

PSORIASIS A CHRONIC, NON-CONTAGIOUS AUTOIMMUNE DISEASE: A CONVENTIONAL TREATMENT

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ABSTRACT

Psoriasis is a chronic, non-contagious autoimmune disease that affects the skin and joints. It commonly causes red, scaly patches to appear on the skin. The disadvantages of topical agents are variably that they can often irritate normal skin, can be time consuming and awkward to apply, cannot be used for long periods, can stain clothing or have a strong odor. As a result, it is sometimes difficult for people to maintain the regular application of these medications. Abrupt withdrawal of some topical agents, particularly corticosteroids, can cause an aggressive recurrence of the condition. This is known as a rebound of the condition. While alternative like spa, balneo, ischyotherapy takes long time consuming, TNF- α blockers have the potential to provide symptomatic relief and help prevent disease progression in PsA. Although these drugs are relatively expensive, concerns over an increased drug budget must be balanced against the potential long-term cost savings. At the present time there are no health economic studies concerning the role of TNF- α blockade in PsA. However, possible long- term benefits include: reduced need for joint replacement surgery, reduced demand on therapy services, reduced demands on medical and nursing services, reduced needs for other medicines, reduced demands on social services and carers, improved quality of life, improved prospect of remaining in work, increased life expectancy.

Keywords: Psoriasis, autoimmune disease, corticosteroids, TNF- α blockers.

INTRODUCTION

The scaly patches caused by psoriasis, called psoriatic plaques, are areas of inflammation and excessive skin production. Skin rapidly accumulates at these sites and takes on a silvery-white appearance. Plaques frequently occur on the skin of the elbows and knees, but can affect any area including the scalp and genitals. The cause of psoriasis is not known, but it is believed to have a genetic component. Factors that may aggravate psoriasis include stress, withdrawal of systemic corticosteroid, excessive alcohol consumption, and smoking¹

Epidemiology

Psoriasis affects both sexes equally and can occur at any age, although it most commonly appears for the first time between the ages of 15 and 25 years.

The prevalence of psoriasis in Western populations is estimated to be around 2-3%. The prevalence of psoriasis among 7.5 million patients who were registered with a general practitioner in the United Kingdom was 1.5%²

A survey conducted by the National Psoriasis Foundation (a US based psoriasis education and advocacy group) found a prevalence of 2.1% among adult Americans. The study found that 35% of people with psoriasis could be classified as having moderate to severe psoriasis³

Pathophysiology: In psoriasis, it is believed that an unknown antigen causes APCs to be activated in the epidermis. The APCs internalize and process the antigen, which is then presented on the APC surface. Activated APCs then travel to the lymph nodes and activate naive T cells. During this activation, a T cell and an APC bind to each other at many points on their surfaces by means of receptor-ligand pairs (Figure 1).^{4,5} These binding events are critical to any subsequent immune response. The first such event is the recognition of intracellular adhesion

molecule-1 (ICAM-1) on the surface of the APC by lymphocyte function-associated antigen-1 (LFA-1) on the surface of the T cell. This interaction sends a necessary but insufficient activation signal to the T cell. Also necessary for activation are signals produced by other ligand-receptor pairs. For example, the APC displays antigen on its surface in a format that the T-cell receptor can recognize.

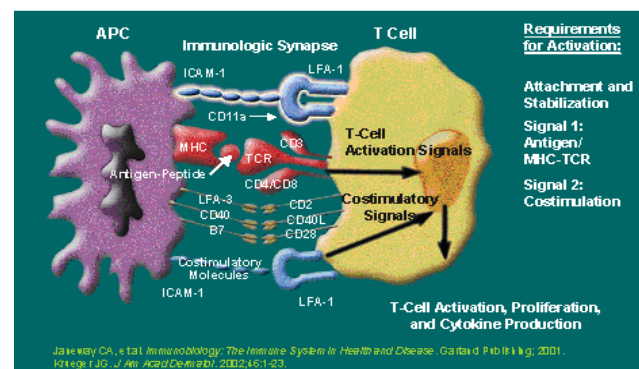


Figure 1 T-Cell activation in Lymph Node

Additional co stimulatory signals are sent to the T cell as a result of several other interactions.^{4,5} These include the binding of leukocyte function antigen-3 (LFA-3) on the APC to the CD2 antigen on the T cell. The net effect of all of these signals is an activated T cell with enhanced affinity for endothelial cells.

