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REVIEW

Trends and Developments in the Pharmacological Treatment of Psoriasis

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INTRODUCTION

In the history of psoriasis pharmacotherapy, the milestone developments have largely occurred by chance. Serendipitous observations in single patients have led to the discovery of such important treatments as methotrexate (1), deltanoids (active form of vitamin D and its analogues) (2), cyclosporin (3) and, most recently, tumour necrosis factor alpha (TNF-α) inhibitors (4). While these observations have been of therapeutic importance, they have also had a major impact on current views on the pathogenesis of this skin disease. From the initial model, where the hyperproliferation of epidermal keratinocytes was considered to be a central event, the current understanding places the immune system at the hub of the pathogenic series of events. Vigorous research and constantly increasing insight into the mechanisms of psoriasis have led to the identification of a number of potential targets for therapeutic intervention. For the first time, the rational, mechanism-based development of new anti-psoriatic therapeutic has become a reality.

The purpose of this article is to present a systematic review of emerging drug therapies for psoriasis that, although in the early stage of development today, may enter the clinical practice of tomorrow. The current, established treatments are not mentioned; readers are referred to recently published excellent reviews on this subject (5–8). The compounds included in this review have been selected from a screening of the Medline records; where references are not cited the information has been obtained from IDdb (Investigational Drugs Database, Current Drugs Ltd., http://www.iddb3.com/) and PharmaProjects (PJB Publications Ltd., 2002

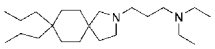
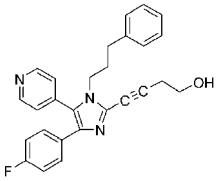
IMMUNOSUPPRESSIVE AND ANTI-INFLAMMATORY DRUGS

The autoimmune cutaneous reaction is believed to play a causative role in the development of skin lesions in psoriasis (9). Most of the compounds under current development for psoriasis belong to different classes of immunosuppressives and anti-inflammatory drugs. The central cell in the current pathogenic model is the memory ($CD45RO^+$) T-lymphocyte mediating the type 1 immune response. A type 1 immune response is mediated by T_H1 and T_C1 lymphocytes secreting a specific cytokine profile (IFN-γ, TNF-α, IL-12). The recently reviewed immunopathogenesis of psoriasis (9, 10) will be mentioned only to the extent necessary for an understanding of the mechanism of action of the drugs included here. The memory T-lymphocytes secrete three major cytokines, IL-2, TNF-α and IFN-γ. IL-2 acts at the early stages of T-cell activation and clone expansion, while TNF-α and IFN-γ have a twofold role: to drive and stabilize the type I immune reaction (11) and by direct action on keratinocytes to stimulate their growth leading to epidermal hyperproliferation (12). The latter aspect is believed to be an aberrant regenerative response of the epidermal stem cells (12, 13).

Immunomodulation. Current therapeutic strategies involve suppression of the type I autoimmune reaction and/or immunomodulation aimed at shifting from the type I to type II immune response. The proof of concept of the latter strategy has been provided in studies demonstrating a beneficial role of type II lymphokines in psoriasis patients. IL-10 (14–16) and IL-11 (17, 18) are type II cytokines whose efficacy has been proved in small, preliminary clinical trials. Another approach is vaccination with killed Mycobacteria (19) or manipulation at the signal tranduction level by affecting the activity of the transcription factors responsible for the T-cell differentiation (GATA 3, HLX, p38 MAPK, junB, c-maf) (20). In particular, the modulation of p38 MAPK can now be accomplished by synthetic molecules. Currently developed immunomodulatory agents are summarized in Table I.

