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## REPORT

# Psoriasis treatment: current and emerging directed therapies

L S Winterfield, A Menter, K Gordon, A Gottlieb

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Quality of life studies in patients with cutaneous psoriasis attest to its significant impact on day to day activities and personal social interactions. Up to 40% of patients with psoriasis may develop psoriatic arthritis, usually within 5–10 years after onset of the cutaneous disease, heightening quality of life issues. These data have prompted an increased awareness and interest in more aggressive management of psoriasis; coupled with a better understanding of immunopathogenesis, this has led to the development of new agents targeting specific cells and molecules involved in the development and maintenance of psoriatic plaques. Although non-biological therapies, including methotrexate and ciclosporin, show significant efficacy their side effect profiles have precluded their long term use for moderate to severe psoriasis. This review concentrates on new biological agents, focusing on the three agents approved for psoriasis within the past 18 months (alefacept, efalizumab, and etanercept). Phase II and III trial data on other agents in development (adalimumab and infliximab) are also presented. Surveys show many patients want to be treated more aggressively. It is hoped that the introduction of new agents that are more targeted and that hold the promise of fewer side effects will cause patients and their physicians to reconsider systemic treatment and, as a consequence, stimulate other patients to reconsider treatment for psoriasis. Close cooperation between dermatologists and rheumatologists, particularly in the area of psoriatic joint disease, will enhance these considerations.

Psoriasis vulgaris is a lifelong, chronic, immune mediated, inflammatory skin condition affecting approximately 2% of the general population.<sup>1</sup> Although there are several clinical variations of psoriasis, the typical skin lesions are well defined, red, indurated plaques with silver, micaceous scale. The clinical features of plaque psoriasis vary due to many factors, including chronicity of disease, size of the lesions, body sites, percentage of body surface area (BSA) involved, symptomatology, such as pruritus, burning, or pain, associated joint disease, and prior therapy.<sup>2</sup> Psoriasis commonly presents before the age of 35 years and has no known cure. Quality of life issues in psoriasis often exceed those of many of the chronic diseases.<sup>3</sup>

## MEASURING SEVERITY OF DISEASE

The US Food and Drug Administration (FDA) defines mild, moderate, and severe psoriasis based on BSA involvement, arbitrarily defining “severe” disease as involving 20% or more of the patient’s BSA. To measure therapeutic benefit for the recently approved “biologicals”, the FDA has encouraged the use of change in the Psoriasis Area and Severity Index (PASI) to assess efficacy. PASI is a composite scoring system that

takes into account lesional erythema, induration and scale, and the BSA affected in four specific body regions (head and neck, trunk, and upper and lower extremities). However, recent studies have shown that BSA and PASI do not correlate well with the impact of the disease on patients’ quality of life.<sup>4–8</sup> In response to these findings, the Medical Advisory Board of the National Psoriasis Foundation proposed new criteria for the classification of mild, moderate, and severe disease that include the impact of disease on patients.<sup>9</sup> It is felt that the criteria set forth—which are largely quality of life based—should be the primary consideration when determining the therapeutic regimen for a given patient.

## IMMUNOLOGY

Observations from animal models of psoriasis and treatment with T cell specific inhibitors, such as ciclosporin, point to T cells as the driving force in inducing and maintaining the phenotypic changes seen in psoriasis.<sup>10–19</sup> This concept is supported by histological and immunohistochemical examinations of lesional skin, which reveal infiltration of T lymphocytes in the dermis and epidermis. The T cell infiltrate is primarily activated by memory effector T cells.<sup>20–21</sup> To reach the effector state, T cells must first be activated by antigen presenting cells (APCs), such as dendritic cells. The specific antigen(s) involved in the interaction between T cells and APCs, apart from a few infections, such as streptococcal, are unknown. Further details of the pathogenesis of psoriasis are discussed in this supplement by Krueger and Bowcock.<sup>22</sup>

## BIOLOGICALS

Elucidation of the immunopathogenesis of psoriasis has led to the emergence of new therapies targeting the immune cells and molecules that induce and maintain the clinical changes seen in psoriatic plaques. Biological agents are proteins derived from recombinant DNA technology, hybridomas, blood, and whole human cells. In psoriasis, these agents are designed to specifically interfere with T cell activation and effector functions. Many of these drugs are also effective in treating psoriatic arthritis (PsA).

