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New Drugs in the Management of Psoriasis

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For many years psoriasis was considered a disorder of keratinocyte proliferation with secondary inflammation. In line with this idea mainstream antipsoriatic therapy had focused on antiproliferative (and anti-inflammatory) agents for example vitamin D analogues, retinoids, corticosteroids, anthralin, tar and UV therapy. In recent times psoriasis has become recognized as a primarily inflammatory disorder induced by skin infiltrating T lymphocytes with a secondary hyperproliferation of keratinocytes.

A battery of novel drugs has been established which work by modulating and down regulating immune responses, and for the most part are aimed at suppressing T cell function. These new drugs can be classified according to their mechanism of action (i.e. how exactly they modulate/down-regulate the immune response). This review aims to give the reader a general overview of the categories of novel antipsoriatic drugs now available with particular emphasis on some of the more important examples.

Four novel drugs have either been approved for use in the treatment of psoriasis or are soon to be approved:

1. Alefacept (LFA3TIP), *blockade of costimulatory signals*[1,2]. The co- stimulatory signal (signal 2) is provided primarily by binding or pairing between cell-surface molecules on naive T cells and antigen presenting cells (APCs). A protein molecule on the surface of the APC binds to a protein molecule on the surface of the T cell. Receptor pairs important in generating signal 2 are LFA-3/CD2, CD80/CD28 and LFA-1/ICAM-1. Interference with receptor–pair binding can disrupt signal 2, preventing T-cell activation. Without signal 2, T cells cannot be activated and may become anergic and eventually die. Alefacept blocks signal 2 by preventing LFA3-CD2 interaction. It is well tolerated and leads to significant clinical improvement. It can be administered by intravenous or intramuscular injection weekly for 12 weeks. It has been approved for the treatment of moderate to severe chronic plaque psoriasis in the USA.

2. Efalizumab (anti-CD11a-Ab), *blockade of initial T-cell activation*. Efalizumab is a humanized monoclonal Ig G antibody. It binds to CD11a, the alpha-subunit of leucocyte function associated antigen -1(LFA-1) that is expressed on the surface of T-cells[3]. Anti-CD11a antibody inhibits the costimulation of T cell activation, and is thought to prevent T cells from entering psoriatic lesions by blocking the interaction

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with ligands on keratinocytes and endothelial cells. Efalizumab, which was recently approved for the treatment of psoriasis in the USA and Europe, is applied as weekly subcutaneous injections that offer the possibility of self-medication at home. It shows a faster initial clearance rate than alefacept, but not comparable remission after the end of treatment.

3. Infliximab, *immunosuppression, blockade of effector cytokines*[4].
As psoriasis is induced and maintained by a complex pattern of overexpressed T helper 1 (Th1) cytokines such as IL-2, -6, -8, IFN-gamma and TNF-alpha, cytokine balance can be restored by blocking these important signals. Inflixmab is an antibody against TNF-alpha that neutralizes both soluble cytokine as well as blocks the membrane-bound cytokine. Administered intravenously it has been shown to cause rapid improvement in psoriasis and psoriatic arthritis as early as two weeks after initiation up to four weeks after the last infusion. Adverse effects reported include cardiac decompensation and appearance of antinuclear antibodies. As with other immunosuppressants caution must be taken when treating patients with infection.

4. Etanercept, *immunosuppression, blockade of effector cytokines.* Etanercept functions as a competitive inhibitor for binding of TNF-alpha at its receptor[5]. It has been approved for the treatment of psoriatic arthritis in the USA and Germany. Reasonable therapeutic results are achieved with etanercept, although infliximab has an even better effect. This could be attributed to the different routes of administration (infliximab i.v. vs. etanercept s.c.) or to the ability to achieve cell lysis (infliximab can, etanercept cannot). Infliximab is however still undergoing clinical trials.

There are numerous other drugs that are currently undergoing clinical trials for the treatment of psoriasis. They achieve clinical improvement by a variety of mechanisms all of which are aimed at modulating or suppressing the immune system. A brief description of some of these drugs now follows:

Mycophenolate mofetil (MMF) is the morpholinoethylester prodrug of mycophenolic acid (MPA). MPA blocks the de novo synthesis of guanosine nucleotides, and therefore cells such as lymphocytes which rely primarily on the de novo synthetic pathway of DNA are mostly affected[6]. MPA has shown good results in the treatment of psoriasis but enthusiasm for it is limited in some quarters by virtue of its severe GIT adverse effects and suggestions of carcinogenicity.

MEDI 507 (Siplizumab) is a humanized monoclonal antibody to CD2. By targeting the LFA3-CD2 signalling pathway MEDI 507 causes a selective depletion of antigen-specific activated T cells. Thus far results have been promising and adverse effects only mild to moderate[7].

Immunosuppressant agents such as tacrolimus (FK506), pimecrolimus and sirolimus which are used for the prevention of kidney and liver transplant graft rejection are currently being tested in clinical trials for the treatment of psoriasis[8].

Other miscellaneous agents currently being tested include recombinant cytokines e.g. the anti-inflammatory cytokines IL-4, IL-10, and IL-11[9].

Peptide T, a component of gp120 the envelope glycoprotein of HIV, interferes with T cell function by binding to CD 4 and also appears to block the monocyte and lymphocyte chemotactic properties of RANTES, a beta-chemokine found in increased amounts in psoriatic skin[10]. Early results in the treatment of psoriasis are promising especially when taken intranasally.

CONCLUSION

As a result of improved understanding of the pathogenic processes involved in psoriasis researchers have been able to develop a broad range of novel pharmaceutical agents that interfere with specific immunological pathways and lead to amelioration of psoriatic lesions. Such new rational approaches in the therapy of psoriasis are urgently needed as current treatments have limitations, for example, carcinogenic potential and skin aging with UV therapy, nephrotoxicity and hypertention with cyclosporine and hepatotoxicity with methotraxate. Currently the most advanced and promising biological agents are alefacept, efalizumab, etanercept and infliximab.

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