Immunosuppression. Many currently used antipsoriatic

Table I. *Immunomodulatory drugs*

Drug	Status for psoriasis	Mode of action/Remarks
Atiprimod dimaleate (AnorMED) 	Preclinical	Azaspirane immunomodulators of unclear mechanism of action, developed mainly for rheumatoid arthritis. The azaspiranes demonstrated activity in adjuvant arthritis and in several transplant models.
T-cell switch factor (Boston Life Sciences)	Preclinical	Gene therapy targeting the T_H1/T_H2 switch factor, c-Maf. Affects the balance between type 1 and type 2 immune response.
PVAC (Corixa)	Phase II	Heat-killed Mycobacterium vaccae for intradermal administration. Works probably via skewing the immune response towards type 2. A study (21) of 20 patients with moderate to severe psoriasis showed that 65% showed marked improvement in the PASI ($>$50% reduction).
Interleukin-10 (Schering-Plough)	Phase II	A recombinant IL-10 shown to ameliorate psoriasis due to skewing the immune response from type 1 to type 2 (15, 16).
Interleukin-11 (Neumega®) (Wyeth)	Preclinical	Human recombinant interleukin-11 showing promise in the therapy of psoriasis (17, 18).
BIRB-796* (Boehringer-Ingelheim)	Phase II	Selective p38 MAPK inhibitors developed for rheumatoid arthritis, psoriasis and Crohn's disease. In animal models shown to suppress type 1 immune response by inhibiting TNF-α and IL-1β.
RWJ-67657 (Johnson & Johnson) 	Preclinical	
T-cell receptor peptides (Xoma)	Preclinical	Synthetic T-cell receptor peptides for the treatment of autoimmune diseases, mostly multile sclerosis. The peptides suppress specifically the activity of pathogenic T-lymphocytes.

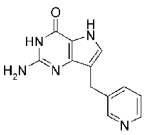
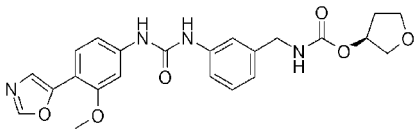
*Chemical structure not disclosed.

esters, azathioprine or mycofenolate mofetil belong to this group. Although, as described below, current efforts aim at the development of specific immunosuppressive drugs, there is also considerable new progress within the non-specific immune-suppressing agents (Table II). Ascomycins and tacrolimus, whose mechanism of action resembles that of cyclosporin (22), have been developed for topical use in inflammatory skin diseases. They seem to work in atopic dermatitis, but their activity in psoriasis is relatively low and requires occlusion for optimal efficacy (23). These drugs might be useful, however, for certain clinical types of psoriasis, such as inverse psoriasis, where preliminary evidence of topical tacrolimus has been presented (24). An interesting development in systemic immunosuppressive drugs has been the introduction of purine nucleoside phosphorylase (PNP) inhibitors (25). PNP is essential for T-cell proliferation and cellular immune response. Currently

autoimmune diseases and Crohn's disease and the antipsoriatic activity has not been tested in clinical trials. Other systemic immunosuppressive drugs with their mechanisms of action are summarized in Table II.

The main effort of most of the pharmaceutical industry has been towards the development of specific immunosuppressive agents. Recent developments in biotechnology, such as the large-scale production of humanized, primatized or purely human antibodies (27), and advances in the anti-sense approach (28) have made the development of such agents possible. The easiest but least attractive way is to delete the subpopulation of T-cells participating in the autoimmune reaction. Selective T-cell depletion, such as that achieved by a fusion toxin protein DAB_{389}IL-2 (depletion of activated T-cells expressing IL-2 receptor) works, but the side effects are severe and prolonged immunosuppression

