

# Biologics in General Medicine

Bearbeitet von  
W.-H Boehncke, H.H Radeke

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# Biologics in Psoriasis

W.A. MYERS, W.-H. BOEHNCKE, A.B. GOTTLIEB

## 9.1 Introduction

As a better understanding of cutaneous diseases has been gained, more specific, targeted therapies have emerged. More recently, many of the T-cell immune mediated inflammatory changes seen in psoriasis have been elucidated, leading to the development of biologics that specifically act on immunological mechanisms, which are thought to be pathogenic in psoriatic lesions. By acting on specific immunological actions in the large cascade that results in psoriasis, many of the systemic toxicities that accompanied older treatments such as methotrexate and cyclosporine may be avoided. Currently, there are three biologics approved in the United States for the treatment of psoriasis including alefacept, efalizumab, and etanercept, with several others currently under clinical investigation. A summary of the biologics currently used for the treatment of psoriasis can be found in Table 9.1.

### 9.1.1 Psoriasis

Psoriasis is a very common and chronic papulosquamous skin disease that affects approximately 0.5–4.6% of the total population, depending on race and country. The National Psoriasis Foundation states that 4.5 million people in the United States are affected by psoriasis and an additional 150,000–260,000 are newly diagnosed each year. It is diagnosed in patients of all ages, while the median age of onset is 29.1 years of age. It has been found that women have an earlier age of onset, but no difference in the prevalence between sexes has been observed.

### 9.1.1.1 *Plaque Psoriasis*

Plaque psoriasis or psoriasis vulgaris is the most common form of psoriasis, occurring in more than 80% of cases. Clinical features include sharply demarginated, erythematous plaques with non-adherent, silvery scales (Fig. 9.1A). Pain, itching, and cracking of the skin may be prominent as well. These lesions most typically affect the elbows, knees, scalp, lumbar area, umbilical area, and gluteal cleft. A characteristic sign called the Auspitz sign results from the mechanical removal of the non-adherent scale, resulting in pinpoint bleeding. Another additional finding seen in patients with psoriasis, called the Koebner phenomenon, is the predilection for new lesions to appear at sites of previous trauma such as burns, infections, or vaccinations.

### 9.1.1.2 *Guttate Psoriasis*

Guttate psoriasis is often a form that begins in childhood or early adulthood. A variety of conditions have been known to precipitate guttate psoriasis including infections, such as streptococcal infections, as well as stress, injury to the skin, or certain medications. Strep throat is a common trigger, and can be associated with flares as well, even if the infection is not clinically evident. Guttate psoriasis appears as an eruption of scattered 0.1–1 cm “drop” shaped, erythematous, scaling papules of the trunk and extremities primarily (Fig. 9.1B). This type of psoriasis often has a more rapid response to therapy than other forms of psoriasis.