The activated T cell rolls along the microvasculature toward peripheral tissues, a process mediated in part by the binding between T-cell LFA-1 and endothelial ICAM-1 (Figure 2).^{5,6} Persons with psoriasis have activated T cells that traffic into the dermis and then into the epidermis.

Once in the skin, activated T cells undergo a second activation (reactivation) similar to the previous encounter with APCs in the lymph node. Reactivated T cells are then able to produce cytokines (soluble proteins that can exert both direct and indirect effects on other cells). These cytokines include interleukin-2 (IL-2) and interferon-gamma (IFN- α). Such factors may induce other cells to produce the postsecretory cytokines tumor necrosis factor-alpha (TNF- α), interleukin-8 (IL-8), and granulocyte-macrophage colony-stimulating factor (GM-CSF). Regardless of the mechanism, activated T cells and the cytokines they produce because aborted maturation and excessive proliferation of the keratinocytes. Such advances in our understanding of the path physiology of psoriasis suggest several new targets for therapeutic intervention. An agent that disables the psoriatic cascade of immunological events (Figure 3) at any point from T-cell activation to cytokine binding would have the potential for clinical benefit. The biologic agents currently available or in development for the treatment of moderate to severe psoriasis have been specifically designed to interfere at one or more points in this disease pathway.

Some of the specific strategies that have been employed in the development of biologic agents include:

Blockade of interactions leading to T-cell activation or migration to tissue, Elimination of the pathologic T cells by therapies targeted against activated T cells, Alteration of the balance of T-cell types, for example, by redirecting T-cell differentiation away from the T_H1 type implicated in psoriasis toward the T_H2 type.

Binding of cytokines following their secretion by T cells before they can act on keratinocytes to drive the formation of psoriatic plaques

Types of Psoriasis

Plaque psoriasis (psoriasis vulgaris)

It is the most common form of psoriasis. It affects 80 to 90% of people with psoriasis. Plaque psoriasis typically appears as raised areas of inflamed skin covered with silvery white scaly skin. These areas are called plaques. Plaque psoriasis is most typically characterized by circular-to-oval red plaques distributed over extensor body surfaces and the scalp. The plaques usually exhibit scaling as a result of epidermal hyper proliferation and dermal inflammation.

Flexural psoriasis (inverse psoriasis)

Appears as smooth inflamed patches of skin. It occurs in skin folds, particularly around the genitals (between the thigh and groin), the armpits, under an overweight stomach (pannus), and under the breasts (inframammary fold).

Guttate psoriasis

It is characterized by numerous small round spots (differenfungal infections.tial diagnosis—pityriasis rosea—oval shape lesion). These numerous spots of psoriasis appear over large areas of the body, such as the trunk, limbs, and scalp. Guttate psoriasis is associated with

streptococcal throat infection. Guttate psoriasis refers to a distinctive, acute clinical presentation of an eruption characterized by small, drop like, 1-10 mm in diameter, salmon-pink papules, usually with a fine scale⁸

Pustular psoriasis

Appears as raised bumps that are filled with non-infectious pus (pustules). The skin under and surrounding the pustules are red and tender. Pustular psoriasis can be localised, commonly to the hands and feet (palmoplantar pustulosis), or generalized with widespread patches occurring randomly on any part of the body.

Nail psoriasis

Produces a variety of changes in the appearance of finger and toe nails. These changes include discoloring under the nail plate, pitting of the nails, lines going across the nails, thickening of the skin under the nail, and the loosening (onycholysis) and crumbling of the nail. Approximately 7 million people in the United States have psoriasis. About 150,000-260,000 new cases of psoriasis are diagnosed each year. US physicians see 1.5 million patients with psoriasis per year.