Table II. *Non-specific immunosuppressive and cytostatic drugs*

Drug	Status for psoriasis	Mode of action/Remarks
A-86281 (ABT-281) (Abbott)	Phase I	Immunosuppressive ascomycin analogue.
Pimecrolimus (SDZ ASM 981) (Novartis)	Phase II	Same as above. Pimecrolimus has now been registered for the topical use in atopic dermatitis.
Sirolimus (Rapamycin) (Wyeth Ayerst)	Phase II	Immunosuppressive macrolide antibiotic, blocker of S6 kinase. Clinical effect in psoriasis in combination with cyclosporin (26).
Paclitaxel gel (Angiotech)	Phase II	Well-known drug in oncology, β-tubulin antagonist. Probably anti-psoriatic activity in topical application.
BCX-1777* (BioCryst Pharmaceuticals)	Preclinical	Purine nucleoside phosphorylase antagonist.
Paldesine (BioCryst Pharmaceuticals) 	Phase II	Purine nucleoside phosphorylase antagonist.
Merimempodib (Vertex pharmaceuticals) 	Phase II	A small molecule inositol-5-monophosphate (IMPDH) inhibitor. Like azathioprine and mycofenolate mofetil (both currently used for psoriasis) merimempodib is a blocker of the de novo synthesis of guanosine nucleotides selectively in lymphocytes.

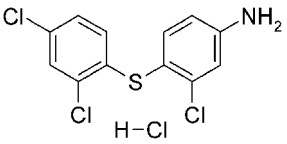
*Chemical structure not disclosed.

function blocking of T-cells. This has been achieved mostly by directly targeting the critical surface proteins involved in the process of T-cell activation or by blocking the critical type I cytokines. Targeted surface molecules are mostly those involved in the interactions between T-cells and antigen-presenting cells (Table III). An approach that has already shown promise is the function blocking of type 1 cytokines (31, 32). During the immune response, there seems to exist a positive feedback loop of type I cytokines where IL-12 augments IFN-γ release; IFN-γ in turn stimulates TNF-α release and TNF-α upregulates itself (33). IL-6 is another pro-inflammatory lymphokine involved in type I immune reactions and overexpressed in psoriasis (34, 35). Drugs neutralizing type I cytokines, such as TNF-α, are listed in Table IV.

Several of the compounds listed in Tables III and IV have already shown considerable clinical efficacy in well-designed clinical studies. In a phase II multi-centre study on 145 patients, efalizumab (Xanelim®) brought about an improvement of more than 50% in the physician's global assessment after 8 weeks of treatment in 48% of patients treated with anti-CD11a antibodies. Biogen's alefacept (Amevive®) soon to be registered for psoriasis also showed a marked clinical effect in a placebo-controlled study involving 229 patients (36). The mean reductions in PASI were 38%, 53% and 53%, respectively, in the active groups compared to 21% in the placebo groups after 12 weeks of treatment intravenously. Alefacept caused a similar correlated decrease in $CD45RO^+$ cells. Infliximab (Remicade®) and etanercept (Enbrel®) (both anti-TNF-α) are in phase III clinical studies (31, 32) and etanercept has recently been approved for the treatment of psoriatic arthritis.

An ingenious approach to the treatment of autoimmune diseases is a selective deletion or function-blocking of the autoreactive clone only. Methotrexate seems to work in part via the induction of selective apoptosis within the pool of autoreactive lymphocytes; however, a search for a methotrexate analogue devoid of the side effects has been unsuccessful. Another way is the blocking of T-cell antigen receptor (TCR) taking advantage of the fact that autoreactive T-cells in psoriasis are oligoclonal (44, 45). Several companies are working on small blocking peptides selectively binding to the Vα

