New approaches to psoriasis treatment. A review

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SUMMARY

Psoriasis is one of the most frequent inflammatory skin disorders in Caucasians. It is genetically determined and often reveals autosomal dominant features. The inheritance seems to be polygenic, but the exact mechanisms are still not clear. Eight gene loci are reported in the literature as contributing to expression of psoriasis. They are designated as PSORS 1 to PSORS 8, the first one being the most important. During the last 10 years or so a number of immunologic mechanisms provoking psoriatic lesions have been reported, some authors even stress the autoimmune traits. Activated T lymphocytes seem to play the crucial role, but other immunologically competent cells and molecules are also relevant. Clinical studies have revealed that a substantial reduction of CD4 T lymphocytes in the dermis and of the CD8 in the epidermis essentially ameliorated the psoriatic lesions.

The new biologic preparations inhibit the T-cell activation and migration, interfere with the immune deviation or block the activity of inflammatory cytokines. Alefacept, efalizumab, etanerscept, infliximab and oprelevkin are discussed in detail.

KEY WORDS

psoriasis, genetics, immunologic aspects, treatment, alefacept, efalizumab, oprelevkin, etanercept, infliximab

Introduction

Psoriasis is one of the most frequent inflammatory skin disorders in Caucasians. It is a genetically determined disease that affects the skin, scalp and nails. It is characterized by sharply demarcated erythematous plaques with silvery scales, which appear typically on the knees, elbows, sacral region and scalp, but the entire skin may be involved. Nail changes include distal onycholysis, pitting and "oil spots". Clinically a spectrum of different subtypes may be observed: psoriasis vulgaris, guttate psoriasis, erythrodermic psoriasis, pustular psoriasis, inverse psoriasis, and sebopsoriasis. The prevalence of psoriasis is estimated to be 2% of Cocasian the Caucasian population and it may develop at any age (1).

Psoriatic arthritis occurs in 5-30% of patients with cutaneous psoriasis (1,2) and can appear in 10-15% of patients before involvement of the skin. It can be manifested as mono- and asymmetrical oligoarthritis, arthritis of the distal interphalangeal joints, rheumatoid arthritis-like changes, arthritis mutilans, and/or spondylitis and sacroileitis.

