to home in on inhibition of each of these steps.

Biologic therapies

From advances in understanding the molecular biology of T cells, we now have a level of appreciation for how the immune response functions to identify potential targets to control T cells. As a result, various biologic therapies have been designed by genetic engineering in the form of monoclonal antibodies and receptor–antibody fusion proteins and aimed at various stages of T cell activation and function. Upon clinical testing, these new therapies have been found to be effective in controlling T cell-mediated skin diseases. Biologic therapies target cell surface molecules, thereby thwarting T cell activation and trafficking, and cytokines, including TNF- α and IL-12, which have been shown to promote inflammatory responses.

Moreover, in contrast to traditional drugs that have extensive organ toxicity (i.e. methotrexate–hepatotoxicity, cyclosporine–nephrotoxicity) from a broad effect on cells of

different organs, biologic therapies can potentially limit adverse systemic side effects because of their high specificity directed towards pathogenic cells without affecting cells of other organs. By initiating treatment at an earlier point in the inflammatory cascade in immune diseases, biologic therapies have the benefit of halting tissue damage associated with irreversible changes that affect quality of life and morbidity. Specifically, they have been found to preserve joint function in rheumatoid arthritis by inhibiting erosive synovial inflammatory damage [35].

The main classes of biologics in dermatology include monoclonal antibodies and receptor–antibody fusion proteins. Monoclonal antibodies can be derived from genes that have different amount of murine sequences in the variable region. Chimeric antibodies have approximately 30% murine genes in the variable region, humanized antibodies have approximately 10% murine sequences and human antibodies are derived from human immunoglobulin genes. Because humanized monoclonal antibodies are composed of more human genetic sequences than chimeric, and thus express less murine epitopes, humanized antibodies have a lower incidence of auto-reactivity due to the presence of auto-antibodies [36]. Meanwhile, fusion receptor–antibody proteins are split into two proteins. One portion has two sites that bind to proteins of interest, while the other part contains the Fc portion of human immunoglobulin, which brings stability to the protein structure.

Alefacept

Originally known as LFA-3 T cell inhibitor protein (LFA-3TIP), alefacept is a chimeric fusion protein of LFA-3 to the constant region of IgG₁ that targets CD2⁺ cell populations, including T cells and natural killer (NK) cells, via the extracellular domain of LFA-3 (Table 1). Because memory T cells contain the highest level of CD2 on their surface membrane, alefacept is effective in inhibiting T cell function [37]. This specific binding prevents formation of signal 2 between T cells and APCs crucial to the activation of T cells. In addition, the IgG₁ portion of alefacept binds to the FcγRIII receptor on NK cells and macrophages, thereby inducing selective apoptosis of CD2⁺ cells [38]. In vitro studies have demonstrated that alefacept mediates NK cell-mediated cytotoxicity of activated memory T cells [39]. Through its ability to use both LFA-3 and IgG₁ to target T cells, alefacept has been able to reduce circulating memory CD4⁺ and CD8⁺ T cells after 12 weeks of treatment in psoriasis patients and proportionally improve Psoriasis Area Severity Index (PASI) scores in a dose-dependent fashion [40]. The PASI score (0–72) is derived from a measurement of psoriasis severity that takes into account the extent of body surface involvement, the degree of scales, the elevation and the redness of psoriasis plaques [41,42]. In general, mild psoriasis has a score of less than 10, moderate psoriasis has a score between 11 to 20, and severe psoriasis has a score greater than 20. In addition, alefacept also decreased CD4⁺ and CD8⁺ T cells in lesional psoriatic skin, which proportionally correlated with clinical improvement [43]. In fact, decreases in T cell population in psoriatic skin have correlated even better with clinical improvement than reductions in circulating T cell population [44]. Despite the decrease in memory T cells, alefacept does not inhibit primary or secondary antibody responses to foreign antigens, suggesting that patients taking alefacept may not be at higher risk for infections. This may be explained by the finding that alefacept does not affect the naïve T cell population, enabling these cells to respond appropriately to foreign

antigens, and the possibility that alefacept may not target memory T cells in lymphoid tissues which are vital to the immune response [45]. Recently, it has been shown that alefacept decreases not only T cells but also DCs and expression of pro-inflammatory genes such as cytokines (IFN- γ , IL-12, IL-23) and chemokines (Mig, IL-8) associated with T_H1 cells in psoriatic lesions of responding patients. While the results of the study confirmed alefacept's ability to target T cells, the explanation as to how alefacept could decrease DCs in psoriatic plaques remained elusive [44].