Erythrodermic psoriasis

It involves the widespread inflammation and exfoliation of the skin over most of the body surface. It may be accompanied by severe itching, swelling and pain. It is often the result of an exacerbation of unstable plaque psoriasis, particularly following the abrupt withdrawal of systemic treatment. This form of psoriasis can be fatal, as the extreme inflammation and exfoliation disrupt the body's ability to regulate temperature and for the skin to perform barrier functions⁹

CONVENTIONAL TREATMENT

Topical treatment

Medicated creams and ointments applied directly to psoriatic plaques can help reduce inflammation, remove built-up scale, reduce skin turn over, and clear affected skin of plaques. Ointment and creams containing coal tar, dithranol (anthralin), corticosteroids like desoximetasone (Topicort), fluocinonide, vitamin D₃ analogues (for example, calcipotriol), and retinoids are routinely used. Argan oil has also been used with some promising results.¹⁰

Systemic treatment

Psoriasis which is resistant to topical treatment and phototherapy is treated by medications that are taken internally by pill or injection. This is called systemic treatment. Most people experience a recurrence of psoriasis after systemic treatment is discontinued.

The three main traditional systemic treatments are methotrexate, cyclosporine and retinoids. Methotrexate and cyclosporine are immunosuppressant drugs; retinoids are synthetic forms of vitamin A.

Biologics are manufactured proteins that interrupt the immune process involved in psoriasis. These drugs (interleukin antagonists) are relatively new, and their long-

term impact on immune function is unknown, but they have proven effective in treating psoriasis and psoriatic arthritis. They include Amevive, Enbrel, Humira, Remicade and Raptiva. Raptiva was withdrawn by its

maker from the US market in April, 2009. Ustekinumab (IL-12 and IL-23 blocker) shows hopeful results for psoriasis therapy.

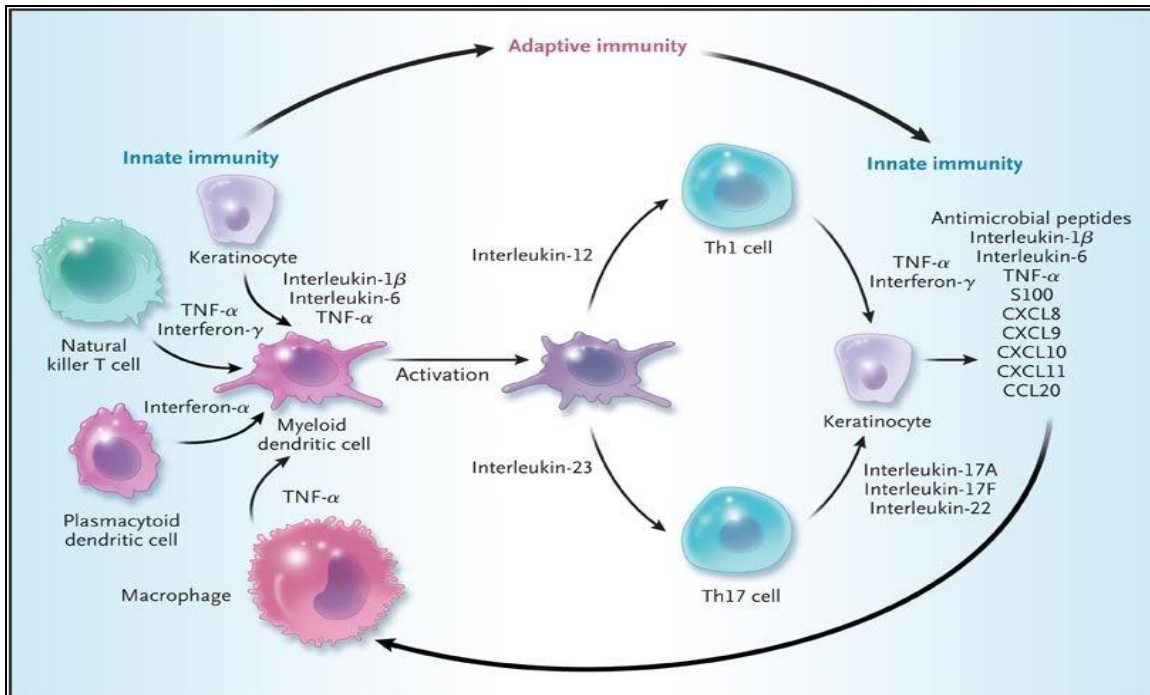


Figure 5: Key Cells and Mediators in the Transition from Innate to Adaptive Immunity in Psoriasis.