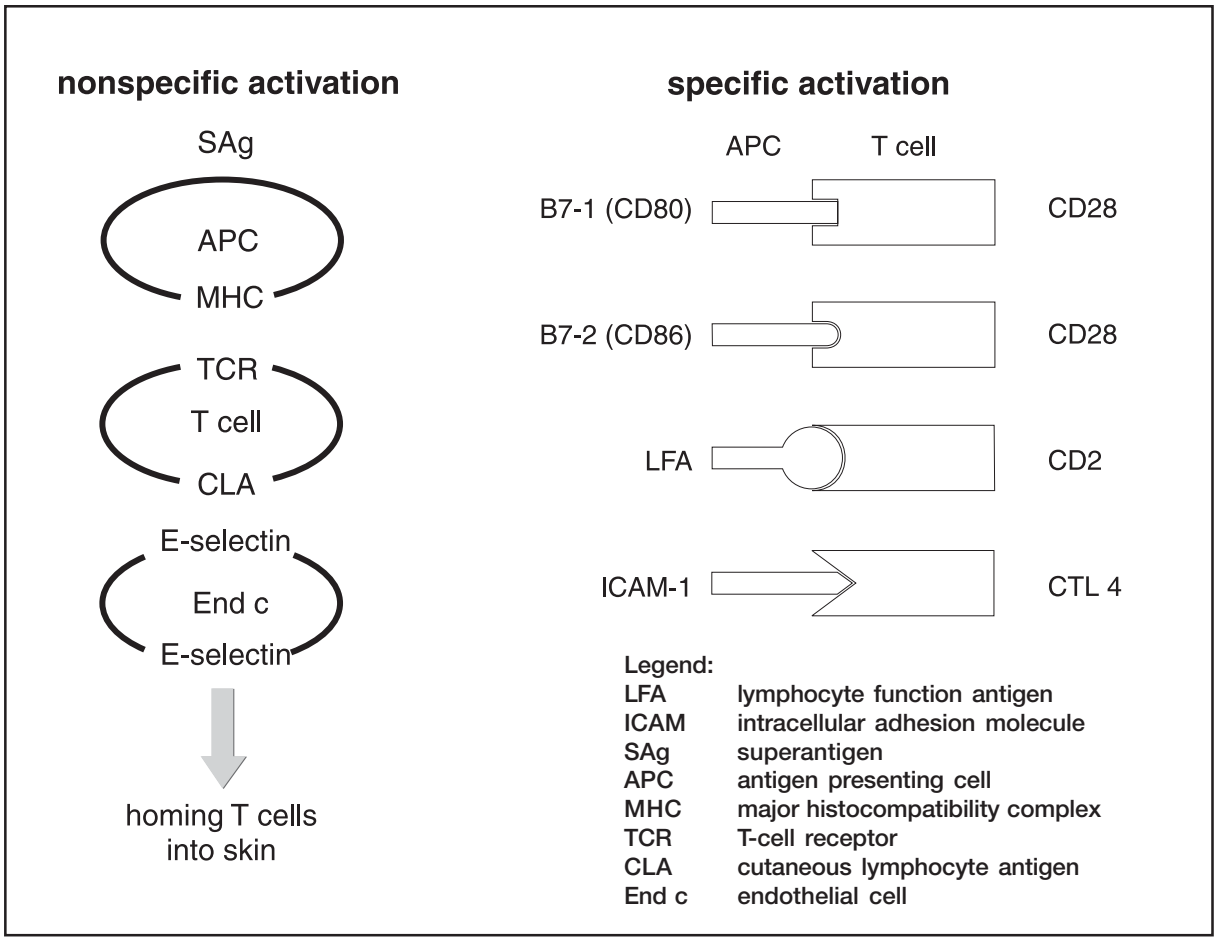

Figure 1. Signals for specific and nonspecific activation of T-lymphocytes. A simplified presentation.

Histological characteristics of psoriasis are hyperkeratosis, parakeratosis, acanthosis of the epidermis, tortuous and dilated capillary vessels and an inflammatory infiltrate composed mainly of lymphocytes and is located in the upper dermis. Such pathology reflects the abnormal epidermal proliferation and differentiation as well as the deviated activation of the immune system.

Genetics

Based upon analyses of family pedigrees, a polygenic inheritance provides the best model for the complex genetics of psoriasis. Linkage studies have demonstrated several genetic loci potentially responsible for development of psoriasis (3). PSORS1 has been mapped to chromosome 6p21.3, and is considered to be the major gene locus involving psoriasis. The critical region appears to be a 300 kb interval around the centromere of class I major histocompatibility complex (MHC). Other gene loci linked to psoriasis are PSORS2 on chromosome 17q, PSORS3 on chromosome 4q, PSORS4 on chromosome 1q, PSORS5 on chromosome 3p, PSORS6 on chromosome 19p, and PSORS7 on chromosome 1p. The locus on chromosome 16q12-13, known also as PSORS8 has been shown to have linkage with both psoriasis and Chron's disease (4).

Immunology

As it has been mentioned ample data indicates the importance of genetics, but the immunologic mechanisms, however, seem to be responsible for the immediate development of skin lesions. Psoriasis is now recognized as the most prevalent T-cell mediated inflammatory disease in humans (5).

The Köbner phenomenon has inspired researchers to investigate the stratum corneum as a possible source of antigens responsible for a specific immune response in psoriasis (6). Although the presence of circulating anti-stratum corneum antibodies and deposits of immunoglobulins and C3 in lesional epidermis were demonstrated some decades ago, the identity of stratum corneum antigens remains to be disclosed. Observations on the investigated subpopulations of T-lympho-

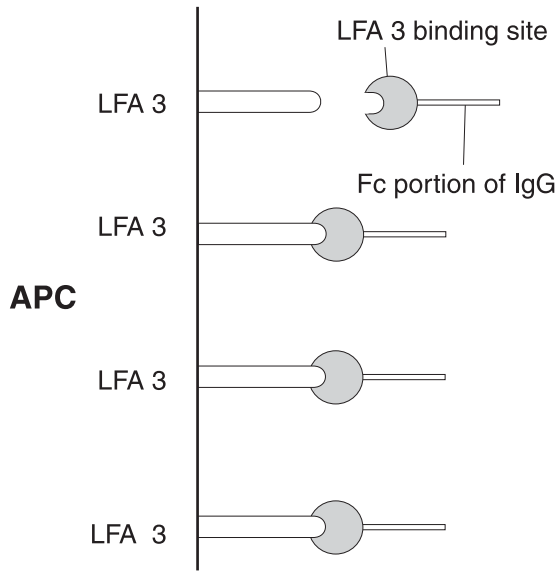

Figure 2. Sites of action of alefacept.

cytes and antigen presenting cells (APC) in psoriatic plaques suggest that a specific immunologic response and/or super antigen-induced activation of T-lymphocytes are the major pathogenetic factors. Streptococcal antigens have also been suggested to activate T-lymphocytes in psoriasis (7), but such an activation is less convincing in plaque psoriasis.