**Table 9.1.** Summary of biologics used for psoriasis

| Drug       | Indication (USA)                                                                                          | Mechanism of action                                                                                                                         | Dose                                                                                                                | Efficacy                                                                                                                                                   | Safety                                                                                                                                                                                                                                                                       |
|------------|-----------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Alefacept  | Moderate to severe chronic plaque psoriasis                                                               | Inhibits T-cell activation and proliferation; induces selective T-cell apoptosis                                                            | 15 mg intramuscular injection once weekly for 12 weeks                                                              | PASI-75 results of phase III IM study: 33 % patients on alefacept 15 mg/week vs. 13 % receiving placebo (at any time)                                      | Similar to placebo, injection site pain/inflammation; no increased incidence of infections                                                                                                                                                                                   |
| Etanercept | RA, polyarticular-course RA, AS, psoriatic arthritis, moderate to severe psoriasis                        | Dimeric TNF- $\alpha$ receptor antagonist competitively inhibits interaction of TNF with cell-surface receptors                             | 50 mg twice weekly by subcutaneous injection for 3 months followed by reduction to maintenance dose of 50 mg weekly | PASI-75 in one phase III study on 50 mg twice weekly: 47 % vs. 4 % in placebo after 12 weeks; after 24 weeks, PASI-75 in 50 mg twice weekly group was 54 % | Well tolerated in clinical trials: extended use does not result in cumulative toxicities. Most common adverse event is injection site reaction. Avoid in patients with demyelinating disease, congestive heart failure and active, significant infection, e.g., tuberculosis |
| Efalizumab | Chronic moderate to severe plaque psoriasis                                                               | Monoclonal antibody which binds CD11a, blocking interaction with ICAM-1 resulting in decreased T-cell activation, adhesion, and trafficking | First dose 0.7 mg/kg, then 1.0 mg/kg subcutaneous injection once weekly                                             | At 12 weeks of therapy, a phase III study found that 27 % of patients receiving efalizumab achieved PASI-75 vs. 4 % in placebo                             | Most common include headaches, myalgia, pain, and fever                                                                                                                                                                                                                      |
| Infliximab | RA, Crohn's disease, AS, moderate to severe plaque psoriasis, psoriatic arthritis, and ulcerative colitis | Chimeric monoclonal antibody which binds with high affinity to free and membrane bound TNF, and inhibits its binding to its receptors       | Studies examining infliximab for psoriasis have dosed using 3 or 5 mg/kg intravenous infusion at weeks 0, 2, and 6  | A phase III study found at 10 weeks, 80 % of subjects achieved PASI-75 on 5 mg/kg (weeks 0, 2, and 6 dosing) vs. 3 % in placebo                            | Well tolerated. Headache, nausea, upper respiratory infections seen. Avoid in patients with demyelinating disease, congestive heart failure and active, significant infection, e.g., tuberculosis                                                                            |
| Adalimumab | RA, psoriatic arthritis                                                                                   | Monoclonal antibody which binds and inhibits TNF- $\alpha$                                                                                  | 40 mg subcutaneous injection every other week                                                                       | 53 % of patients in a phase II study achieved a PASI-75 with 40 mg every other week compared to 4 % in placebo                                             | Rates of adverse events comparable between adalimumab and placebo. Avoid in patients with demyelinating disease, congestive heart failure and active, significant infection, e.g., tuberculosis                                                                              |

**9.1.1.3****Erythrodermic Psoriasis**

Erythrodermic psoriasis is a very inflammatory psoriasis that affects most of the body. It presents as generalized indurated erythema with diffuse exfoliation of fine scales, often accompanied by severe itching and pain (Fig. 9.1C). The patients may also present with fever, chills, rigors, arthralgias, and trouble maintaining core body temperature. Triggers for an episode of erythrodermic psoriasis include severe stress, discon-

tinuation of a systemic medication such as methotrexate, cyclosporine, or oral corticosteroids, diffuse phototherapy burns, and infections. Reports of patients with erythrodermic psoriasis suffering staphylococcal sepsis have been reported, and inpatient management with blood cultures and systemic antibiotics should be considered accordingly. Special attention must be paid to maintaining the appropriate fluid status in these patients, as they are highly susceptible to insensible losses.



**Fig. 9.1.** Clinical features of psoriasis. The typical psoriatic lesion is a sharply demarcated erythematous plaque covered by silvery white scales, often appearing on the extensor sites of the extremities (A). Initial eruptions of psoriasis may exhibit a guttate distribution pattern and are often triggered by streptococcal infections (B). In a dark-skinned patient, erythrodermic psoriasis (C), a clinical subtype of the disease, affects the entire body surface. If the scalp is involved, the lesions typically extend a short distance beyond the region covered by terminal hair (D). Inverse psoriasis (E) is located at intertriginous areas and usually lacks scaling.