Table III. *Targets for drugs inhibiting T_H1 and T_C1 cells*

Surface protein	Comment	Targeting compound, status for psoriasis
TCR	Antigen receptor, crucial for the initiation of immune response. Binds to MHC-I or MHC-II on APC.	**Zorcell** (Immune Response): a combination of two T-cell derived peptides in Freund's adjuvant believed to inactivate autoreactive T-cells. Phase II. **T-cell receptor peptides** (Xoma): synthetic TCR peptides suppressing the activity of autoreactive T-cells. Preclinical.
CD2	Binds to LFA-3 on APC. Activated during proliferation and differentiation of T-cells.	**Alefacept** (Amevive®; Biogen): LFA-3/IgG1 fusion protein. Prevents T-cell activation by binding to the CD2 receptor on memory effector T lymphocytes. Activity proven in clinical studies and soon to be launched (36). **Siplizumab** (Biotransplant): Humanized anti-CD2 antibody. In preliminary phase II clinical 70% of patients experienced at least 25% improvement in PASI. Phase II.
CD3	A component of the TCR protein complex on all T-lymphocytes.	**Visilizumab** (Protein Design): A probably discontinued anti-CD3 antibody, anecdotal evidence of therapeutic activity in psoriasis (37).
CD4	A component of the TCR protein complex on TH.	**HuMax-CD4** (Genmab): Human monoclonal anti-CD4 antibody. In a preliminary phase II study, 85 patients received 4 weekly subcutaneous injections of the antibody in 4 concentrations. 38% patients obtained $>25\%$ reduction in PASI, 19% obtained $>50\%$ reduction (38). **HumaT4** (Intracel): A human Fab fragment against CD4, preclinical development for the treatment of various autoimmune diseases **OKT(R)cdr4a** (Ortho): A probably discontinued, non-depleting anti-CD4 humanized antibody. A study on 6 patients with recalcitrant plaque psoriasis showed the mean decrease in PASI score by 46% (39).
CD8	A component of the TCR protein complex on T_C.	**ß2 microglobulin** (Avidex): ß2 microglobulin modified to block CD8 binding. Preclinical developed for autoimmune diseases.
CD28	Binds to CD80 and CD86 on APC. Activated during proliferation and differentiation of T-cells.	**IDEC-114** (IDEC): anti-B7-1, primatized antibody genetically engineered from *Cynomolgus* macaque monkey and human components. Clinical phase II trials ongoing.
CD40L	Binds to CD40 on APC. Activated during proliferation and differentiation of T-cells.	**5D12** (Chiron): Humanized, anti-CD40 antibody under preclinical development for various autoimmune diseases. **IDEC-131** (IDEC): Antibody against tiGp39 that is expressed on CD4 cells and serves as a ligand for CD40. Clinical phase II trials ongoing.
LFA-1	Consists of 2 proteins: CD11a and CD18. Binds to ICAM-1 on APC. Involved in the initiation of the immune response.	**Efalizumab** (Xanelim®; Genentech): Humanized monoclonal antibody against CD11a subunit of LFA-1. In a recent double-blind, placebo-controlled, phase II, multicenter study (40) on 145 patients with moderate psoriasis 48% of patients achieved $>40\%$ improvement when the drug was administered intravenously in 8 weekly doses of 0.3 mg/kg. Progressed to phase III. **IC-747 (ICOS)**  Orally-active synthetic compound able to block LFA-1 (CD18/CD11a) and ICAM-1. Phase II.
CTLA4	Binds to CD86 on APC. Activated during proliferation and differentiation of T-cells.	**BMS-188667** (Bristol-Myers): Chimaeric immunosuppressant antibody against B7. No results from clinical trials on psoriasis reported, but in phase II for several autoimmune diseases.

TCR: T-cell receptor, APC: antigen presenting cells.

another autoimmune disease, multiple sclerosis (46). No reports are yet available on the use of TCR-binding peptides in psoriasis.

Inhibition of chemotaxis and tissue migration. Reactive lymphocytes and leucocytes infiltrate the skin due to assist in cell activation and stimulate the expression of several adhesion molecules involved in the interaction between the leucocytes and the endothelia (extravasation) or the target tissue. Because of the importance in other autoimmune and infectious diseases (e.g. HIV infection) there is extensive research within the field of