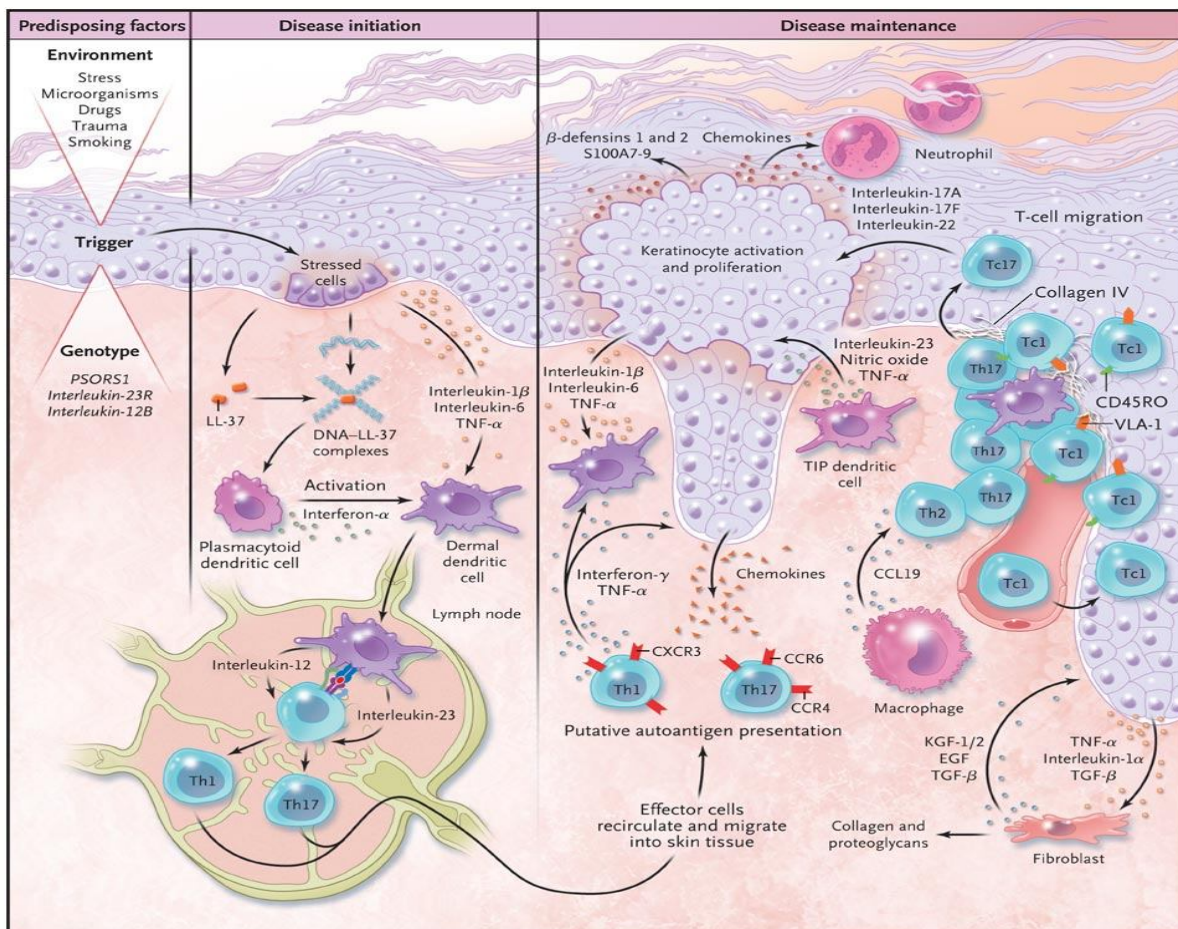


Figure 6: Proposed Schema of the Evolution of a Psoriatic Lesion from Initiation to Maintenance of Disease.