Pustular forms of psoriasis also exist (F, G). Localized forms of psoriasis include palmo-plantar psoriasis (H) and acrodermatitis continua suppurativa, or Halo-Heau's disease, leading to severe dystrophy (I) or even loss of nails. Joint involvement (psoriatic arthritis) is frequently observed (J). Mild cases of nail involvement are characterized by small pits and yellowish discoloration of the nail plate (K), which were also created in a wax-model moulage, manufactured around 100 years ago (L, item 1766 from the collection of the Johann Wolfgang Goethe University, Frankfurt am Main). (Reproduced with permission from: *N Engl J Med* 2005; 352:1901)

**9.1.1.4*****Pustular Psoriasis***

Pustular psoriasis is a rare form of psoriasis that typically affects adults. Sterile, white pustules in areas of erythema and scale characterize this form of psoriasis (Fig. 9.1F, G). There are several subtypes of pustular psoriasis including von Zumbusch pustular psoriasis, palmoplantar pustular psoriasis, and acropustulosis (acrodermatitis continua of Hallopeau). Von Zumbusch pustular psoriasis is characterized by abrupt waves of widespread, erythematous patches of skin, which become painful and sore. Typically within a few hours, pustules appear, which then peel off after 1–2 days. These waves of pustules may last days to weeks. Patients may also report fever, chills, muscle weakness, and weight loss. Von Zumbusch pustular psoriasis may be triggered by infections, withdrawal of topical medications, pregnancy, and certain medications such as lithium and some hypertension medications.

**9.1.1.5*****Palmoplantar Pustulosis***

This is a condition characterized by erythematous and scaly plaques studded with sterile pustules on the palms and soles, typically the insteps, sides, and back of the heel as well as the thenar and hypothenar eminences of the hands. This type of psoriasis affects patients between the ages of 20 and 60 years, and commonly affects females more than males. Topical treatments are typically prescribed first but this form of psoriasis can be very difficult to manage, and systemic treatments are often necessary.

**9.1.1.6*****Acropustulosis (Acrodermatitis Continua of Hallopeau)***

This rare form of pustular psoriasis is often localized to the tips of digits and occasionally toes. There is usually scaly inflammation and sterile pustules at the tip of the digit, typically after a recent injury or infection to the digit (Fig. 9.1H). This form of psoriasis can often be disabling, with secondary nail changes including separation from the nail plate, ridging, crumbling, and total destruction of the nail. Although acropustulosis can affect all age groups, it is typically seen in adults.

**9.1.1.7*****Flexural Psoriasis***

Also known as inverse psoriasis, this form of psoriasis is typically localized to the axilla, submammary folds, genitocrural area, and neck. These lesions usually have no scale and appear as well-demarcated, salmon red plaques that can fissure (Fig. 9.1E). The lesions can be very painful as perspiration becomes trapped in the skin folds, causing irritation and maceration of the tissue. Lesions tend to be difficult to treat because of their location and a tendency for superimposed fungal infections to occur.

**9.1.1.8*****Palmoplantar Psoriasis***

Palmoplantar psoriasis, as its name indicates, is a form of psoriasis that affects the palms and soles, presenting as discrete, erythematous, scaling patches and plaques. These lesions are usually bilateral, and involvement of the palms typically stops at the wrist-palm junction, but the dorsal aspect of the hand can be involved. Patients often find this form of psoriasis very disabling from fissuring that makes walking painful, as well as embarrassing, due to prominent scaling on very publicly visual areas such as the hands.

In addition to the above types of psoriasis, the scalp and nails may also be affected (Fig. 9.1D, J, K). Approximately 79% of patients with psoriasis have involvement of the scalp. Nail changes can occur in up to 50% of people with psoriasis and up to 80% of people with psoriatic arthritis. The proximal nail fold, nail matrix, nail bed, and hyponychium can be involved with nail psoriasis. Patients may see discoloration of the nail with yellow-brown changes, pitting, nail thickening, and separation of the nail from the nail bed (onycholysis).

**9.1.1.9*****The PASI Score***

The PASI score (Psoriasis Area Severity Index) is a common tool in clinical trials used to assess psoriasis activity and to follow response to treatment. The PASI evaluates the erythema, scaling and thickness of psoriatic plaques, as well as assessing the area of involvement in the four areas of the body (head, trunk, upper, and lower extremities). Scores range from 0 to 72, providing a subjective estimate of disease activity.