As the first biologic to be approved by the Food and Drug Administration (FDA) for moderate to severe psoriasis, alefacept has helped 70% of patients reach at least PASI 50, a clinically significant endpoint for psoriatic patients that indicates 50% improvement in PASI scores [46], in a randomized controlled trial [47]. It is administered as 15 mg IM weekly doses for 12 weeks, with a subsequent rest period of at least 12 weeks. Clinical improvement develops slower than that observed with other biologics with changes presenting up to 8 to 10 weeks after therapy begins. The peak benefits observed were measured after completion of the 12-week administration. This suggests that the mechanism of alefacept may target a step in the pathogenesis of psoriasis that is earlier than other therapies. Stable control of psoriatic skin lesions averages about 7 months [48]. A phase III trial revealed several minor side effects in alefacept including headache, injection site reaction and mild infections [49]. In spite of decreasing CD4 and CD8 counts associated with alefacept, CD4 and CD8 levels normalize upon withdrawal of therapy. More importantly, an integrated study of 13 clinical trials of chronic plaque psoriasis patients taking alefacept for up to nine courses over a five-year period did not reveal an increased risk of infections or malignancies [50]. Alefacept does not affect the normal immune response to antigens, suggesting that vaccine administration would be effective in patients taking alefacept [51].

Efalizumab

As a recombinant humanized monoclonal antibody, efalizumab exhibits specificity towards the CD11a subunit of LFA-1 (Table 1). The inhibition of the binding between LFA-1 and ICAM-1 affects both T cell activation and trafficking. Efalizumab's ability to block signal two, which involves LFA-1 and ICAM-1 on the surface of T cells and APCs, respectively, deters the activation of T cells. This also potentially prevents the reactivation of T cells in the dermis and epidermis when they re-encounter their cognate antigens. In addition, this same inhibition limits the T cell's ability to leave the vasculature into the skin by preventing the firm adhesion of the leukocyte to the vessel wall [52]. Subsequent increases in circulating populations of naïve and memory CD4⁺ and CD8⁺ T cells have been demonstrated in efalizumab-treated patients [53]. Efalizumab appears to not only affect T cells but also other hematopoietic cells. While the level of CD11a expressed on circulating T cells was decreased by 70–85% at one to 3 days after efalizumab administration, CD11a was also diminished to a lesser extent on the surface of monocytes, neutrophils, B cells and NK cells [52]. Also, efalizumab has been shown to decrease the number of DCs in psoriatic lesions. The authors hypothesize that efalizumab may directly target DCs because the reduction in DCs precedes the decrease in epidermal thickness [54]. A decrease in several adhesion molecules including very late antigen-4 (VLA-4), β 7-integrin and L-selectin has been noted in peripheral blood mononuclear cells of efalizumab-treated patients. The down-

regulation of these molecules bolsters efalizumab's ability to prevent leukocytes from leaving the vasculature [52].

Also FDA-approved for psoriasis, efalizumab is administered in weekly 1 mg/kg subcutaneous injections after an initial 0.7 mg/kg injection. In a randomized controlled clinical trial, 27% of chronic plaque-type psoriasis patients reached PASI 75 after 12 weeks of therapy as opposed to 4% from the placebo group [55]. The response is usually seen within the first three months of therapy. However, without any increase in toxicity, 50% of 228 patients with chronic plaque psoriasis achieved PASI 75 after 15 months of continuous efalizumab treatment as opposed to 41% after three months of treatment, suggesting sustained efficacy with efalizumab [56]. Side effects with efalizumab have ranged from severe arthropathy to thrombocytopenia to the development of a transient papular eruption named transient neutrophilic dermatosis [54,57]. The mechanism for these unusual effects is not known and may be related to the mechanism of action of efalizumab in affecting cells of the immune response. This rash has not been seen with other biologic agents but may have similarities to the tachyphylactic pustular eruption seen in psoriasis patients treated with systemic steroids [58]. After cessation of efalizumab, patients, especially poor responders, may have significant worsening of their psoriasis, requiring other systemic treatments [57] or re-introduction of efalizumab [59] for control. Other side effects include headaches and acute flu-like symptoms with the initial dose have also been observed.