Several strategies are used to block the induction or maintenance of T cell activation in psoriatic disease.<sup>23</sup> The first is to reduce the number of pathogenic T cells. Alefacept employs this strategy. It is a fusion protein composed of leucocyte function associated antigen (LFA)-3 with the Fc portion of human IgG. Alefacept binds to CD2 on T cells to block costimulation or signal 2 by preventing CD2 from binding LFA-3 on APCs.<sup>24–26</sup> It also triggers apoptosis of activated memory T cells expressing high levels of CD2 via binding of FcγRIII IgG receptors on natural killer cells and macrophages.<sup>27</sup> Alefacept has been approved by the FDA for

**Abbreviations:** APC, antigen presenting cell; BSA, body surface area; FDA, Food and Drug Administration; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis

the treatment of moderate to severe psoriasis as a 12 week course of 15 mg weekly intramuscular injections. In clinical trials of a 12 week course of therapy, 33% of patients achieved PASI 75 (75% improvement in baseline PASI score) and 57% of patients achieved PASI 50 at some time during the 24 week study period.<sup>28</sup> A proportion of responding patients enjoyed long remissions from their psoriasis. Alefacept has also been shown to decrease synovial tissue T cell and macrophage infiltration in PsA.<sup>29</sup> The most significant laboratory abnormality with this medication is reduction of the CD4 count, with a theoretical concomitant increased risk of infection. However, no increases in infections have been seen in clinical trials of alefacept. Nonetheless, in clinical practice, patients are monitored with weekly CD4 counts while on the drug. The weekly dose is withheld for a CD4 count of less than 250 cells/ $\mu$ l, and therapy is discontinued if the CD4 count remains below 250 cells/ $\mu$ l for more than four weeks. A second course extends the period of remission without additional risk of adverse events. Preliminary data show that concomitant ultraviolet light appears to speed the response and that extending the dose to 16 weeks causes more patients to have clinically meaningful improvement.

The second strategy is blockade of T cell activation and/or migration. Efalizumab is a humanised monoclonal anti-CD11a antibody that binds to the CD11a portion of human LFA-1 and blocks the LFA-1/intercellular adhesion molecule (ICAM) interaction, thus blocking both signal 2 and T cell migration.<sup>30–32</sup> Response to efalizumab has also recently been shown to correlate with a decreased number of dendritic cells.<sup>33</sup> Efalizumab has been approved by the FDA for the treatment of moderate to severe psoriasis. In phase III clinical trials, 27% of patients who were given efalizumab as a 1.0 mg/kg weekly subcutaneous injection for 12 weeks achieved PASI 75.<sup>34</sup> Efalizumab has not been shown to be effective in treating PsA. The commonest side effects were headache, chills, fever, nausea, vomiting, or myalgia occurring on the day of injection or in the following two days during the initial three weeks of therapy. Adverse effects associated with this drug are a “rebound” phenomenon post discontinuation of therapy (14% of patients) and a worsening of disease in unresponsive patients during therapy. In some cases, the rebound may present as a different clinical subtype of psoriasis.<sup>35</sup> Careful monitoring of unresponsive patients, especially during weeks 6–12 of therapy, as well as transitioning patients to alternative forms of therapy while slowly tapering efalizumab, may minimise this risk. In open trials, continuous weekly treatment data show that nearly 44% will achieve a 75% reduction in PASI by 24 weeks.

The third strategy for biological agents to treat psoriasis involves induction of immune deviation, a shift from T cell production of T helper (Th) 1 to Th2 type cytokines. T cells in psoriasis produce a predominantly Th1 cytokine profile.<sup>36</sup> Theoretically, inducing a switch from a Th1 to Th2 profile could alleviate psoriatic disease. One approach has been to use Th2 cytokines, such as interleukin (IL)-4, IL-10, or IL-11, to tilt the balance and inhibit the Th1 response. Alternatively, specific cytokine antagonists may prevent T cell differentiation towards the Th1 phenotype. One such antagonist drug is CNTO-1275, an anti-IL-12 p40 monoclonal antibody that inhibits the action of IL-12, a crucial cytokine involved in differentiation of Th1 cells. It also inhibits IL-23, another cytokine recently shown to be involved in the pathogenesis of psoriasis.<sup>37</sup> This drug is currently in early stages of phase II trials.

