Review

Biologic therapy for psoriasis

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Psoriasis is an common inflammatory skin disease that affects approximately 1.5% of the world's population. It is considered to be a chronic condition although its course may be variable with relapses and remissions[1]. Most patients require lifelong treatment after diagnosis. Chronic plaque psoriasis is the most common form of the disease (85 – 90% of cases) and is characterised by red, scaly plaques most commonly on the extensor surfaces of the limbs, and scalp but any skin surface can be affected.

Psoriasis can be graded by the amount of surface area affected, disease activity, response to therapy and the impact of the disease on the individual. Moderate to severe psoriasis can cause significant morbidity including limited movement, painful skin fissures and pruritus and although rarely life-threatening it can have a major psychological impact on an individual's quality of life[2]. Notably, the results of a questionnaire revealed that patients with psoriasis reported reduction in physical and mental functioning similar to that observed in patients with other major medical illnesses, including heart disease, diabetes and depression[6]. Most patients (75%) have mild disease and can be treated satisfactorily with topical therapy which includes emollients, vitamin D analogues, coal tar and dithranol.

Approximately 25% of patients have moderate to severe disease that requires photo- and/or systemic therapy[5,7]. The most frequently used systemic therapies for these patients include ciclosporin, methotrexate, oral retinoids, phototherapy (PUVA) and, increasingly, narrow band UVB[10]. Traditional systemic therapy for psoriasis is limited by insufficient clinical response, lack of long-term efficacy, contraindications and importantly the long-term side-effect profile of the medications used[4]. Despite phenotypically similar appearances of disease among patients, response to therapeutic modalities is variable even for different plaques on a single patient[8]. In a recent survey of patients with severe psoriasis, 79% reported that psoriasis had a negative impact on their lives, 40% felt frustration with current treatments, and 32% did not perceive their treatment to be sufficiently aggressive[3]. In another survey of 120 patients with psoriasis, nearly 40% reported intentional non-compliance with their prescribed psoriasis treatments[9]. It is therefore important that multiple and new treatment options are available for this group of patients.

Due to advances in knowledge concerning the pathophysiology of psoriasis over the last two decades, development of new, relatively selective, pharmacological and biologic therapies have been developed. Several such agents targeting specific immunological processes involved in the pathogenesis of the disease can provide significant clinical benefit to psoriasis sufferers. In addition, biologic therapies have been used and are in development for other disease areas such as Crohn's disease, rheumatoid arthritis and other inflammatory arthritides.

The objective of this article is to evaluate the potential role of targeted biologic agents for the treatment of moderate to severe chronic plaque psoriasis.

Immunology of psoriasis

Advances in the last two decades have led to a marked change in our views regarding the pathogenesis of psoriasis. Previously it was assumed that epidermal keratinocyte hyperproliferation associated with loss of differentiation was the primary cause and any inflammation coincidental. Although the aetiology and pathogenesis of psoriasis are still not fully understood there is substantial evidence to support a primary role of the immune system particularly relating to the roles of T-cells and cytokines[11-14]. The serendipitous finding that ciclosporin improved psoriasis in patients receiving the drug for treatment of arthritis provided the first evidence of T-cell involvement[15]. Other findings included the discovery that targeted pathogenic probes such as denileukin diftitox (DAB389 IL-2) a fusion protein that specifically targets and lyses activated T-cells resulted in clinical

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improvement[16]. More recently the development of an animal model for psoriasis provided additional evidence that T cells were central to the pathogenesis of the disease[17].

There are two populations of T cells in plaques of psoriasis: dermal cells (primarily CD4+ cells) and epidermal T-cells (predominantly CD8+ cells). T-cells are activated and migrate preferentially to the skin from the peripheral circulation consequent on expression of cutaneous lymphocyte associated antigen (CLA) which facilitates binding to E-selectin on dermal vessels. For these T cells to subsequently drive the formation of psoriatic plaques they must undergo 3 critical steps:

1. binding to antigen presenting cells (APCs);
2. recognition of antigen through the T-cell receptor (signal 1);
3. activation of costimulatory pathways (signal 2)[18]

Currently the identity of any specific psoriasis antigen has not been established. In the epidermis APCs internalise and enzymatically process antigen. Subsequently, major histocompatibility complex (MHC) molecules present fragments of degraded antigen on the APC surface to the T-cell receptor. These APCs then migrate to draining lymph nodes where they initiate clonal expansion of a population of activated memory-effector (CD45RO+) T cells. Step one occurs only once. Steps 2 and 3 repeat thereby resulting in the cyclic persistence of psoriasis[19].