Etanercept

As opposed to targeting T cells, etanercept, which is a fusion product of the p75 TNF- α receptor and the Fc portion of human immunoglobulin G₁ (IgG₁), inhibits TNF- α (Table 1). Because etanercept, which is FDA-approved for psoriasis and psoriatic arthritis, contains two recombinant p75 extracellular receptors that can bind to two free TNF- α molecules [60], etanercept can effectively limit TNF- α 's activity and slow the inflammatory cycle driven by TNF- α . By decreasing NF- κ B transcriptional activity in psoriatic skin, etanercept decreases epidermal thickness [61]. Etanercept also reduces the levels of several chemokines and cytokines, such as IL-8 and MIP-3 α (CCL20), in psoriatic lesions, leading to a subsequent decrease in T cells, DCs and keratinocyte hyperplasia [62].

The dose for the treatment of psoriasis is higher than that indicated for rheumatoid arthritis and may reflect differences in the regulation of TNF- α in these two inflammatory disorders, and the fact that the skin is a larger organ relative to the cells of the synovium. The current suggested treatment regimen is etanercept 50 mg given twice weekly for three months, and then followed by once weekly thereafter. A randomized, multi-center, double-blind controlled study of 112 patients with chronic stable plaque psoriasis taking either etanercept 25 mg SC BIW or placebo was performed. While 30% of the etanercept group versus 2% of the placebo group reached PASI 75 after 12 weeks of treatment, 56% of the etanercept-treated patients versus 5% of the placebo-treated patients achieved PASI 75 after 24 weeks of treatment [63]. Common side effects include injection site reactions, which last approximately three to 5 days [64], cough and other respiratory symptoms, and infections. Etanercept has also been linked to positive ANA and a lupus-like syndrome [65] and increased risk of lymphoma and CNS demyelinating disorders [66].

Infliximab

Infliximab is a monoclonal chimeric antibody composed of murine variable regions that binds specifically to TNF- α and neutralizes its activity linked to the human IgG₁ constant region (Table 1). In addition, through interaction with transmembrane TNF- α , infliximab has been demonstrated to induce apoptosis of activated T cells [67]. Indeed, significant decreases in epidermal T cells in psoriatic lesions have been observed in infliximab-treated patients [68]. Compared to etanercept, infliximab has been shown to form more stable complexes with both soluble and transmembrane forms of TNF- α than etanercept, which could explain the faster clinical response of infliximab in psoriasis patients [69].

Infliximab's suppression of TNF- α activity affects not only T cells but also keratinocytes and endothelial cells. The expression of K16, which is normally observed in the hyperplastic epidermis of psoriatic lesions and is a marker of keratinocyte differentiation, sharply decreased due to infliximab treatment; specifically, K16 levels reached normal amounts in the plaques of all 10 patients receiving 5 mg/kg of infliximab, as opposed to 30% of the plaques in 10 placebo patients. This same study also reported decreases in keratinocyte ICAM-1 expression in all plaques from the 5 mg/kg infliximab group as opposed to 30% in the placebo group [68]. The expression of the endothelial adhesion molecules E-selectin, ICAM-1 and vascular cell adhesion molecule-1 (VCAM-1) were decreased by 95%, 79% and 44%, respectively, compared to pre-treatment levels, in psoriatic lesions of patients at 4 weeks into infliximab treatment [70].

The rapid therapeutic response of infliximab may lie in the observation that infliximab has not only anti-inflammatory activity but also apoptotic and anti-angiogenic properties. In a histologic study where five patients with psoriasis received infliximab, the skin was noted to have apoptotic keratinocytes, which peaked at day 14 after infusions began, on histological sections. It is postulated that keratinocyte cell death may be a result of the decrease in growth signals [71]. Infliximab also has demonstrated decreases in vascularity and a corresponding decline in vascular endothelial growth factor (VEGF) in psoriatic lesions. Because hypervascularity is prominent in the pathology of psoriasis, this antiangiogenic effect may also contribute to the potency of this biologic [70].

For psoriasis patients, infliximab is administered at 3–5 mg/kg intravenously over 2 h at weeks 0, 2 and 6, and then every 8 weeks afterwards. A study with 378 patients with moderate-to-severe plaque psoriasis randomized to 5 mg/kg infliximab or placebo infusions at weeks 0, 2 and 6, and every 8 weeks afterwards have been completed. By week 10, approximately 80% of infliximab-treated patients reached PASI 75, and 57% of these same patients reached PASI 90. At week 50, 61% of these patients were at PASI 75, while 45% achieved PASI 90 [72]. Another double-blind randomized controlled trial of 241 severe plaque psoriasis patients received either 3 or 5 mg/kg of infliximab or placebo at weeks 0, 2 and 6. After 10 weeks, 72% of the patients receiving 3 mg/kg of infliximab, and 88% of those receiving 5 mg/kg of infliximab achieved PASI 75 [73]. Side effects of infliximab include nausea, arthralgias, fatigue and infusion reactions [66]. The causes of these reactions are not known. Because TNF- α is important in the formation of granulomas important in containing intracellular infections, the use of TNF- α inhibitors, especially infliximab, has been linked to reactivation of latent tuberculosis [74]. Tuberculin skin testing is

