Immunobiologics in the Treatment of Skin Disease

a report by

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The popular saying, ‘If it’s dry, wet it; if it’s wet, dry it’ conveys the historical limitations of treating skin disease. But times are changing. Dermatologists have a host of new treatments available to combat skin disease. Our understanding of skin pathophysiology has expanded rapidly over the past few decades. This new information has enabled the identification of molecular targets and the development of new, specific, targeted therapies for treating disease of the skin. This brief review will use psoriasis, one of the most common skin disorders, to highlight how the therapeutic armamentarium has expanded rapidly to enable physicians to very effectively and safely manage their patients with skin disease.

Psoriasis affects approximately 1% to 2% of the US population. It has been estimated that one-third of US adults have moderate-to-severe psoriasis and that a substantial number of these patients would benefit from systemic therapy. Affected individuals typically begin to manifest the symptoms in either the third or the fifth to sixth decade of life, although it can begin in early childhood. The hallmark of the disorder is a well-circumscribed red plaque with a thick, adherent, silvery scale (see Figure 1a). Plaques of psoriasis commonly occur on areas of the skin that are subject to mechanical trauma such as friction. The classic distribution is on the elbows, knees and scalp, but during flares or in particularly severe cases the disease can affect the entire skin surface. Involvement of the nails is another common feature and can lead to severe, disfiguring changes in nail shape. Psoriasis can involve the joints, as well: estimates of the incidence of psoriatic arthritis are as high as 30%. Psoriasis is a lifelong disease highlighted by periods of disease exacerbation and relative quiescence.

When examined under a microscope, samples of psoriatic skin show marked changes from that of normal/non-affected individuals. One of the most obvious changes is a marked thickening of the epidermal layer – a change broadly referred to as acanthosis or psoriasiform hyperplasia (see Figure 1b). Additionally, inflammatory cells are present. Focal collections within the epidermis of polymorphonuclear leukocytes are characteristic of psoriasis and are referred to as Munro microabscesses. CD4+ T-lymphocytes can be found in the dermis, the connective tissue rich layer beneath the epidermis, whereas CD8+ T-lymphocytes localize to the epidermis. The marked thickening of the epidermis led investigators to hypothesize that psoriasis was a disorder of keratinocyte proliferation. The presence of lymphocytes within psoriatic skin suggested the alternative hypothesis that psoriasis was an inflammatory condition.

Historical Treatments for Psoriasis and their Limitations

Therapies for psoriasis include topical and systemic agents, as well as phototherapies. Topical therapies include corticosteroids, coal tar, and its derivatives, anthralins, and derivatives of vitamins A and D. Systemic agents include retinoids, antimetabolites such as methotrexate, and immunosuppressive agents such as cyclosporine. The use of phototherapy to treat psoriasis is based on the ability of various components of the light spectrum to suppress immunologic activity in the skin. Ultraviolet B (UVB, the spectrum of light between 290nm and 320nm) has been shown to induce apoptosis of T-cells (programmed cell death) in the skin. Ultraviolet A (UVA) phototherapy, either alone or more commonly in combination with oral psoralen, is an alternative to UVB. More recently, narrow-band UVB has gained favour over other phototherapies.

Newer Therapies are Targeted to Disrupt Specific Molecular Interactions

The observation that cyclosporine was effective in treating psoriasis was critical to demonstrating the key role of the inflammatory cascade in the development of the subsequent skin changes. Cyclosporine was first developed as an immunosuppressive to prevent the rejection of solid organ transplants and works by inhibiting signaling downstream of the T-cell receptor. Unlike methotrexate, whose inhibition of dihydrofolate reductase could inhibit DNA synthesis and proliferation of both keratinocytes and lymphocytes, cyclosporine is specific for lymphocytes. Keratinocytes do not express...
the T-cell receptor and are not directly affected by the presence of this agent. Cyclosporine’s efficacy in psoriasis demonstrates the key role of the inflammatory cascade in the ensuing skin changes.

**Efalizumab**

Efalizumab (Anti-CD11a): Raptiva™ (Genentech) is a humanized, monoclonal antibody to CD11a, the alpha sub-unit of LFA-1. LFA-1 is a protein that functions in antigen presentation as well as the adhesion of T-lymphocytes to vascular endothelial cells and to keratinocytes, through the ability of LFA-1 to bind the protein ICAM-1 that is present on the surface of the latter three cell types. Humanized, monoclonal antibodies, whose primary structure is predominately derived from human immunoglobulin, have an advantage over murine and chimeric (a half-human and half-mouse primary structure), in that the humanized antibody is less immunogenic and therefore less likely to induce a host immune response to the injected drug. Efalizumab is self-administered by the patient as a once-weekly, subcutaneous injection at a dose of one milligram per kilogram (mg/kg). An initial dose of 0.7 mg/kg is used to lessen the incidence of mild, flu-like symptoms that some patients note with initial doses. In clinical trials, patients experienced significant improvement in their skin disease. The psoriasis area and severity index (PASI) is a quantitative measure of psoriatic clinical disease burden. Approximately 59% experienced at least a 50% reduction in their PASI score and 27% experienced a 75% reduction after 12 weeks of treatment. The percentage of patients experiencing significant improvement increased to 67% after 24 weeks, indicating that the response to the drug is sustained. Long-term, continuous therapy trials that extend the treatment over several years are currently under way. Because of its ability to disrupt key steps in the activation and function of T-lymphocytes, Efalizumab can be classified as an immunosuppressive drug; however, no significant difference in the rate of infection has been observed between patients treated with Efalizumab and placebo in clinical trials. Because a relatively small number of patients (eight out of 2,762) developed thrombocytopenia during treatment with Efalizumab, platelet counts should be assessed initially at monthly intervals and subsequently at quarterly intervals.