The final strategy involves inactivation of secreted effector cytokines. Tumour necrosis factor  $\alpha$  (TNF $\alpha$ ) appears to be a critical cytokine for many of the clinical features of psoriasis, including keratinocyte hyperproliferation, endothelial cell

regulation, and recruitment/effector function of memory T cells. Several anti-TNF drugs have been used successfully to treat psoriasis and PsA.

Infliximab, a chimeric anti-TNF monoclonal antibody administered by intravenous infusion, was the first TNF blocker studied for the treatment of psoriasis. Infliximab has been approved by the FDA for the treatment of moderate to highly active rheumatoid arthritis (in combination with methotrexate) and moderate to highly active Crohn's disease or for those patients with Crohn's and rheumatoid arthritis who have failed to respond to conventional treatment. In subsequent placebo controlled trials, infliximab has been given as monotherapy for psoriasis at 3 mg/kg, 5 mg/kg, and 10 mg/kg doses, initiated with an induction regimen of infusions at 0, 2, and 6 weeks, followed by maintenance dosing every eight weeks. At a dose of 5 mg/kg per infusion in the phase II trial, 87.9% of patients achieved a 75% reduction in PASI at 10 weeks.<sup>38</sup> The commonest side effects with infliximab were headaches and infusion reactions, the vast majority of which were classified as mild. Another concern is increased risk of opportunistic infection, especially tuberculosis. Most of the data regarding this risk come from patients with rheumatoid arthritis and Crohn's disease. Patients who are candidates for this treatment must have tuberculosis skin testing prior to the initiation of therapy to avoid reactivation of latent tuberculosis. Additionally, patients should be strongly advised to be vigilant for early signs of infection. Because infliximab is a chimeric antibody, there is the potential for development of neutralising antibodies. Anti-infliximab antibodies were measured in the phase II psoriasis trial (induction therapy at 0, 2, and 6 weeks). At week 26, 27.5% of patients in the 3 mg/kg group and 19.5% of patients in the 5 mg/kg group had detectable antibody titres. The current phase III one year clinical study will help to determine whether infliximab will retain its efficacy as monotherapy over longer periods of time.

Other biological drugs, including those that are “humanised” or “fully human” also exhibit some immunogenicity when administered to human patients; the clinical relevance of antibody development to each of these drugs remains to be determined in long term studies.

Etanercept is a TNF $\alpha$  receptor fusion protein administered by twice weekly subcutaneous injection. It is the only anti-TNF drug currently approved by the FDA for the treatment of cutaneous psoriasis. It is also approved for the treatment of rheumatoid arthritis, ankylosing spondylitis, juvenile rheumatoid arthritis, and PsA. In clinical trials, etanercept administered at a dose of 25 mg subcutaneously twice weekly achieved a PASI 75 of 30–34% at 12 weeks and 44–56% at 24 weeks.<sup>39–40</sup> At a dose of 50 mg subcutaneously twice weekly, the PASI 75 response increased to 49% at 12 weeks and 59% at 24 weeks.<sup>40</sup> The commonest side effect of etanercept was reaction at the site of injection. As with other anti-TNF drugs, the potential increased risk of infection is a concern. In controlled trials, the rates of infections were not different from those in patients treated with placebo or methotrexate.<sup>38–41–42</sup> However, post marketing surveillance has included reports of serious and, rarely, fatal infections in patients treated with anti-TNF agents.

Adalimumab is a fully humanised anti-TNF monoclonal antibody administered as 40 mg subcutaneously once every other week. It has been approved by the FDA for the treatment of rheumatoid arthritis. Recently completed phase II clinical trials in the treatment of psoriasis showed impressive PASI responses, with 53% of patients on 40 mg every other week and 80% of patients on 40 mg weekly achieving a 75% reduction in the PASI.<sup>43</sup>

Onercept is a recombinant, unmodified, fully human soluble type I p55 TNF $\alpha$  receptor. It is administered as a

150 mg dose subcutaneously three times a week. In phase II psoriasis trials, 54% of patients achieved a PASI 75 after 12 weeks of therapy.<sup>44</sup> Phase III trials are currently underway.