recommended for patients prior to commencing therapy with infliximab and other TNF- α inhibitors to prevent this serious adverse event [64].

Infliximab has been shown to be effective in the treatment of erythrodermic psoriasis and pustular psoriasis [75]. Infliximab has also been shown to be effective in other inflammatory disorders such as Crohn's disease, ulcerative colitis, sarcoidosis and Wegener's granulomatosis, indicating the critical role of TNF- α in the pathogenesis of these diseases.

Adalimumab

A fully humanized IgG₁ monoclonal antibody against TNF- α , adalimumab has high affinity and avidity towards TNF- α (Table 1). With the ability to fix complement, adalimumab, like infliximab, can lyse cells expressing TNF in vitro by binding to both p55 and p75 cell surface TNF receptors. It is thought that this lysis contributes to the efficacy of both monoclonal antibodies in TNF- α -mediated diseases such as Crohn's disease [76]. In addition, adalimumab increases the number of epidermal Langerhans cells in psoriatic plaques, which, in the untreated form, has decreased numbers compared to non-inflamed perilesional skin and other inflammatory disorders such as lichen planus and inflamed seborrheic keratosis. This finding suggests not only that Langerhans cells may have an anti-inflammatory role in psoriasis but also that TNF- α inhibition may restore Langerhans cell migration to the epidermis [77].

Currently under phase III clinical trials for psoriasis and FDA-approved for psoriatic arthritis, adalimumab has demonstrated efficacy in patients with chronic plaque psoriasis. For psoriasis patients, adalimumab is administered by subcutaneous injections of 40 mg over 3–5 min every 2 weeks [66]. A multicenter, randomized, double-blind, placebo-controlled study involving 147 patients with moderate-to-severe psoriasis compared subcutaneous injections of 40 mg of adalimumab weekly, 40 mg of adalimumab every other week and placebo. At week 12 of treatment, 80% of patients receiving the weekly adalimumab treatments, and 53% of those receiving adalimumab every other week reached PASI 75. This response was sustained up to 60 weeks of therapy [78]. Side effects of adalimumab include injection site reactions, positive ANA and hypersensitivity reactions. Neurologic symptoms related to demyelinating events including paresthesias, foot drop and optic neuritis have been linked to adalimumab [79] as well as the other two TNF- α inhibitors, etanercept and infliximab [80]. While a causal relationship has not been established, it is hypothesized that TNF- α inhibitors can increase circulating peripheral autoreactive T cells, which could induce autoimmune demyelination [79]. Despite reports linking adalimumab to a higher risk of lymphoma, the FDA has determined that anti-TNF- α agents including adalimumab do not increase the chance of developing lymphoma [81].

Anti-IL-12 antibody

While TNF- α has been shown to be vital to the pathogenesis of psoriasis, its presence does not explain the T_H1 bias seen in psoriasis, thus sparking further interest in targeting candidate T_H1 cytokines such as IL-12 and IL-23. In fact, a study with an anti-IL-12 monoclonal antibody supports the logic of this approach. An anti-IL-12 antibody has been demonstrated to be effective in the treatment of psoriasis in murine models after being

injected with a specific T cell subset that typically induces psoriatic lesions [82]. Another antibody against the IL-12 p40 subunit (anti-IL-12p40), which binds to IL-12 receptor β 1, was developed because not only IL-12 p40 has been shown to be up-regulated in psoriasis [29], but also the antibody would deactivate both IL-12 and IL-23, since they both share this common subunit (Table 1). A phase I trial was recently performed involving a single anti-IL-12p40 intravenous infusion ranging from 0.1 to 5 mg/kg in 18 chronic plaque-type psoriasis patients with at least 3% body surface area involvement. Two-thirds of the test patients achieve a PASI 75 improvement between 8 and 16 weeks after injection of the antibody, with a greater concentration of patients achieving this at higher doses. The 16-week follow-up period revealed no serious toxicity, but all patients had at least one adverse effect including decreases in T cells, headaches and cold symptoms [83].