### 9.1.2

#### Mechanism of Disease

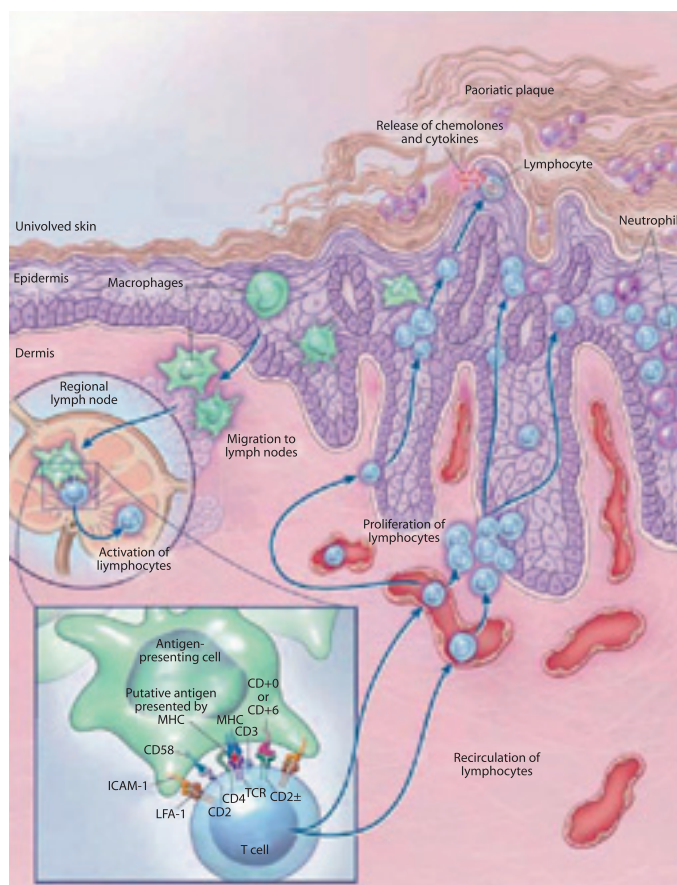
The pathogenesis of psoriasis has undergone several revisions over the past several decades. The most recent evidence has suggested that psoriasis is due to activated T cells present in the psoriatic plaques that produce pro-inflammatory cytokines and mediators that produce the changes seen in psoriasis (Fig. 9.2). Today's newest therapies for psoriasis target specific steps in this cascade of events to specifically inhibit the reactions necessary for the inflammation changes seen in psoriasis.

There are two subsets of T cells that are differentiated by the type of cytokines they release: T1 (type 1) and T2 (type 2). T1 cells produce interleukin (IL)-2 and IFN- $\gamma$ , are in part responsible for cell-mediated immunity and are inflammatory in nature. T2 cells release IL-4, IL-5, and IL-10, which enhance the humoral

immune system and are anti-inflammatory in nature. It is believed that psoriasis is a T1 mediated process, as suggested by the increased levels of IFN- $\gamma$  in psoriatic skin, lesional and non-lesional. IFN- $\gamma$  also induces macrophages to secrete high levels of inflammatory cytokines such as TNF- $\alpha$ , which is present in high levels of psoriatic plaques and synovium of patients with psoriatic arthritis. T2 cytokines levels, on the other hand, have been shown to be low in psoriatic patients.

There are many steps required before the phenotypic production of psoriasis is expressed. Mehlis and Gordon break this process down into three steps: (1) the activation of T cells, (2) the migration of T cells into the skin, (3), and the effector function of T cells or the induction of T cells by the secretions of inflammatory cells. The newer biologic therapies have targeted these specific steps in order to provide specific and less toxic therapy for psoriasis.