What are biologies?

Biologic agents are proteins that possess pharmacological activity. These can be extracted from animal tissue or, much more commonly, synthesised in large quantities through recombinant DNA techniques[20]. Biologics have been used in other specialities of medicine for many years; the most commonly used biologic therapy being insulin. Biologies can be designed to either mimic the actions of normal human proteins or to interact with circulating proteins or cellular receptors. There are three types of molecule used in biologic therapy[20].

Recombinant human proteins

These are either exact replicas or fragments of normal human proteins which interact with normal cellular function to produce their effects[21-23].

Monoclonal antibodies

These specifically bind to proteins on cell surfaces and thereby alter the activity of the target protein. Most monoclonal proteins are now humanised but until relatively recently were murine derived. The risk of a potential immune response to the antibody is significantly reduced due to the new protein "drug" being similar to a normal human antigen. Consequently, prolongation of half-life and increasing safety can be achieved[20].

Fusion proteins

These molecules combine sections of different proteins, either a human protein and toxin or a human receptor and the Fc portion of human immunoglobulin[20].

Biologies have, on first sight, a confusing nomenclature. The suffix of the drug name helps in identification:

- - *ximab*: chimeric monoclonal antibody (may form neutralising antibodies);
- - *zumab*: humanised monoclonal antibody (antibody formation less likely);
- - *umab*: human monoclonal antibody;
- - *cept*: receptor-antibody fusion protein.

A model for the immunopathogenesis of psoriasis has enabled the development of four potential areas as target strategies for biologic immunotherapy. These four strategies include: 1, targeting pathogenic T-cells; 2, blocking T-cell activity; 3, immune deviation; and 4, inactivating cytokines and chemokines.

Strategy 1: Targeting pathogenic T-cells

This is the simplest of the four approaches considering that psoriasis is a T-cell-mediated disease. One of the first biologies studied for psoriasis was the aforementioned denileukin difitox. This IL-2 fusion protein combines enzymatically active diphtheria toxin with the coding sequence for IL-2. This protein binds avidly to the IL-2 receptor. The active diphtheria toxin inhibits protein synthesis and ultimately results in cell death[24]. There is no effect on any cell other than activated T-cells that express the high affinity IL-2 receptor[25]. Secondary to improvements in psoriasis in clinical trials with this drug, researchers focused on blocking T-cells and their function for biologies[26,27].

Alefacept: is a fully humanised recombinant fusion protein that modifies the inflammatory process in psoriasis[28]. It comprises LFA-3 and human IgG and works in two ways. Firstly, the LFA-3 portion binds to its ligand the CD-2 receptor on T cells thereby blocking co-stimulation and thus activation. The constant portion IgG engages the FcγIII receptor on natural killer cells and via granzyme release induces apoptosis specifically of activated CD45RO+ T-cells in the peripheral circulation[29]. Response to therapy correlates with a decrease in circulating CD45 RO+ T cells. Alefacept was the first biologic specifically

developed for the treatment of psoriasis to be licensed/approved for use. Published results have shown efficacy with an excellent safety profile. Circulating CD4+ T-cell counts must be monitored before initiating alefacept therapy and weekly during the 12-week treatment cycle.

Clinically significant improvement in psoriasis has been reported in the more than 1,000 patients with moderate-to-severe chronic plaque psoriasis who underwent randomised, double blind, placebo-controlled phase III trials[30-32]. During the first course of treatment (i.e., 12 weeks of treatment followed by 12 weeks of observation), 56% of patients treated with alefacept 7.5mg intravenous (IV) and 57% treated with alefacept 15mg intramuscular (IM) achieved a reduction in psoriasis area severity index (PASI) by 50% [PASI 50] – at any time during treatment or follow up ($p<0.001$ versus placebo in both studies)[30,32]. Further benefit was achieved by two courses of alefacept with 71% and 69% of patients achieving a PASI 50 in the IV and IM studies respectively[30,31]. It was noted that those patients achieving a PASI 75 (75% reduction in PASI) response during or after a single course maintained a PASI 50 response for a median duration of 216 days (7.5mg IV) or 209 days (15mg IM)[30,31]. However only 20% of patients achieve PASI 75 after a 12 week cycle of therapy.

Preliminary evidence indicates that a subset of 'responders' may go into long-term remission.

Anti-CD4: This has recently been developed and has undergone phase I trials. An example, *Siplizumab*, a humanised monoclonal antibody to an epitope of CD2 appears to be both effective and safe[33,34]. Following trials PASI 75 was achieved (regardless of method of administration) in approximately 50% of patients treated with siplizumab.

