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Review Article

Biotherapy: a novel approach in the treatment of psoriasis

Ravindra Agarwal*, Nitika Vij and Om P. Katare

University Institute of Pharmaceutical Sciences,
Panjab University, Chandigarh, 160 014, India.
**Correspondence*

CONTENTS

Abstract

Psoriasis is a T-cell-mediated inflammatory disease affecting about 80 million people around the globe. The pathogenesis of psoriasis involves abnormality in leukocytes, which control the cellular immunity and T-cell-dependent inflammatory process that accelerates the growth of epidermal and vascular cells. Existing treatment of psoriasis has been associated with limited safety and lack of efficacy for many drugs. However, the recent advances in biotechnoogy have led to the novel approach of biotherapy for the treatment of psoriasis. These newer strategies and agents act specifically on the various components of the immune system. Biological agents appear to be more convenient, nontoxic and provide long-lasting posttreatment remission. These agents are also designed to overcome the adverse effects of existing systemic therapy such as nephrotoxicity with ciclosporin, bone marrow toxicity with methotrexate, skin cancer and malignancies with PUVA, *etc*. This review describes the potential biologic agents under investigation and development for the treatment of psoriasis.

Introduction

Psoriasis is characterized by defects in the normal growth cycle of epidermis that lead to epidermal hyperproliferation, altered maturation of skin cells, vascular changes and inflammation. The condition typically manifests as areas of thickened, flaky, silvery white and reddened skin. Types of psoriasis that may be clinically found include plaque psoriasis, guttate psoriasis, erythrodermic psoriasis and pustular psoriasis. The potential role of immune factors, keratinocytes and fibroblasts in psoriasis etiology has been well established. The role of molecular biochemical markers in psoriatic skin, including changes in levels of protein and peptides, lipids, calmodulin, polyamines, ICAM-1, ELAM-1 and prolactin, have been well reviewed (1). Psoriasis is believed to be genetically linked but can also be triggered by mechanical, ultraviolet and chemical injury, various infections, prescription drug use, psychological stress, smoking, *etc*. Topical treatment of psoriasis is usually the first choice of therapy. Topical treatments consist of emollients and keratolytic agents, anthralin, coal tar, corticosteroids, vitamin D_3 analogues, retinoids, N^G-mono-methyl-L-arginine and psoralens plus ultraviolet A (UVA) light. In patients who do not respond adequately to topical therapy, oral or injectable therapy, such as oral retinoids, methotrexate, ciclosporin, tacrolimus, mycophenolate mofetil and oral psoralens plus UVA light, may be warranted. However, patients receiving systemic treatment should be carefully monitored for adverse effects and drug-drug interactions (2).

The standard systemic therapy for psoriasis comprises relatively nonspecific treatment modalities with many adverse effects that involve multiple organ systems. Recently, biotechnology using genetic engineering has created a real possibility for efficacious and safe psoriasis therapy. Recombinant proteins, the outcome of recent biotechnology research, are the main contributors in biotherapy.

Biologic agents are proteins that possess pharmacological activity and can be extracted from animal tissues or synthesized in large quantities through recombinant DNA technology (3). The main objective of biologic agents is to block molecular activation by binding to

extracellular targets. The efficacy of biologic agents has been examined in a number of areas such as diabetes (*e.g.*, insulin is a recombinant human protein), hematopoietic support (*e.g.*, erythropoietin, granulocyte and platelet growth factors) (4) and solid organ transplantation (*e.g.*, monoclonal antibody used to inhibit rejection) (5).

Due to the success of biotherapy in immune-mediated diseases, psoriasis has now become a prime target for biologic therapy in dermatology.

Existing therapies *versus* biologic agents

Existing therapies for psoriasis have several limitations. Phototherapy with UVB or PUVA requires a treatment center or space in the home to install a home UVB unit; this therapy may also be carcinogenic. Nephrotoxicity is associated with ciclosporin, hepatotoxicity and bone marrow toxicity with methotrexate, carcinogenicity and photosensitivity with PUVA and teratogenicity with retinoids. High levels of immunosuppression may occur with immunomodulators. In addition, many of the existing therapies are associated with a high recurrence rate of lesions without complete remission and poor patient compliance (6).