**Fig. 9.2.** Putative T-cell responses in the pathogenesis of a psoriatic lesion. To generate a cutaneous T-cell response, antigen-presenting cells take up and process antigens and migrate to the regional lymph nodes. There, they come in contact with naïve T cells. Within an immunologic synapse (*inset*), molecular interactions result in T-cell activation. Following the activation signals, T cells differentiate into memory T-cells and re-enter the circulation, where they extravasate at sites of cutaneous inflammation. In the skin, on encountering the respective antigen, T cells exert their effector functions, which include the secretion of pro-inflammatory cytokines. Psoriasis is characterized by a chronically persisting response in effector T-cells. (Reproduced with permission from: N Engl J Med 2005; 352:1905)



T-cell activation is a multi-step process that begins with binding to an antigen-presenting cell (APC) through interactions between LFA-1 (leukocyte function associated antigen), ICAM-1 (intercellular adhesion molecule), and LFA-3. Once bound, the T cell becomes activated by two signals, antigen (it is currently not known which antigen is responsible) bound to class I or II MHC on the APC, and another signal supplied by a number of different cell surface molecules including LFA-1, ICAM-1, CD-2, and LFA-3 (Gottlieb 2003). Alefacept is a fusion protein that consists of the extracellular domain of LFA-3 fused to hinge sequences of IgG<sub>1</sub>. This biologic binds CD-2 on T cells, which results in the inhibition of T-cell costimulation and a reduction in memory effector cells. By binding CD-2 on memory effector T cells, alefacept facilitates apoptosis of the cell.

T cells must also be present in the skin to produce the inflammatory changes, and therefore must migrate from the circulation. The activated T cell must slow and then bind the endothelium before it can enter the affected tissue. Several surface molecules are responsible for this process including CLA (cutaneous lymphocyte antigen) on the T cell and E selectin on the endothelium. This interaction slows the cell along the endothelial surface. The interaction between LFA-1 and ICAM and VLA and VCAM allows the T cell to bind to the endothelium. Once bound, the cell can cross the endothelium. Efalizumab is a monoclonal antibody that binds LFA-1 and blocks its interaction with ICAM, and inhibits migration and possibly activation.

Once in the skin, T cells and the inflammatory changes they can induce, alter keratinocytes. As previously mentioned, the cytokines released in psoriatic plaques are primarily T1, and include TNF- $\alpha$ , which in turn increases the production of other inflammatory cytokines such as IL-1, IL-6, and IL-8. Therapies such as etanercept, infliximab, and adalimumab work to block the effects of TNF- $\alpha$  and therefore its actions including the increased production of pro-inflammatory cytokines, adhesion molecules, vascular endothelial growth factor, and keratinocyte hyperproliferation.

## 9.2

### Etanercept

Etanercept was first used in human clinical trials in 1992, and in 1995 studies on the use of etanercept for

rheumatoid arthritis were initiated. Currently, etanercept is approved for the treatment of rheumatoid arthritis, polyarticular-course juvenile rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and moderate to severe psoriasis.

#### 9.2.1

##### Structure and Mode of Action

Etanercept is a fully human, soluble TNF- $\alpha$  receptor dimeric fusion protein produced by recombinant technology using Chinese hamster ovary cells. It consists of two molecules of the p75 TNF- $\alpha$  receptor linked to the constant Fc portion of IgG<sub>1</sub>. The dimeric structure of etanercept permits the molecule to bind to two molecules of TNF- $\alpha$ , either free or membrane bound, simultaneously, and thereby neutralizing TNF- $\alpha$ 's proinflammatory actions. The dimeric structure of etanercept also causes it to have a 50- to 1,000-fold higher affinity for TNF- $\alpha$  than the naturally occurring monomeric soluble form of the receptor.

#### 9.2.2

##### Pharmacokinetics and Pharmacodynamics

Once administered by subcutaneous injection, etanercept is slowly absorbed in both healthy volunteers and in patients with psoriasis, with time to peak serum concentrations in excess of 50 h. In addition, the drug appears to be widely distributed, including in the synovium, and is likely metabolized by proteolytic processes before recycling or elimination in the bile or urine. Elimination half-lives are similar for etanercept in patients with psoriasis and rheumatoid arthritis, with 68 h being seen in healthy volunteers and 102 h in patients with rheumatoid arthritis. In addition, steady-state pharmacokinetic properties of etanercept administered twice weekly are similar to those in patients with rheumatoid arthritis. Lastly, studies examining intermittent and continuous etanercept administration have found no differences in the pharmacokinetic profiles of the two dosing regimes.