## RETINOIDS

Acitretin is an oral retinoid approved for the treatment of psoriasis. It is most effective as monotherapy for pustular psoriasis, rather than for chronic plaque, guttate, or erythrodermic psoriasis.<sup>45</sup> Acitretin has not been shown to be effective in treating PsA. The initial dose of acitretin monotherapy is 25–50 mg per day.<sup>46</sup> Acitretin may be combined with phototherapy (UVB or PUVA),<sup>47–49</sup> topical calcipotriene,<sup>50</sup> oral methotrexate, or ciclosporin. Like all retinoids, it is highly teratogenic and is pregnancy category X. Acitretin has a serum half-life of 50 hours, but concomitant consumption of ethanol and acitretin may cause acitretin to be converted to its prodrug etretinate. Etretinate can be detected in the serum for up to two years, posing long term risk of teratogenicity. Therefore, acitretin should not be administered to women who may not be reliably compliant with contraception for three years after cessation of the drug. In women of childbearing potential, isotretinoin, a retinoid with a much shorter half-life, may be given at doses of 1.5 mg/kg/day. Side effects associated with these drugs include cheilitis, skin peeling, alopecia, xerosis, rhinitis, nail dystrophy, epistaxis, sticky skin, retinoid dermatitis, myalgias, pseudotumour, hyperostosis, decreased night vision, slowed wound healing, hyperlipidaemia (25–50%), hepatotoxicity (33% of patients show transient increase in liver function tests), and gastrointestinal symptoms. Unlike with isotretinoin, depression has not been reported in association with acitretin. The efficacy of isotretinoin for psoriasis has not been studied, either singly or in combination, under controlled and properly powered studies.

Oral tazarotene is a newer retinoid under evaluation for the treatment of moderate to severe psoriasis. It is administered as a daily dose of 4.5 mg. In clinical trials, oral tazarotene shared only a few of the retinoid associated mucocutaneous side effects—for example, cheilitis. It also showed no dose related effect on liver function tests and serum lipids.<sup>51–52</sup> There has been no reported association with depression; with a short half-life (6.68–11.8 hours), it may reduce the concern of long term teratogenicity, allowing women of childbearing potential access to retinoid therapy with appropriate pregnancy prevention programmes.<sup>51 52</sup>

## OTHER THERAPIES

Systemic therapies that have not been approved by the FDA are used less commonly in the treatment of psoriasis. These include hydroxyurea,<sup>53</sup> mycophenolate mofetil,<sup>54</sup> 6-thioguanine,<sup>55</sup> sulfasalazine,<sup>56</sup> and azathioprine,<sup>57</sup> as monotherapy or in combination—on rotational or sequential regimens.<sup>58</sup>

Topical immunomodulators (pimecrolimus and tacrolimus) offer an advantage over corticosteroids for treating intertriginous and facial skin. They avoid cutaneous atrophy and acneiform eruptions that are likely to occur with corticosteroid use.<sup>59–61</sup>

## Phototherapy

UV light is thought to exert its immunomodulatory effects via acute and subacute changes. Acutely, it induces membrane damage, production of cytoplasmic transcription factors, and isomerisation of urocanic acid. Subacute changes include alteration of the APC population and modification of cell–cell signalling. The general effect is a shift in the cytokine profile from Th 1 to Th 2 type cytokines.<sup>62</sup>

Phototherapy, PUVA or UVB, is commonly used in combination with other systemic treatments, particularly

retinoids,<sup>45 46 63 64</sup> which may in fact help reduce the potential for skin cancer inherent in phototherapy. Methotrexate has also been used in combination with UVB and PUVA.<sup>65 66</sup> Combination regimens employing the biological agents with phototherapy may also yield additive or synergistic effects. Further information on phototherapy and other traditional forms of PsA treatment can be found in this supplement in the report by Lebwohl *et al.*<sup>67</sup>

## FUTURE DIRECTIONS

Research in the past decade has brought much progress in the understanding of the immunopathogenesis and genetics of psoriasis, leading to the development of more targeted therapies. Systemic biological agents that target T cells and cytokines offer new hope to psoriasis patients who suffer significant impact on their quality of life. In addition to biological agents, there are many other promising therapeutic strategies including angiogenesis inhibitors, new retinoids, oral pimecrolimus, lasers, and photodynamic therapies. As further research identifies new therapeutic targets, collaboration between scientists, clinicians, industry, and patients will continue to advance our understanding of this disease and significantly improve the quality of life of our patients.

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