On the other hand, biologic agents for the treatment of psoriasis possess several outstanding promising features. These agents are not associated with major organ damage such as hepatotoxicity or nephrotoxicity and clinically significant immunosupperssion does not occur with any of them. Drug interactions are few as compared to methotrexate or ciclosporin; new biologics do not interact with cytochrome P450 enzymes. Moreover, these agents are not associated with bone marrow toxicity as seen with methotrexate or with the teratogenicity seen with retinoids and methotrexate. As a result, it is obvious that these agents could be used in combination with other psoriasis therapies. Efalizumab and infliximab are already used with methotrexate and there are possibilities for their concomitant use with phototherapy, topical medications or oral retinoids. Thus, combination therapy with biologic agents may provide higher efficacy and better safety profiles (6).

Immunologic basis of psoriasis

Keratinocyte hyperproliferation occurs due to the activation of the immune system in focal skin regions, which in turn is mediated by CD8+ and CD4+ T-lymphocytes that accumulate in diseased skin. Psoriasis is recognized as the most prevalent T-cell-mediated inflammatory disease in humans (7). However, certain major histocompatibility complex (MHC) antigens (*e.g.*, HLA-CW6, HLA-B13 and HLA-BW57) along with genes at chromosomes 17q, 4q and 6q have been associated with psoriasis (8). Microsatellite markers over the whole genome have also been used to identify the susceptibility genes. Evidence that T-cells are pivotal in the pathogenesis is provided by the efficacy of T-cell specific immunotherapies like ciclosporin, and monoclonal antibodies (anti-CD3, anti-CD4), the macrolide tacrolimus and ascomycine and fusion protein (9, 10). Briefly, the pathogenesis occurs when immature Langerhans cells (LCs) identify the foreign antigen and the antigen binds to the dendritic surface of LCs via MHC-I or MHC-II molecules. Subsequently, maturation of LCs occurs after which they migrate to lymph nodes. Mature LCs coupled with foreign antigen are identified by naive T-cells and moleculer interation between the two cell types results in activation of naive T-cells. Kreuger has discussed the process of maturation and activation in detail (7). After activation, T-cells can differentiate into the following cell types: type 1 CD4+ (Th1) and CD8+ (Tc1) effector cells that produce type 1 cytokines such as IFN-γ, IL-2 and TNFα but not IL-4; type 2 CD4+ (Th2) and CD8+ (Tc2) effector molecules that releases type 2 cytokines such as IL-4, IL-6 and IL-10 but not IFN-γ; or natural killer cells that react with some protein antigen (11). Psoriasis is predominantly characterized by type 1 cytokines and with an abundance of CD8+ cells in the epidermis and CD4+ cells in the dermis. Both cell types produce type 1 cytokines, although the mechanism that controls the type 1/type 2 balance is unknown. There is systemic T-cell activation in psoriatic patients which is indicated by increased serum levels of soluble IL-2 receptor. Epidermal keratinocyte proliferation results from the release of cytokines produced by activated T-cells (12).

Steps in the cutaneous T-cell immune response are as follows: i) immature LCs in the epidermis capture the antigen which then activates maturation and migration to lymph nodes draining skin sites; ii) molecular interaction between a mature LC and a naive T-cell in a lymph node activates the T lymphocyte; iii) activated lymphocytes acquire the skin homing receptor cutaneous lymphocyte associated antigen (CLA) and differentiate into type 1 or type 2 effector lymphocytes; iv) CLA+ memory T-cells enter the circulation and exit via cutaneous blood vessels at the sites of inflammation; v) T-lymphocytes in the dermis or epidermis become activated to release cytokines upon encountering the initiating antigen. Thus, psoriasis is a disease in which type 1 T-lymphocytes are expanded and effector actions in skin involve the release of IFN-γ.