Most data on the biological effects of etanercept have been conducted in those patients with rheumatoid arthritis. In this population, etanercept therapy has been found to reduce plasma levels of IL-6 and matrix metalloproteases (MMP), and the immunohistochemical staining of CD3+ T cells, CD 38+ T cells, IL-1 $\beta$ , and vascular cell adhesion molecule (VCAM). In addition,

long-term treatment reduces the numbers of TNF- $\alpha$  and IL-1 producing cells to the numbers seen in healthy controls. Gottlieb and colleagues studied histological response, inflammatory gene expression, and cellular infiltration in psoriatic plaques of patients receiving etanercept, 25 mg subcutaneously twice weekly for 6 months. After 6 months of treatment with etanercept, nine out of the ten patients treated had thinning of the epidermis and normalization of keratinocyte differentiation, and eight of the ten displayed an absence of keratin 10 (K 16), indicating normalization of keratinocyte differentiation and proliferation. A rapid and complete reduction of both IL-1 and IL-8 were observed, with maximal suppression seen by 1 month of treatment. Unlike IL-1 and IL-8, which are early TNF- $\alpha$  induced genes, most other inflammatory genes, such as STAT-1, inducible nitric oxide synthase (iNOS), IL-23, and IP-10 (IFN- $\gamma$ -inducible protein-10, CXCL 10), showed a more gradual response and generally were most suppressed at 6 months. Slower reductions in infiltrating myeloid cells (CD11c+ cells) and T lymphocytes were also observed. In another study, NF- $\kappa$ B, a nuclear transcription factor central in the cell stress response and keratinocyte differentiation, was found to be upregulated in the epidermis of normal epidermis of psoriasis patients, and even more so in the plaques of these patients. Treatment with etanercept correlated with downregulation of phosphorylated NF- $\kappa$ B as well as decreases in epidermal thickness, return of normal markers of keratinocyte differentiation, and lastly clinical outcomes.

### 9.2.3

#### Efficacy

The efficacy of etanercept for the treatment of plaque psoriasis has been evaluated in four placebo-controlled studies, one of which evaluated psoriasis in the setting of psoriatic arthritis. This study by Mease and colleagues which evaluated etanercept in the treatment of psoriatic arthritis also examined a subset of 38 patients who had more than 3 % of their body surface area (BSA) covered with plaque psoriasis. Of the 38 patients, 19 received etanercept, 25 mg subcutaneous twice weekly, while the remaining 19 received placebo. After 12 weeks of therapy, 26 % of those subjects receiving etanercept achieved PASI-75 compared to 0 % of those receiving placebo.

A larger, phase 2, randomized, double-blind and placebo controlled study by Gottlieb and colleagues (Gottlieb, Chaudhari, et al. 2003) examined the efficacy

and safety of etanercept, 25 mg subcutaneously twice a week compared to placebo, as monotherapy for moderate to severe plaque psoriasis. After 12 weeks of therapy, 30 % of patients achieved a PASI-75 compared to 2 % in the placebo group. After 24 weeks of continuous therapy, 56 % of patients receiving etanercept achieved PASI-75 compared to 5 % in the control group. In addition, by 24 weeks, psoriasis was clear or minimal by the physician's global assessment in more than 50 % of patients who received etanercept.

Leonardi and colleagues later conducted a phase 3, placebo-controlled, double blind study that evaluated etanercept for psoriasis. Patients with moderate to severe psoriasis who were not receiving any other therapies including systemic, phototherapy or topical treatments, were enrolled. Six hundred and seventy-two patients underwent randomization and 652 received either placebo or received etanercept subcutaneously at low dose (25 mg once weekly), medium dose (25 mg twice weekly), or high dose (50 mg twice weekly). After 12 weeks, patients who were in the placebo group began twice weekly treatment with 25 mg of etanercept. After 12 weeks of therapy, 4 %, 14 %, 32 %, and 47 % of patients achieved a PASI-75 on placebo, 25 mg once weekly, 25 mg twice weekly, and 50 mg twice weekly, respectively. After 24 weeks of continuous therapy, the PASI-75 score in the low dose group was 21 %, 41 % in those receiving 25 mg twice weekly, and 54 % in those receiving the high dose of 50 mg twice weekly.