Mechanism of TNF alpha

Innate immune cells produce key cytokines (tumor necrosis factor α [TNF- α], interferon- α , interferon- γ , interleukin-1 β , and interleukin-6) that activate myeloid dendritic cells. Activated dendritic cells present antigens and secrete mediators such as interleukin-12 and interleukin-23, leading to the differentiation of type 17 and type 1 helper T cells (Th17 and Th1). T cells, in turn, secrete mediators (e.g., interleukin-17A, interleukin-17F, and interleukin-22) that activate keratinocytes and induce the production of antimicrobial peptides (e.g., LL-37 cathelicidin and β -defensins), proinflammatory cytokines (TNF- α , interleukin-1 β , and interleukin-6), chemokines (CXCL8 through CXCL11 and CCL20), and S100 proteins. These soluble mediators feed back into the proinflammatory disease cycle and shape the inflammatory infiltrate.

Infliximab

Formula: C₆₄₂₈H₉₉₁₂N₁₆₉₄O₁₉₈₇S₄₆

Drug class: Infliximab is an antibody that blocks the effects of tumor necrosis factor alpha (TNF alpha)

Mechanism of action: According to product labeling, Infliximab neutralizes the biological activity of TNF α by binding with high affinity to the soluble (free floating in the blood) and transmembrane (located on the outer membranes of T cells and similar immune cells) forms of TNF α and inhibits or prevents the effective binding of TNF α with its receptors. Remicade and Humira (another TNF antagonist) are in the subclass of "anti-TNF antibodies" (they are in the form of naturally occurring antibodies), and are capable of neutralizing all forms (extracellular, transmembrane, and receptor-bound) of TNF alpha.¹¹ Enbrel, a third TNF antagonist, is in a different subclass (receptor-construct fusion protein), and, because of its modified form, cannot neutralize receptor-bound TNF α .¹² Additionally, the anti-TNF antibodies Humira and Remicade have the capability of lysing cells involved in the inflammatory process, whereas the receptor fusion protein apparently lacks this capability.¹³ Although the clinical significance of these differences has not been absolutely proven, they may account for the differential actions of these drugs in both efficacy and side effects.

Infliximab has high specificity for TNF- α , and does not neutralize TNF beta (TNF- β , also called lymphotoxin α), a related but less inflammatory cytokine that utilizes the same receptors as TNF α . Biological activities that are attributed to TNF α include: induction of proinflammatory cytokines such as interleukin (IL) 1 and IL 6, enhancement of leukocyte movement or migration from the blood vessels into the tissues by increasing the permeability of endothelial layer of blood vessels; and increasing the release of adhesion molecules. Infliximab prevents disease in transgenic mice (a special type of mice that are biologically engineered to produce a human form of TNF α and which are used to test the results of these drugs that might be expected in humans). These experimental mice develop arthritis as a result of their production of human

TNF α , and when administered after disease onset, infliximab allows eroded joints to heal.

Dose: 3 mg/kg (0, 2, 6), 5 mg/kg (0, 2, 6) 10mg/kg IV at week 0, 2, 5 than every 8 weeks

Side effect: The most common side effects of infliximab are upper respiratory tract infections, urinary tract infections, cough, rash, back pain, nausea, vomiting, abdominal pain, headache, weakness and fever, low or high blood pressure, chest pain, difficulty breathing, rash, itching, fever and chills may occur during or shortly after administration.

Etanercept

Formula: C₂₂₂₄H₃₄₇₅N₆₂₁O₆₉₈S₃₆

Drug class: Etanercept is a dimeric fusion protein consisting of the soluble TNF receptor fused to the Fc portion of human IgG. It prevents interaction between TNF and its receptor(s) thus neutralising TNF activity.

Mechanisms of action: Etanercept inhibits TNF activity by competitively binding to it and preventing interactions with its cell surface receptors. Elevated levels of TNF have been found in psoriatic skin lesions, and in synovial explants and fluid from patients with psoriatic arthritis.¹⁶⁻¹⁸ Furthermore, TNF levels in the serum of patients with plaque psoriasis,¹⁹ and in blister fluids of involved psoriatic skin²⁰ have also been shown to be higher than in those of controls. These values were significantly correlated with the psoriasis area and severity index (PASI) scores, and TNF levels were reduced in association with clinical resolution after effective treatment.¹⁹

The production of chemokines, and the expression of adhesion molecules by keratinocytes and vascular endothelial cells can be stimulated by TNF produced within psoriatic lesions. These signals then cause recruitment of additional inflammatory cells into the plaque. Krueger suggests that TNF may function as part of a positive feedback loop, which acts to amplify and sustain the inflammatory process within psoriatic plaques.²¹ Biologic responses that are induced or regulated by TNF are modulated by etanercept. It may, therefore, serve to reduce inflammation within plaques by breaking this cycle.