Types of biologic therapy for psoriasis

Biologic agents target specific receptors or cytokines and block specific steps in the pathogenesis of psoriasis. Biologic agents either mimic the action of normal human proteins or interact with circulating proteins or cellular receptors. These agents are categorized into 3 classes, *i.e.*, monoclonal antibodies (MAbs), fusion proteins and recombinant cytokines, all of which are engineered using DNA technology (3).

Monoclonal antibodies

Monoclonal antibodies (MAbs) are proteins that specifically bind to proteins on cell surfaces in the circulation or in tissues. This interaction alters the activity of the target protein. The targets of MAb therapy are human proteins; thus, by inhibiting the effects of the protein, MAbs alter the course of the disease. These antibodies were originally produced in other species, usually in mice, and have been used for short-term therapy. For example, with the anti-CD-3 clone, OKT-3, patients developed immune response to the foreign protein which led to their discontinuation for nonlethal diseases. The MAbs currently in therapeutic trials are mainly chimeric (*i.e.*, fused segments of mouse and human antibody), humanized (*i.e.*, individual amino acids in a human backbone replaced with specific binding sequences derived from a murine monoclonal) or human sequences (*i.e.*, generated in genetically engineered mice). The majority of therapeutic antibodies in clinical trials are humanized because this technology allows flexibility in the design of immunoglobulin G (IgG) isotypes and it permits reengineering of some antibody characteristics (7). Some examples are efalizumab, ICM-3, IDEC-114, siplizumab, visilizumab and daclizumab.

1) Efalizumab

Efalizumab (hu1124, anti-CD11a, Raptiva®; Genentech, Xoma) causes integrin blockade. The MAb selectively inhibits T-cells causing a pathologic immune reaction in psoriasis (13). At therapeutic doses, efalizumab not only blocks binding of LFA-1 to ICAM but also decreases the surface expression of CD11a by about 90% (14). The expression of VLA-4, a structurally unrelated antigen, is also decreased on the surface of circulating T-cells (15) by an effect called transmodulation. Evidence of the efficacy of this MAb is marked lymphocytosis, which indicates reduced binding of T-cells to inflamed endothelium in skin. There is also a decrease in the number of dermal T-cells suggesting reduced trafficking of T-cells from vascular stores.

2) IDEC-114

IDEC-114 (IDEC) is a primatized anti-B7.1 MAb that specifically blocks B7.1 and CD28 costimulation without affecting interactions with CTLA-4. The optimal blockade might require the infusion of both B7.1 (CD80) and anti-B7.2 (CD86) antibodies (16).

3) Siplizumab

Siplizumab (MEDI-507; MedImumne) is a humanized anti-CD2 MAb that targets the LFA-3/CD2 signalling pathway. It is designed to block costimulation by inhibiting LFA-3/CD2 interaction. Peripheral lymphocyte counts are diminished in patients administered this MAb. Siplizumab leads to a selective deletion of antigen-specific activated T-cells (17).

4) Daclizumab

Daclizumab (Zenapax®; Protein Design Labs) is a humanized MAb approved by the FDA for the prevention of renal transplant rejection (18) and is being investigated for possible use in psoriasis. Daclizumab binds to the CD25 subunit of IL-2 receptors on T-cells, thus blocking T-cell proliferation and responses to IL-2, an important T-cell growth factor. Because CD25 is expressed in high levels in psoriasis, the inhibition of IL-2 binding could play a role in suppressing psoriasis.

5) Basiliximab

Basiliximab (Simulect®; Novartis) also targets the CD25 subunit of IL-2 receptors and is indicated for the prevention of graft rejection. This MAb has been shown to be effective in the treatment of severe psoriasis (19, 20).

6) Visilizumab

Visilizumab (SMART®-anti-INF-γ, Nuvion™; Protein Design Labs) is a humanized MAb that binds and inactivates IFN-γ and could be an excellent molecule for the treatment of psoriasis. IFN-γ is a primary target for the treatment of psoriasis because it is common in the Th1 cytokine profile and is implicated in keratinocyte hyperproliferation in this disease (3).