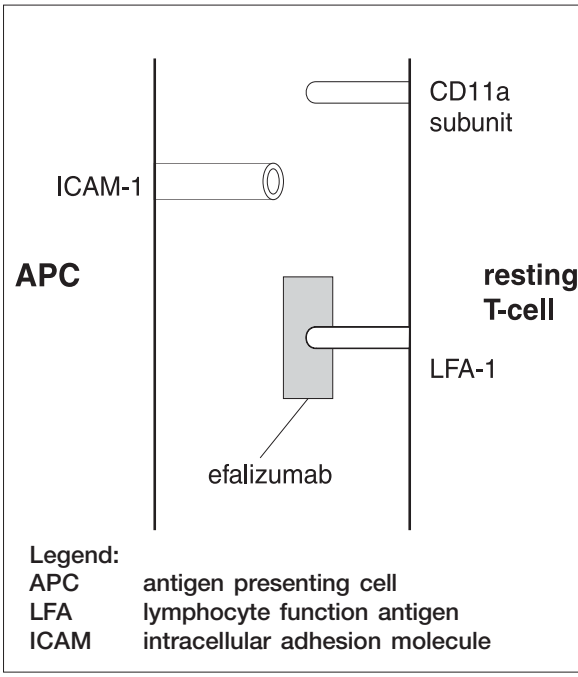

Figure 3. Sites of action of efalizumab.

Several observations suggest that psoriasis is a T-lymphocyte-mediated autoimmune disease. T-lymphocyte already predominate in the cell infiltrate in psoriatic plaques in early lesions (7). T-lymphocytes, both CD4+ and CD8+ cells, are activated (HLA DR+ and CD 25+). In the dermis the CD4+ cells predominate, while CD8+ cells prevail in the epidermis. One of the earliest events in the psoriatic plaques is the influx of activated CD4+ cells. In resolving plaques an influx of CD8+ cells predominates, while there is a decrease of CD4+ cells. CD4+ cells interact with APCs, expressing MHC class II antigens, while CD8+ cells interact with APCs, expressing MHC class I antigens. The induction of T-cell activation by psoriatic epidermal cells is highly dependent on the population of CD1a-DR+ dendritic cells (8), while CD1a+ Langerhans cells, HLA-DR+ keratinocytes and dermal dendrocytes might also be relevant APCs in psoriasis.

Activated T-lymphocytes produce two different patterns of cytokines: Th1 cells produce IL-2 and IF-γ, whereas Th2 cells produce IL-4, IL-5, and IL-10. Psoriasis can be considered as a Th1 dominant disease. Activated T-cells in the psoriatic plaques and other blood derived cells have been shown to secrete a series of cytokines which may account for many characteristics of the psoriatic lesion. TNF-α, IL-3, IL-6, GM-CSF and IF-γ are responsible for epidermal proliferation, TNF-α has been linked to the production of skin-associated antileukoproteinase and β defensins by epidermal cells, and to IL-8 for neutrophil accumulation (9). On the other hand, IL-10 which is secreted by Th2 lymphocytes, has been shown to inhibit the production of Th1 cytokines. The interaction between integrins of blood derived cells and ICAM-1/VCAM-1 on endothelial cells of vessels in psoriatic plaques promotes cell migration to psoriatic plaques and is crucial in the pathogenesis of psoriasis (10).

Interactions between T-lymphocytes and antigen presenting cells

For a better understanding of the mechanisms involved in the biologic treatment a short outline of the interactions between T lymphocytes, antigen presenting cells and active molecules has to be given. For more detailed information see the article by JM Kruger (5).