Strategy 2: Blocking T-cell activation

Activated T-cells are key drivers of the psoriatic process. Therefore if T-cells are unable to become activated they cannot induce psoriasis. Strategy 2 blocks cell-cell interaction at any of the 3 stages of T-cell activation. Biologics are therefore designed to interact with either signal 1 or signal 2 thus blocking T-cell activation. Activation and migration are coupled in this model because some of the cell-cell interactions are mediated by the same receptors.

Efalizumab: is a humanised monoclonal antibody that binds to CD11a at the α subunit of lymphocyte function associated antigen (LFA)-l. By blocking the interaction of LFA-1 with intercellular adhesion molecule-1 (ICAM-1), efalizumab abrogates the binding of T-cells to APC[35], endothelial cells and keratinocytes[36].

More than 1,100 patients with moderate-to-severe chronic plaque psoriasis were studied during 2 randomised, double-blind, placebo-controlled, phase III trials[37,38]. Between 52% and 59% of patients achieved a PASI 50 after 12 once weekly subcutaneous injections of 1mg/kg ($p<0.001$ versus placebo) approximately 25% achieved PASI 75.

Efalizumab was generally well-tolerated in clinical trials[37-39]. It does however need to be used continuously to maintain control. Patients self-administer efalizumab sub-cutaneously[39]. Side-effects are few and monitoring limited to quarterly assessment of platelet count.

Daclizumab: a humanised monoclonal antibody, binds to the CD25 subunit of the IL-2 receptor on T-cells therefore blocking T-cell proliferation. Vehicle controlled studies have suggested benefit in extensive, severe psoriasis[40].

CTLA4Ig: is a soluble chimeric protein. A key costimulatory signal in T-cell activation is provided by binding of the B7 family of molecules on APCs with their T-cell associated ligands - CD28 and CD152 or cytotoxic T lymphocyte-associated antigen-4 (CTLA4)[41]. Following IV administration during a 26 week, phase 1, open-label study 46% of patients achieved a ≥ 50% sustained improvement in psoriasis severity[41].

Strategy 3: Immune deviation; cytokine switching (Th1 – Th2)

Often there is an inverse relationship between the balance of Thl and Th2 cytokines in inflammation. By the addition of Th2 cytokines, a decrease in Thl activity should occur through promoting a Th2 response, restoring the balance could lead to benefits in inflammatory skin diseases. Psoriasis has a relative predominance of Thl over Th2 cytokines in involved skin. Cytokines of the Thl subtype include interferon-γ, interleukin (IL)-2 and IL-12; examples of Th2 cytokines are IL-4 and IL-10. IL-4 is the primary cytokine which inhibits the activity of type 1 T-cells. Small studies have demonstrated some efficacy in psoriasis with use of recombinant IL-4[42]. Subcutaneous injection of recombinant IL-10 has been shown to decrease Thl cytokines and improve psoriasis[43]. Recombinant IL-11 has similarly induced a Th2 response and improvement in psoriatic plaques. Human IL-11 was given by subcutaneous injection daily for 8 weeks, 11 out of 12 patients with psoriasis had improvements ranging from 20% to 80%[44].

Strategy 4: Inactivating cytokines and chemokines

There are several cytokines and chemokines implicated in the pathogenesis of psoriasis. The proinflammatory cytokines, secreted by T-cells, dendritic cells, monocytes and local keratinocytes are

key for angiogenesis and further activating the immune response. A key proinflammatory cytokine for inflammation whether it be in skin, bowel or joints is tumour necrosis factor-α (TNF-α). This strategy uses antibodies to target inflammatory mediators that are still either bound to cells or have been excreted[45].

Anti-TNF-α: overexpression of TNF-α occurs in plaques of psoriasis. Inappropriate production of TNF-α leads to chronic inflammation, tissue damage and excessive keratinocyte proliferation. TNF-α is actually beneficial in activating the immune response but naturally occurring TNF-α receptors are not sufficient to block elevated TNF-α levels seen in inflammatory diseases. For sometime colleagues in gastroenterology and rheumatology have used anti-TNF-α treatments for Crohn's disease and rheumatoid arthritis to considerable effect.