Fusion proteins

In fusion proteins the receptor domain of a human protein is fused to constant region sequences of human IgG so that the molecule has binding specificity for a particular ligand or coreceptor and solubility in plasma. There are two distinct types of fusion proteins. One type combines a human protein with a toxin. In this case, the human protein binds to a cell and causes internalization of the entire complex. The complex releases the toxin once inside the cell, thus killing the cell. An example is DAB 389 IL-2. The second type of fusion protein is identical to humanized MAb. These agents use the human receptor for proteins that bind to the Fc portion of human Ig (14). Some examples are CTLA-4Ig, etancercept and alefacept.

1) Etanercept

Etanercept (Enbrel®; Amgen, Immunex) is a TNF blocker already approved by the U.S. FDA for the

treatment of Crohn's disease, rheumatoid arthritis and psoriatic arthritis. Etanercept inhibits TNF, a proinflammatory cytokine involved in many inflammatory disorders particularly psoriasis and psoriatic arthritis. TNF has been shown to be increased in synovial fluid and synovium in psoriatic arthritis and in the skin of psoriatic lesions (21-24). Results from clinical trials have shown that etanercept provides clinically significant benefit to patients with active psoriatic arthritis when administered subcutaneously. Because it is fully homogenized, it has less immunogenicity. Non-neutralizing antibodies develop only in approx. 5% of patients. Antinuclear antibodies, anticardiolipin antibodies and anti-double stranded DNA antibodies commonly occur but systemic lupus erythematosus is rare and there is no major organ involvement. The most important advantage of etanercept therapy is the prevention of joint destruction. Etanercept has been proven to be superior to methotrexate in preventing radiographic progression of rheumatoid arthritis (25).

2) Alefacept

Alefacept (Amevive®; Biogen) is a dimeric fusion protein consisting of the Fc portion of human IgG linked to the extracellular binding portion of human lymphocyte function associated antigen-3 (LFA-3) (26). The drug is administered either intravenously or intramuscularly. Alefacept prevents T-cell activation by blocking the LFA-3/CD2 pathway via binding to CD2 receptors. Clinical clearing of psoriasis was noted in patients treated with alefacept during phase II clinical trials. Long-term remissions of psoriasis were reported in patients. The major drawback of alefacept is that it does not clear psoriatic lesions in everyone. Patients treated with alefacept have a reduction in CD45RO+ memory T-cells and that reduction correlates with improvement in psoriasis without significant immunosuppression (6).

3) Denileukin diftitox

Denileukin diftitox (Ontak®; Ligand) is one of the first biologic agents used in the treatment of psoriasis (27). DAB 389 IL-2 consists of human IL-2 sequences fused to a fragment of diphtheria toxin. The use of DAB 389 IL-2, a rationally engineered biologic immune antagonist, opened the door to treatment of psoriasis with other biologic agents that modify cellular immune reaction. Because IL-2 is internalized exclusively in activated T-cells, the toxin will only eliminate cells that are active when the drug is given (28).

Cytokines

Activated T-cells not only proliferate in a clonal fashion but also differentiate into type 1 or type 2 cells. Psoriasis is a type 1 disease characterized by type 1 cytokines (*e.g.*, IFN-γ) that lead to keratinocyte hyperproliferation. The therapeutic strategy of manipulating the Th1/Th2 and Tc1/Tc2 balance by exogenously administered cytokines is called immune deviation.

In psoriasis, the differentiation of type 1 cytokine producing T-cells can potentially be deviated to produce type 2 cytokines by administration of exogenous IL-2, IL-10 and IL-11 as these cytokines influence endogenous differentiation of type 2 lymphocytes in normal immune responses (7). In a recent phase II trial, recombinant IL-10 was shown to exert antipsoriatic effects by reducing the level of B7.2 (CD86) on skin-derived dendritic cells and a 50% reduction in T-cell stimulating capacity was noted (29). Recombinant IL-11 has also shown interesting antipsoriatic effects in phase I clinical trials (30).