APCs present antigens to T-lymphocytes causing their activation. Activation of T-lymphocytes is followed by clonal expansion of T cells' population in psoriatic plaques. It is believed that T-lymphocyte receptor rearrangements suggest that specific antigen stimulation is relevant in the pathogenesis of psoriasis (9,10). Antigens activate lymphocytes in two ways: specific and nonspecific. Streptococcal super antigens may bind in

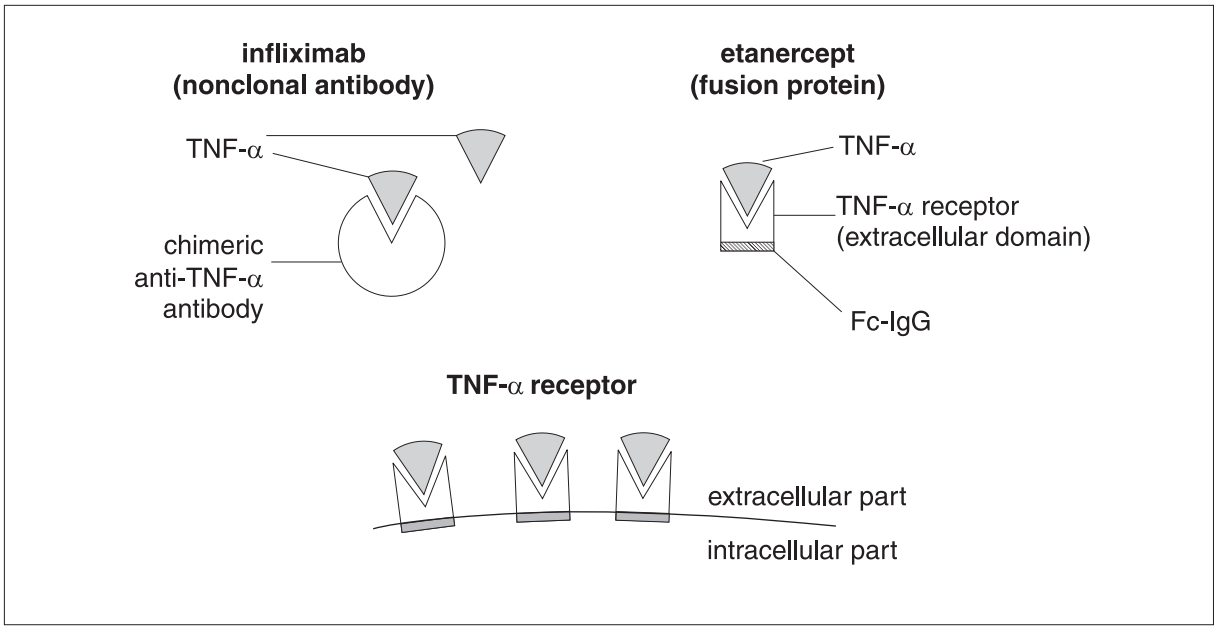

Figure 4. Mechanisms of action of etanercept and infliximab.

a nonspecific way to the MHC complex on one hand and with a variable region of the β-chain of the T-lymphocyte on the other hand (9). Super antigens activate T-lymphocytes in a nonspecific way and induce the expression of cutaneous lymphocyte-antigen (CLA) on T-lymphocytes (11). CLA binds to E-selectin proteins on the endothelial cells resulting in a preferential homing of T-lymphocytes into the skin. In the *process of activation* three sets of signals between Langerhans cells and T cells take place: *primary signals* (e.g. TCR to MHC I or to MHC II), *accessory signals (co stimulation)* and *proliferation and differentiation signals*. Co stimulatory pathways between APC and the T-lymphocyte are required for full T-lymphocyte activation. One of these pathways is LFA-3 on the APC and CD2 on the surface of the T cell resulting in T-lymphocyte activation. Another co stimulatory pathway is between CD80 and CD86 (B7 molecule) on the APC and CD28 or CTLA4 on the T-cell. CD28 transmits activation and CTLA4 inhibits T-lymphocyte activity (Fig. 1).

Established treatments for psoriasis

Topical and/or systemic treatments, UV irradiation as well as balneologic procedures are widely used. The therapeutist has to take into consideration the pathogenesis, the subtype of the disease, triggering factors and the patient's personality. The rather long-term management requires individualization of the therapy, reconciling the extent of the disease and the patient's perception of the disease as well as the potential side effects of the specific medications.

Topical treatment

Emollients and baths are helpful in restoration of the stratum corneum barrier function, since it is disturbed in psoriasis and is characterized by an increased transepidermal water loss (12). At the beginning keratolytic agents should be administered for shedding the scales and for a better penetration of antipsoriatics are given (13). Other substances like urea, tar, selen disulfide, pyrithion zinc, tioxolon and sodium bituminosulfonate are used. Retinoids (14), vitamin D analogues (15), and corticosteroids (16,17) are also prescribed. New preparations are tacrolimus and pimecrolimus.