Conclusion

The cutaneous immune system coordinates a wide variety of cells in order to mount an effective defense against pathogens that invade the skin and potentially threaten the body. As T cells play a prominent role in the immune response, unregulated T cell activity can disrupt the function of the cutaneous immunosurveillance system and subsequently contribute to the pathogenesis of several cutaneous disorders. A thorough understanding of the multiple aspects of this defense mechanism has translated into effective treatments that counteract the deviant T cells, either by directly or indirectly inhibiting activators of T cells. Specifically, the capability of biologic treatments that are specifically aimed against T cell activation and function, or designed to neutralize the actions of cytokines testifies to the validity of this notion as demonstrated in psoriasis. Nonetheless, further knowledge uncovering the mechanisms controlling the differentiation of activated T cells during an immune response will undoubtedly contribute to the quest to enhance the development of more effective treatments of inflammatory skin diseases.

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Figure 1.

Pathways for differentiation of memory/effector T cells. Naïve T cells (CD45RA⁺) are activated by cognate antigens presented in the context of MHC on the surface of dendritic cells, clonally proliferate and acquire either a memory or effector phenotype (CD45RO⁺). Effector T cells migrate into peripheral tissue, expressing homing molecules that target them to specific organs. T cells also further differentiate into either CD4⁺ helper cells, or CD8⁺ cytolytic cells. CD4⁺ cells contain two subsets, T_H1 and T_H2, distinguished by their cytokine production, cytokine stimuli, and the types of cells activated. Memory T cells, which persist longer than effector T cells, can be further divided into central memory and effector memory T cells. Effector memory T cells share a similar surface phenotype as effector T cells, allowing them to migrate to peripheral tissue. Like naïve T cells, central memory T cells migrate to secondary lymphoid organs due to their expression of L-selectin (CD62L) and CCR7.

Figure 2.

Mechanisms of biologic therapies. Biologic therapies affect T cell activation, T cell trafficking into inflamed cutaneous lesions and T cell effector function under the influence of cytokines.

Table 1

Biologic therapies in psoriasis

Name of drug (generic)	Mechanism of drug	Dose for psoriasis	Comments
Alefacept	Recombinant LFA-3-IgG ₁ fusion protein that binds to CD2, a co-stimulatory molecule, on CD45RO ⁺ memory T cells, prevents T cell activation, causes effector memory T cell apoptosis	15 mg IM qwk × 12 weeks	Decreases circulating T cells and lesional T cells in psoriasis patients, also diminishes dendritic cells, cytokines (IFN- γ , IL-12, IL-23), chemokines (Mig, IL-8) in psoriatic skin
Efalizumab	Humanized monoclonal antibody that binds to CD11a subunit of LFA-1, inhibiting signal two involved in T cell activation and T cell migration into skin	0.7 mg/kg initial SC injection, then 1 mg/kg SC qwk	Increases circulating population of T cells, decreases dendritic cells in psoriatic skin, decreases adhesion molecule expression (VLA-4, β 7-integrin, L-selectin)
Etanercept	Recombinant fusion protein containing p75 TNF- α receptor and Fc portion of IgG ₁ that acts as a soluble TNF receptor and inhibits TNF function	50 mg SC BIW × 12 weeks, then 50 mg SC qwk	Can bind to two free TNF- α molecules, decreases epidermal thickness and dendritic cells in psoriatic skin
Infliximab	Chimeric monoclonal IgG ₁ monoclonal antibody against TNF- α with murine variable regions and human IgG ₁ constant region, inactivates TNF	3–5 mg/kg IV at weeks 0, 2, 6, then q8 weeks thereafter	Triggers apoptosis of activated T cells, binds more stably to TNF- α than etanercept, decrease K16 and ICAM-1 expression in keratinocytes in psoriatic skin, can cause keratinocyte apoptosis, decrease in vascularity in psoriatic lesions
Adalimumab	Humanized IgG1 monoclonal antibody against TNF- α , thus blocking its activity	40 mg SC over 3–5 min q2 weeks × 12 weeks	Efficiently interacts with TNF- α by binding to p55, p75 TNF- α receptors, increases Langerhans cells in psoriatic plaques
Anti IL-12 antibody	Antibody against IL-12 p40 subunit	Phase I trials–0.1 to 5 mg/kg IV infusion	Deactivates both IL-12 and IL-23 (share common p40 subunit)