- *Etanercept* is a fusion protein of the extra-cellular ligand-binding domains of the TNF-α receptor II. In a trial of etanercept for psoriatic arthritis an additional observation was a noticeable improvement in the plaques of psoriasis[46]. Mean improvement in PASI was 46% with 12 out of 30 patients achieving at least a 50% improvement. The largest trial of etanercept included 652 patients with moderate to severe chronic plaque psoriasis[47]. Patients were separated into four different dosing regimens for 24 weeks. At week 12, 41%, 58% and 74% of patients in the etanercept low, medium and high dose groups, respectively achieved a PASI 50. All doses of etanercept significantly improved mean PASI compared with placebo as early as week 2. PASI 75 was achieved by 34% of patients on 25mgs twice weekly by week 12, this can be increased to 49% of patients with 50mgs dosing; 48 weeks of continuous therapy produced further benefit.

- *Infliximab* is a mouse monoclonal antibody directed against human TNF-α. Studies have showed a PASI 75 response at 10 weeks in 82-88% of patients treated with a single infusion of infliximab. The mean time to response is 4 weeks[48]. These responses are an order of magnitude greater then those achieved with the aforementioned biologies. Therapy has been tolerated in the short term and may be beneficial in combination with methotrexate – as is used for treatment of rheumatoid arthritis.

  Phase 1 trials of a human IL-12 p40 antibody delivered by infusion are very promising with 100% of patients in the high dose 5mg/kg group achieving PASI 75[49].

Other cytokines which have been targeted include IL-8 and IL-15. *Anti-IL-8* uses a fully human monoclonal antibody to bind free IL-8 and deactivates it in the skin. Anti IL-8 has been shown to be moderately effective in the treatment of psoriasis[50]. *Anti-IL-15* is a pro-inflammatory cytokine which mediates T-cell proliferation, inflammatory cell recruitment, angiogenesis and cytokine generation. Currently phase I/II trials are ongoing in patients with rheumatoid arthritis are using an anti-IL-15 compound Humax-IL-15[51,52].

Side effects

Biologic therapy has proven to be relatively safe in the short and intermediate time frames of administration. Data from studies concerning administration of *efalizumab* therapy for up to 24 months and up to 9 cycles of *alefacept* have shown that in addition to sustained efficacy there appears to be no increase in toxicity over time[53-55]. Rare cases of reversible thrombocytopenia have been observed in *efalizumab* treated patients during clinical trials (0.3%)[55,56]. *Infliximab and etanercept* have been studied for much longer periods in rheumatoid arthitis were they have been proven to be relatively safe although potential concerns such as serious infusion reactions with infliximab[48], infections – such as tuberculosis – [48], drug-induced autoimmune disorders[57,58], heart failure[59] demyelination[60] and increased prevalence of lymphoma have been observed.

Preliminary data has shown that combination therapy using biologies may allow for improved therapeutic efficacy with fewer side-effects, including decreased risk of hepatotoxicity and nephrotoxicity commonly associated with the most widely used systemic agents, methotrexate and ciclosporin[61]. However some concerns have been raised regarding the increased immunosuppression, increased risk of infection, potential for development of certain types of malignancy, as well as significant costs of therapy.

Costs of biologic therapies will be greater than for traditional therapies although other factors should be examined when determining true cost differences. Patients who receive methotrexate therapy should undergo liver biopsies and the renal function of those receiving ciclosporin must be assessed regularly. Additional costs of iatrogenic hepatotoxicity and nephrotoxicity are important. Patients receiving *alefacept* will require weekly T-cell monitoring, however regular monitoring is not considered necessary for *efalizumab, etanercept or infliximab.* As the population of patients with psoriasis suffering moderate to severe disease is small, treating this subgroup with biologic agents is not expected to have

a profound economic impact overall[61]. The efficacy and safety of biologics may improve outcomes so much so that costs such as hospitalisation may be avoided. Furthermore the ability of patients to self administer many of the biologic agents at home decreases the need for frequent hospital visits. Long-term clinical studies are warranted to more accurately quantify the risks and future benefits. Until the impact is finally established, psoriasis patients treated with biologies should be observed carefully probably under the auspices of registries for pharmacovigilance.

Conclusion

Traditional systemic therapy for psoriasis is limited by either lack of efficacy or the long term, side effect profile. Advances in our understanding of the pathophysiology of psoriasis has led to new perspectives on developing targeted therapies. Using these techniques agents can be designed to act specifically on the immune targets, which potentially could prove to be safer for chronic continuous therapy than traditional therapies. Some of these approaches could lead to the approval of new drugs to treat psoriasis and to enhance and/or replace already existing therapeutic options.

While biologics have been approved and embraced by other specialities for several years they could revolutionise the management of psoriasis leading us into an exciting era for dermatologists and patients alike.

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