Systemic medications and photo(chemo)-therapy

Cyclosporine (18), retinoids (19,20), methotrexate (21,22,23), mycophenolate mofetil (24), fumaric acid derivatives (25), oral calcitriol (26), hydroxyurea (27), and 6-thioguanin (28), which suppress the T cells are still used. Psoriasis patients also tolerate well UV treatment, which can be administered as selective ultraviolet phototerapy (SUP), narrow band UVB (311-313 nm) phototherapy, balneophototherapy, and systemic, bath or topical photo chemotherapy (PUVA) (29,30,31). Photodynamic therapy (PDT) (32), 308-excimer laser therapy (33), bexarotene (34) and 4-hydroxilase inhibitors (35) are some of the newer therapeutic possibilities.

Biological approach

Knowledge of the immunopathogenetic processes inducing psoriasis has contributed to the development of new biologic therapeutic agents. These biologic agents are proteins that possess pharmacologic activity and can be extracted from animal tissue or synthesized through recombinant DNA techniques. Biologic molecules either mimic the actions of normal human proteins or they interact with circulating proteins or cellular receptors. There are three distinct types of molecules that have been developed for use in psoriasis and some other disorders: recombinant human proteins, monoclonal antibodies, and fusion proteins.

Recombinant human proteins are exact replicas of normal human proteins that have been developed through DNA combinations, and in physiological doses they exert specific effects (36). *Monoclonal antibodies* are chemically and immunologically homogeneous proteins that specifically bind to proteins on cell surface. Initially murine monoclonal antibodies were used, but patients frequently developed allergic responses to the foreign protein. Since recently the so called *humanized antibodies* are available (37): the specific binding site from a murine antibody is attached to the Fc portion of human immunoglobulin (38). *Fusion proteins* are molecules that combine sections of different proteins. The receptor domain of a human protein is fused to the constant region sequences of human IgG, thus the fusion protein has binding specificity for a particular ligand and is soluble in plasma. Two distinct types of fusion proteins are recognized: it may be combined with a toxin (39) or it may be similar to humanized monoclonal antibodies. In the last mentioned combination, fusion proteins use human receptors for proteins to confer specificity instead of using a mouse antibody binding site (38). Receptors are then bound to the Fc portion of human immunoglobulin in a similar manner to humanized monoclonal antibodies.

The mechanisms of action of biologic agents include four strategies: *reduction of pathogenic T cells, inhibition of T-cell activation, immune deviation* and *blocking the activity of inflammatory cytokines.*

Reduction of pathogenic T cells

The ideal strategy would be to reduce activated T cells responsible for induction of psoriasis, which produce Th1 cytokines ($CD45RO^+$), without altering other immunologic processes (40). The advantage of such a strategy is a prolonged remission because it may be assumed that the involved T cells need time to repopulate the skin. A representative drug in this group is *alefacept* (LFA-3TIP, Amevive®). It is a fusion protein combining the *binding site* of lymphocyte function-associated antigen-3 (LFA-3) with the *Fc portion of human IgG.* This medication binds specifically to T cells expressing CD2, the natural ligand of LFA-3. The CD2 is expressed maximally in T cells that have been activated and express CD45RO, the sign of a memory T-cell phenotype (Figure 2). These cells are most important for the spreading and persistence of psoriasis. Certain results show that psoriatic lesions as measured by Psoriasis Activity and Severity Index (PASI) (41), considering the baseline values, improve in 50-60% of patients by 50% and in 20-30% of patients by 75% (42). It was also proven that the mean duration of remission lasted eight months, which reflects the slow repopulation of the skin with native T cells (40).