1) Blockade of effector cytokines

Cytokines secreted by activated T-cells cause inflammatory response and effector immune responses, and therapeutic strategy is to selectively deactivate specific cytokines by antibodies or fusion proteins (7). In this regard, TNFα has an important role in the pathogenesis of psoriasis. It induces the expression of intercellular adhesion molecule (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), both of which are involved in trafficking lymphocytes to inflammatory lesions (31). LCs are one of the main antigen-presenting cells (APC) of the skin, which are responsible for the activation of T-cells. TNFα stimulates the capability to present antigens to the primed T-cells (32).

Like IFN-γ, TNFα is expressed at increased levels in psoriatic lesions and expression of several genes regulated by nuclear factor κB (transducer TNFα signal) is also increased. NFκB is a transcription factor that regulates the expression of genes that encode adhesion molecule, cytokines and immune receptors. TNFα activates NFκB which causes inflammation in psoriasis. Two types of biologic TNFα antagonists are infliximab, a chimeric anti-TNFα MAb, and etanercept, a TNFα receptor antagonist for Ig fusion protein (33).

2) Infliximab

Clearance of psoriasis skin lesions in patients treated with infliximab (Remicade®; Centocor) for inflammatory bowel disease led to phase II trials in patients with psoriasis vulgaris. Good to excellent clearance of psoriasis was observed (34). Infliximab is a chimeric MAb that has high specificity, avidity and affinity for TNFα. Therefore, by blocking TNFα activity it can reduce inflammation, keratinocyte proliferation and differentiation abnormalities in psoriasis (35). Infliximab initiates complement-mediated lysis of TNFα (36) whereas etanercept does not cause T-cell lysis (37). Infliximab-TNFα complex is much more stable than etanercept-TNFα complex (38). Infliximab has the ability to turn off already activated T-cells in psoriatic

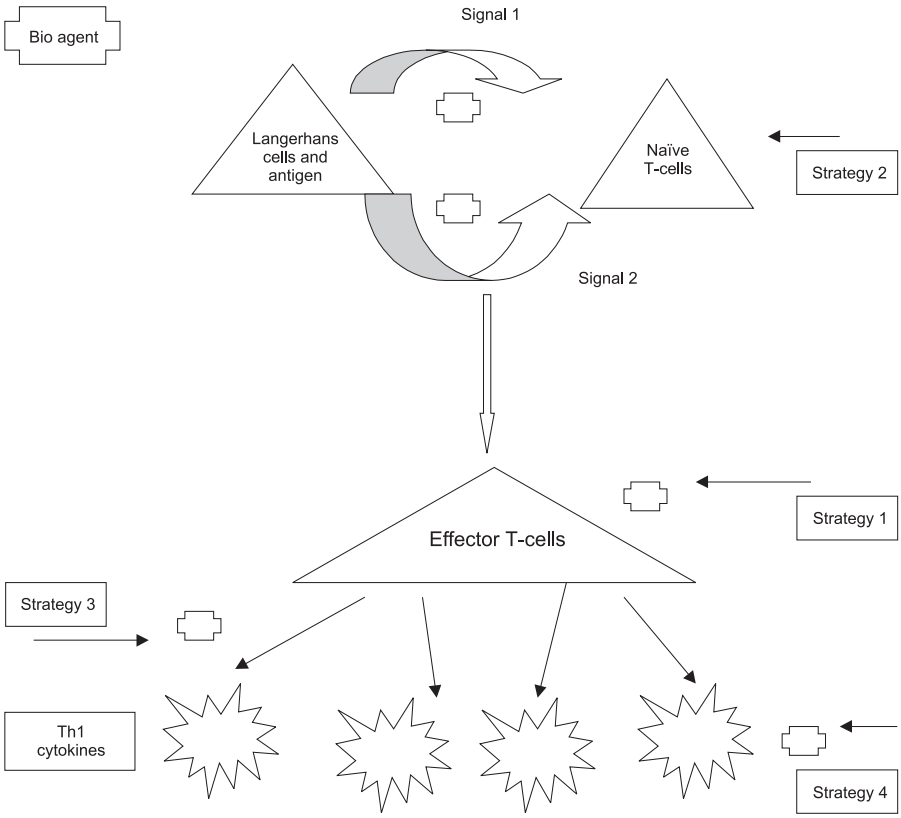

Fig. 1. Sites of action of biologic agents for different strategies in the immunological sequence of psoriasis. Strategy 1: action on effector T-cells; strategy 2: blockade of T-cell activation by inhibiting signal 1 or signal 2; strategy 3: inhibition of Th1 cytokine secretion; strategy 4: binding and blocking of cytokine actions.