Table IV. *Type 1 cytokines as targets for new drugs*

Lymphokine	Function	Targeting compounds, status for psoriasis
IL-2	Proliferation and T-cell differentiation during the type-1 immune response.	**Basiliximab** (Simultec®; Novartis): A probably discontinued anti-IL-2 receptor antibody; case reports on the favourable effect of basiliximab in psoriasis (41, 42). **Daclizumab** (Protein Design): A humanized anti-IL-2 receptor chain launched for the treatment of organ transplant rejection. A small clinical study on 19 patients with psoriasis daclizumab was administrated at weeks 2, 4, 8 and 12. A 30% reduction in PASI was detected at 8 weeks (43). Phase II. **Denileukin diftitox** (Ligand): A fusion toxin composed of human interleukin-2 and fragments of diphtheria toxin (DAB_{389}IL-2). Two papers (29, 30) on a total of 33 patients showed beneficial effect of this antibody; however, the treatment was associated with severe side effects and therefore probably discontinued.
IL-6	A pro-inflammatory cytokine synthesized in the epidermis.	None available.
IL-12	Released from antigen presenting cells and T-cells. Stimulates immune response maturation into the type 1. Blocks keratinocyte apoptosis.	None available.
IL-15	Pro-inflammatory cytokine synthesized by keratinocytes and upregulated in psoriasis. Blocks apoptosis of keratinocytes.	**Anti-IL-15 Mab** (Genmab): Monoclonal human anti-IL-15 antibody in preclinical developed for autoimmune diseases.
IL-20	A homolog of IL-10. IL-20 and its receptor is upregulated on psoriatic keratinocytes; considered to be a pro-inflammatory cytokine.	**IL-20 antagonists** (ZymoGenetics): synthetic inhibitors, structure not disclosed. Preclinical.
IFN-γ	Type-1 lymphokines secreted by T_C1, T_H1 and macrophages.	**Anti-γIFN** (Protein Design): Monoclonal humanized antibody neutralizing IFN-γ in phase I for psoriasis and Crohn's disease. Clinical efficacy in psoriasis unknown, but promising results in Crohn's disease. Preclinical.
TNF-α	Type-1 lymphokines secreted by T_C1, T_H1 and macrophages.	**Etanercept** (Enbrel®; Immunex): Potent anti-psoriatic activity in a randomized, double-blind, placebo-controlled, study on 60 patients with psoriatic arthritis and psoriasis (13) 26% of etanercept-treated patients achieved a 75% improvement in the PASI; the median PASI improvement was 46%. Launched for psoriasis arthritis. **Infliximab** (Remicade®; Johnson & Johnson): A monoclonal antibody against TNF-α. In a double-blind, placebo-controlled study (31) on 33 patients with moderate to severe plaque psoriasis, 82% showed a good or excellent response. Probably soon launched for psoriasis. **ISIS-104838** (ISIS): A second-generation antisense TNF-α inhibitor as an anti-inflammatory for the treatment of rheumatoid arthritis (RA), psoriasis (topical cream) and Crohn's disease. Phase II. **UR-1505** (Uriach): A small molecule blocker of TNF-α synthesis (structure not disclosed). Claimed to inhibit the mice oxazolone-induced delayed hypersensitivity (topically) and rat adjuvant-induced arthritis (oral). Preclinical.

of selective drugs (which may be considered both anti-inflammatory and immunosuppressive) is complicated by the fact that leucocyte chemokinesis is governed by a complicated network of many, partly redundant, chemokines and their receptors. Neutrophil chemokinesis is mainly affected by IL-8 and GRO-α, both of which bind to the receptor CXCR2 (48). Pilot studies with the humanized anti-IL-8 antibody have shown a significant clinical effect (10, 55). The lymphocyte-attracting chemokines are less well investigated and fall into two major families. Many of these chemokines are detectable in significant quantities in psoriasis lesions and are believed to be important (Table V). The chemokine-targeting drugs have been developed but none have been tried in psoriasis.

Migration of lymphocytes to the tissue is accomplished with the help of adhesion molecules, usually classified within three major groups: 1. selectins (E, P, L selectins), 2. adhesion molecules from the immunoglobulin superfamily (ICAM-1, ICAM-2, VCAM-1) and 3. integrins (including

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