Inhibition of T-cell activation and migration

Pathogenic cells in psoriasis are activated T-lymphocytes. T-cell activation requires interactions between an APC (e.g. Langerhans cell) and a T cell (43) (referred to as signal 1 and 2.). APC presents a specific antigen to the T cell mediated through the MHC which associates with CD4 or CD8 on the T cell and ICAM-1 with LFA-1 (signal 1). The T lymphocyte recognizes this antigen through the T-cell receptor (and signals through CD3). The costimulatory signal, referred as signal 2, is accomplished through the APC-T-cell interactions (CD80/CD86 with CD28 and LFA-3 with CD2) (44,45). Biologic agents interact with either signal 1 or 2 and may block the T-cell activation. One of the representative drugs in this group is *efalizumab* (Raptiva®, anti-CD11a). It is a humanized antibody which binds to CD11a on T cells, which is a part of LFA-1, thus blocking the binding to intracellular adhesion molecule-1 (ICAM-1) (Figure 3). The LFA-1 to ICAM-1 interaction is also important for T-cell adhesion to endothelial cells and prevents T-cell migration into the inflamed skin. Clinical studies demonstrated improvement of the PASI index in 62% of patients by 50%, while 30% of patients had a 75% improvement (5,42,46).

Deviation of a Th1 immune response

As mentioned before, the activated T cells in psoriatic plaques produce cytokines of the Th1 phenotype, which include IL-2 and IFN-γ. On the other hand, cytokines produced by Th2 T cells (IL-4, IL-10 and IL-11) tend to reduce the activity of Th1 cells, which are most important in pathogenesis of psoriasis. Th2-type cytokines are important in the down-regulation of outgoing Th1 immune response. Such deviation of an immune response results in improvement of psoriasis (47). *Oprelevkin*, a recombinant form of human IL-11, induce immune deviation in psoriasis. The same effect is noticed when IL-10, an important Th2-type cytokine, is administered subcutaneously in psoriasis patients. There was a mean reduction of 55% in the PASI index in patients receiving recombinant human IL-10, the effect persisted several months after the last dose (48, 49).

Blocking the activity of cytokines

Biologic agents from this group of medications bind to secreted cytokines and thus interfere with the development of psoriasis. Tumor necrosis factor α (TNF-α) is a central cytokine for both the persistence of the immune response that maintains psoriasis and for the aberrant keratinocyte response (50). The anti-TNF-α agents *etanercept* and *infliximab* bind to TNF-α and inhibit its activity through two different mechanisms (Figure 4). *Etanercept* (Enbrel®) is a fusion protein using the extracellular domain of the TNF-α receptor to block the circulating TNFα. It is administered subcutaneously and is approved for rheumatic and psoriatic arthritis. *Infliximab* (Remicade®) is a monoclonal antibody directed against human TNF-α and is given intravenously. In psoriatic arthritis trials with etanercept, there was a noticeable response in several patients with cutaneous lesions. Mean improvement in the PASI index was at least 46-50% (42). Likewise, a number of case reports and studies demonstrated an excellent response of psoriatic lesions to *infliximab*, with a more than 75% improvement in the PASI index (51,52).

It should be mentioned that additionally to the four mentioned substances, other similar substances are already available, while more are being developed.

Adverse effects of biological medications

Biologic agents are metabolized similarly to endogenous proteins, therefore severe drug reactions are unlikely. There are two major concerns with biologic therapy that should be addressed. *Cytokine release syndrome* (CRS) has been observed in solid organ transplant patients who were treated with OKT3, which is a humanized monoclonal antibody that binds to CD3, the initial signaling step in the T-cell receptor. CRS evolves due to a rapid release of TNF-α and IFN-γ (53,54). It is potentially life threatening, and is characterized by fever, hypotension, headache, skin rash, and abdominal symptoms (55). *Immunosuppression* is an additional concern. Current evidence indicates that the risk of immunosuppression from biologic agents used in psoriasis exists. One has to consider its use carefully in patients at high risk for malignancy or with diabetes in whom the risk of an infection is increased.

The most common adverse reactions, usually associated with the first dose, are headache, fever, chills, nausea or myalgia. Before starting the treatment it is recommended that baseline laboratory tests are performed, including hepatitis and HIV serology and also the tuberculin skin test (56).

Conclusions

Knowledge of the pathogenesis and new treatment modalities of psoriasis have been substantially expanding during the last two decades. Psoriasis is now considered by many authors to be an autoimmune disease. New therapeutic modalities, especially biological immunomodulators, promise extremely good results, are relatively safe, easy to produce, and will come to take an important place in the future of psoriasis treatment. A certain restraint is probably justified concerning their possible long range effects on the immune system.

alefacept: (Amevive®, Biogen, Cambridge, MA, USA)
efalizumab: (Raptiva®, Genentech, South San Francisco, CA, USA)
etanercept: (Enbrel®, Amgen, Seattle Washington, USA)
infliximab: (Remicade®, Centocor, Malvern, PA, USA)

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