plaques that are soluble, expressed on cell surface or even when associated with TNFα receptors (34). It is not associated with nephrotoxicity or hepatotoxicity.

Strategies for biologic therapy

The most important aim of biologic therapy is to prevent a pathologic effector immune response in skin tissue. Ideally, the goal would be to obtain effective clinical control of psoriasis with the least amount of immunosuppression. The four major strategies affecting different steps involved in the T-cell inflammatory pathway in psoriasis are briefly described below (Fig. 1).

Reduce the number of pathogenic T-cells

Obviously, psoriasis can be controlled or cured by reducing T-cells. This strategy involves targeting CD45RO+ T-cells in the skin that produce Th1 cytokines which are mainly responsible for psoriasis without affecting immune responses. The main advantage of this strategy is that it results in long-lasting remission. Drugs having this type of action are alefacept, denileukin diftitox and siplizumab.

Inhibit T-cell activation and migration

The cells responsible for psoriasis are mainly activated T-cells. Therefore, by blocking their activation the disease can be cured. T-cell activation requires interaction between an APC and a T-cell (39). There are two signals which indicate interaction. Signal 1 indicates interaction in which APC presents a specific antigen to the T-cells and antigens are recognized by TCR complex that is present on the surface of T-cells (40, 41). Signal 2 is the costimulation that is critical for optimal T-cell activation. The costimulatory signal is transduced through a glycoprotein on the surface of the T-cell termed CD28. CD28 binds to two distinct B7 molecules, CD80 and CD86 that are upregulated on the surface of dendritic cells during antigen-triggered maturation (42). Agents that act on signal 1 or signal 2 and can block T-cell activation include efalizumab, daclizumab, IDEC-114 and siplizumab.

Immune deviation

As discussed above, in psoriasis, activated T-cells produce the Th1 cytokines IL-2 and IFN-γ, which have an important function in psoriasis. Cytokines produced by

Th2 cells include IL-4 and IL-11 which tend to reduce the activity of Th1 cells (43, 44). Immune deviation is triggered by the deviation of a Th1 immune response towards a Th2 response using these Th2 cytokines. Hence, the activity of psoriasis can also be reduced by Th2 cytokines in order to inhibit Th1 cytokine production (45). Oprelvekin (Neumega®; Genetics Inst., Wyeth) and ilodecakin (Tenovil®; Schering-Plough) are two drugs that trigger immune deviation.

Block the activity of inflammatory cytokines

As mentioned above, the pathogenicity of psoriasis can be reduced by blocking cytokines. Cytokines induce keratinocyte changes, induce angiogenesis and increase the activated immune response. Therefore, drugs that bind to secreted cytokines and block them so that they are not able to contribute to psoriasis would be useful for this strategy (46). Drugs that act by blocking cytokines include etanercept, infliximab, ABX-IL-8 and visilizumab.

Conclusions

Only after years of experience will the adverse effects of biologic therapy be known. In the meantime, this approach offers the advantage of a better safety profile since biologic drugs act selectively on target tissues. Secondly, immunosuppression is a significant concern with antipsoriatic drugs such as ciclosporin, methotrexate, psoralen-UVA and corticosteroids, all potent immunosuppressants. Although biologic agents also inhibit some functions of the immune system, current evidence indicates that there is no significant risk of immunosuppression from biologic agents. Biotherapy should prove to be a safer therapy for the treatment of psoriasis in the near future and holds promise for revolutionizing the treatment of patients whose quality of life is reduced by this chronic, debilitating disease.

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