Dose: A 50 mg subcutaneous (SC) injection, using either. (two 25 mg SC injections the same day or 3 or 4 days apart) for adult patients is a 50 mg dose given twice weekly (administered 3 or 4 days apart) for pediatric patients ages 2 to 17 years with active polyarticular-course JIA is 0.8 mg/kg per week (up to a maximum of 50 mg per week).^{14,15}

Side effect: Erythema and edema, Serious infections^{25,26}, Demyelinating disorders¹⁸, Tuberculosis, Solid tumors/lymphomas^{18,20-22}, Hepatitis B Virus (HBV) relapse²⁷ Congestive heart failure (CHF)

Adalimumab

Formula: C₆₄₂₈H₉₉₁₂N₁₆₉₄O₁₉₈₇S₄₆

Drug class: An antibody that blocks the effects of tumor necrosis factor alpha (TNF alpha)

Mechanism of action:

CNTO 1275 is designed to interfere with the triggering of the body's inflammatory response through the suppression of certain cytokines. Specifically, CNTO 1275 blocks interleukin IL-12 and IL-23 which help activate certain T-cells.

Use: psoriasis, inflammation, in moderate to severe Crohn's disease and the joint inflammation of juvenile rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, in treating the inflammation of uveitis, and for sarcoidosis.

Dose: 40 mg every other week, 80 mg Week.

Certolizumab:

Drug class: only PEGylated, Fc-free anti-TNF,

Mechanism of action: It has a high affinity for human TNF-alpha, selectively neutralizing the pathophysiological effects of TNF-alpha. This cytokine plays a key role in mediating pathological inflammation, and excess TNF-alpha production has been directly implicated in a wide variety of diseases.

Use: psoriasis, arthritis, Crohn's disease,

Dose: Certolizumab is not approved by FDA; SC certolizumab 400 mg was associated with efficacy in inducing and maintaining a clinical response and/or remission in patients when administered at Weeks 0, 2, and 4, and every 4 weeks thereafter.

T Cell Mediators

Alifacet

Drug class: Inhibits T-cell activation and trafficking. (a recombinant humanized monoclonal antibody that binds specifically to the CD11a subunit of LFA-1 (lymphocyte function-associated antigen-1), a leukocyte cell surface protein.)

Mechanism of Action: Amevive (alefacept) is an immunosuppressive dimeric fusion protein that consists of the extracellular CD2-binding portion of the human leukocyte function antigen-3 (LFA-3) linked to the Fc (hinge, CH2 and CH3 domains) portion of human IgG1. Alefacept is produced by recombinant DNA technology in a Chinese Hamster Ovary (CHO) mammalian cell expression system. Amevive interferes with lymphocyte activation by specifically binding to the lymphocyte antigen, CD2, and inhibiting LFA-3/CD2 interaction. Activation of T lymphocytes involving the interaction between LFA-3 on antigen-presenting cells and CD2 on T lymphocytes plays a role in the pathophysiology of chronic plaque psoriasis. The majority of T lymphocytes in psoriatic lesions are of the memory effector phenotype characterized by the presence of the CD45RO marker²⁸,

express activation markers (e.g., CD25, CD69) and release inflammatory cytokines, such as interferon γ .

Amevive also causes a reduction in subsets of CD2+ T lymphocytes (primarily CD45RO+), presumably by bridging between CD2 on target lymphocytes and immunoglobulin Fc receptors on cytotoxic cells, such as natural killer cells. Treatment with Amevive results in a reduction in circulating total CD4+ and CD8+ T lymphocyte counts. CD2 is also expressed at low levels on the surface of natural killer cells and certain bone marrow B-lymphocytes.