**Alefacept**

Alefacept (Amevive™; Biogen, Inc.) is a recombinant, fully human LFA-3-IgG1 fusion protein that binds to CD2 on T-cells and functions to block the CD2-LFA-3 co-stimulatory signal for CD45RO+ memory effector T-cell activation. Alefacept also depletes the pool of activated T-cells by enabling natural killer cells to bind to activated T-cells, an interaction mediated by the Fc region of the bound fusion protein. It is this T-cell-depleting activity that explains the remittent function of Alefacept; namely, that patients continue to experience clinical improvement after therapy has ended. At 12 weeks, 57% and 33% of patients experienced improvements in their PASI scores of 50% and 75%, respectively. Increased response rates were observed with a second course of Alefacept (69% and 43% of patients experienced a improvement in their PASI scores of 50% and 75%, respectively). In clinical trials, the median remission time is seven months, although two-year remissions have been observed.

Alefacept is approved by the US Food and Drug Administration (FDA) for treating moderate to severe psoriasis and is administered by a healthcare professional as a weekly 15mg intramuscular (IM) dose for 12 weeks. Because it is T-cell depleting, CD4 counts are monitored at weekly intervals. The drug is held for decreases in CD4 count below 250/ul and discontinued if the CD4 count stays below 250/ul for two additional weeks.

**References**

over a month. Approximately 2% of patients receiving the drug intravenously were withdrawn from clinical trials because of depressions in their CD4 counts; however, no patients receiving the drug IM were discontinued, suggesting that IM doses may minimize this complication.6

Infliximab

Infliximab (Remicade™, Centocor, Inc.) is a humanized, monoclonal antibody directed against the pro-inflammatory cytokine tumor necrosis factor alpha (TNF-α). Although not yet FDA-approved for skin disease, Infliximab has shown good clinical efficacy in the treatment of both psoriasis and psoriatic arthritis in initial clinical studies.7 Infliximab is administered intravenously (IV) with a dosing schedule of 5mg/kg in weeks 0, 2 and 6 and subsequently at eight-week intervals. Increased efficacy has been observed with concurrent treatment with methotrexate. Patients with a history of demyelinating disorders or with congestive heart failure should not be treated with Infliximab, because TNF-α blockade has been observed to exacerbate these conditions. The response to Infliximab is more rapid than the other biologic agents described in this review, probably due to its route of administration. Some patients have developed hypersensitivity reactions, serum sickness, and/or autoantibodies.9

Etanercept

Etanercept (Enbrel™, Amgen/Wyeth) is a fusion protein of the human TNF type II receptor (TNF-RII) binding domain and the human IgG1 Fc region. Etanercept binds to and functions to inhibit the pro-inflammatory cytokine TNF-α and is FDA-approved for inflammatory bowel disease, rheumatoid arthritis, and psoriatic arthritis; but it has also shown very good efficacy in the treatment of psoriatic skin disease. Etanercept is self-administered subcutaneously (SQ) either as a twice-weekly 25mg or a once-weekly 50mg dose; however, a recent study demonstrated a dose response with increased efficacy at 50mg SQ twice a week and additional improvement when treatment was extended from 12 to 24 weeks.10 In this large (672-patient), 24-week, double-blind, placebo-controlled trial, improvements in the PASI score of 50% and 75% were observed in 44% and 70% of patients, respectively, receiving 25mg SQ twice a week. Notably, 59% of patients receiving 50mg SQ twice a week experienced a 75% improvement in their PASI score. Like other TNF-α blocking agents, Etanercept is contraindicated in patients with a history of demyelinating disorders or congestive heart failure. Although it is suggested that either a purified protein derivative or a chest X-ray be used to screen patients for tuberculosis prior to initiating treatment, because of its remarkable safety profile, no additional laboratory monitoring is required during treatment with Etanercept.11,12 This should be considered when comparing the costs of biologic therapy to systemic agents that require routine laboratory monitoring, such as methotrexate and cyclosporine.

In our practice, these new agents have provided effective therapy for many of our patients who have failed other systemic agents, including methotrexate and cyclosporine. Biologic agents may have utility in treating other refractory, inflammatory skin diseases. For example, Infliximab has recently been used with good success in the treatment of hidradenitis suppurativa,13 a notoriously difficult to treat, suppurative, and scarring disorder of apocrine glands. Patients with previously treatment-resistant disorders are now clearing and looking forward to a life free from the burden of skin disease.

Additional Reading