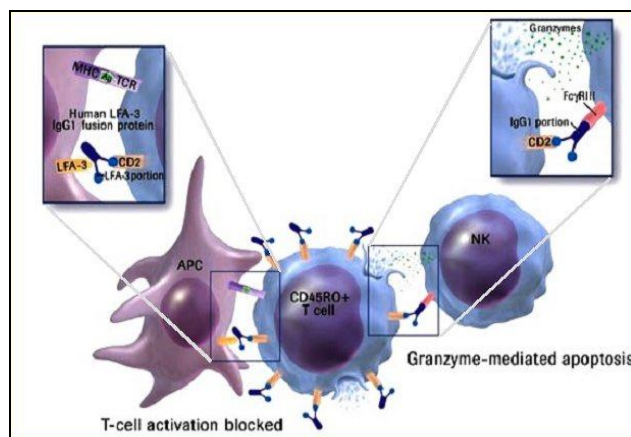


Figure 8: Dual mechanism of action

Use: Treatment of moderate to severe chronic plaque psoriasis and psoriatic arthritis in adults, who are candidates for systemic or chemotherapy.

Dosing: Adult Usual dose: 7.5 mg IV bolus or 15 mg IM injection once weekly for 12 weeks

A 12 week retreatment regimen may be initiated following a 12 week treatment free interval, provided CD4+ T lymphocyte counts are within the normal range.²⁸

Pediatric use: Alefacept is not indicated for use in pediatric patients.²⁸

Geriatric use: No dosage change is recommended. Caution should be used in this population as geriatric patients have an increased risk of developing infections and certain malignancies.²⁸

Side Effects: Serious Infections, Malignancies, Lymphopenia, Dizziness, Cough, Nausea, Itching, Muscle Aches, Chills

Abatacept

Abatacept is a fusion protein composed of the extracellular domain of CTLA-4 with the hinge, CH2, and CH3 domains of IgG1.²⁹

Drug class: It is a fusion protein composed of an immunoglobulin fused to the extracellular domain of CTLA-4, a molecule capable of binding B7. Abatacept is a selective co stimulation modulator as it inhibits the co stimulation of T cells.

Mechanism of action: Ordinarily, full T cell activation requires 1) binding of the T cell receptor to the antigen-MHC complex on the antigen presenting cell (APC) and 2)

a co stimulatory signal provided by the binding of the T cell's CD28 protein to the B7 protein on the APC. Abatacept, which contains a high-affinity binding site for B7, works by binding to the B7 protein on APCs and preventing them from delivering the costimulatory signal to T cells, thus preventing the full activation of T cells.^{30,31}

Abatacept is the basis for the second-generation belatacept currently being tested in clinical trials. In organ transplantation, it is intended to provide extended graft survival while limiting the toxicity generated by standard immune-suppressing regimens such as calcineurin inhibitors (eg, cyclosporine).

Use: Abatacept is for use in psoriasis, rheumatoid arthritis²⁸, in combination with anakinra or TNF antagonist nephritis when used in combination with cyclophosphamide therapy.³¹ and in organ transplantation, ulcerative colitis³¹, Type 1 Diabetes³², National Institute of Allergy and Infectious Diseases, lupus nephritis when used in combination with cyclophosphamide therapy.

Dose: 500 mg for patients weighing less than 60 kg, 750 mg for those weighing 60 to 100 kg, and 1,000 mg for patients weighing more than 100 kg. IV infusion over 30 minutes, at week- 2 and -4 after the first infusion, 5, 7.5, or 10 mg/mL.

Onercept

Drug class: anti-TNF agent,

Mechanism of action: TNF-binding protein has shown similar promising results as the other anti-TNF medications in a phase II study.

Dose: Two doses were used of this subcutaneous medicine: 50 mg and 100 mg three times a week. 100 mg dose (This has been shown with switching in multiple different directions, such as from etanercept to infliximab and vice versa, as well as from both of these to adalimumab.³⁰⁻³³

CONCLUSION

The change in the treatment paradigm for psoriasis, which is attributable to the emergence of the biologic agents, is that these drugs can be given safely over long periods; we do not have to keep patients on a roller coaster any more. Patients now can be kept under control, without interruption, over long periods. The biologic agents represent a refined approach to targeted immunosuppression. At present, it is unclear why not all patients respond to each agent. It is likely that different immune pathways may lead to the psoriatic phenotype and thus different co stimulatory molecules may have different relevance to disease in a specific person. The diversity of biologic agents with their relative safety may yield additional effective treatment options for moderate to severe psoriasis.

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