A second large, phase 3, double-blind study evaluating etanercept for moderate to severe plaque psoriasis was conducted in the US, Europe, and Canada by Papp and colleagues. The study involved three groups of patients, each receiving placebo twice weekly, etanercept 25 mg twice weekly, or etanercept 50 mg twice weekly, for the first 12 weeks. After 12 weeks, all three groups were continued on etanercept 25 mg twice weekly for 12 weeks. After the first 12 weeks of therapy, 3 %, 34 %, and 49 % of patients receiving placebo, 25 mg twice weekly, and 50 mg twice weekly, achieved PASI-75 respectively, findings consistent with those results seen in the US studies. During the second 12-week period during which all patients received 25 mg, those patients who were previously receiving 25 mg twice weekly continued to improve, with 45 % achieving PASI-75 at week 24. The high dose group (50 mg twice weekly) who were then placed on 25 mg twice weekly maintained their previous improvements, with 54 % achieving PASI-75 at week 24, and of those patients who were

previously receiving placebo, 28% achieved a PASI-75. These finds suggested that induction with high-dose etanercept can then be maintained with a lower dose and still preserve PASI-75 scores.

#### 9.2.4 Safety

In psoriasis clinical trial experience, etanercept has been well tolerated. The most common adverse event in patients receiving placebo or any dose of etanercept was injection site reaction, where rates in the previously mentioned two phase 3 trials ranged from 6% to 18%. These reactions typically occur 2–3 weeks into treatment and consist of erythema, pain, itching, and/or swelling, and typically resolve in 3–5 days. In addition, upper respiratory tract infections (5–11%) and headache (3–12%) were also seen. In the study by Leonardi and colleagues, serious infectious adverse events were infrequent and were not more frequent in the high dose etanercept groups when compared to the placebo-crossover group of lower dose groups. In placebo-controlled trials for all uses of etanercept, the most common type of adverse event was an upper respiratory tract infection, which occurred in between 12% and 20% of patients, but not at an increased frequency when compared with placebo groups.

##### 9.2.4.1 *Serious Infections*

In rheumatoid arthritis patients in whom there is more long-term data, it appears that etanercept may increase the risk of serious infection. In clinical trials, the rates of infection that required hospitalization or parental antibiotic therapy were 0.04 per patient-year in etanercept treated groups, which is very similar to the total population. In post marketing data on the use of etanercept, serious infections and sepsis were reported in patients using etanercept, but most of these cases were in patients receiving concomitant immunosuppressive therapies. Great care should be practiced when placing a patient on multiple immunosuppressive therapies, and they should be monitored closely. Rare cases of reactivation of tuberculosis have been noted in patients receiving etanercept, and consideration should be given to performing a purified protein derivative (PPD) skin test prior to initiation of treatment, especially if geographic location makes a patient more at risk.

##### 9.2.4.2 *Malignancy*

The rates of malignancy in patients with psoriasis do not appear to be increased in those receiving etanercept. In placebo-controlled, randomized studies, 8 of 933 etanercept treated patients were diagnosed with malignancy whereas 1 in 414 patients receiving placebo were diagnosed with malignancy. The rate of lymphoma was threefold greater in patients receiving etanercept than in the general population. A cohort study by Gelfand though found that both rheumatoid arthritis and psoriasis patients are at a threefold increased risk of developing lymphoma. Taking this into account, analysis of the effects of etanercept or any other immunosuppressive therapy must consider the inherited risk of lymphoma to that specific disease population.

##### 9.2.4.3 *Demyelinating Disease*

TNF- $\alpha$  inhibition should not be initiated in patients with a history of demyelinating disorders such as multiple sclerosis (MS). Post-marketing surveillance has reported rare incidences of demyelinating disorders or exacerbations of pre-existing multiple sclerosis in patients receiving etanercept. In addition, early studies examining the use of a TNF- $\alpha$  inhibitor, lenercept, in the treatment of multiple sclerosis found increased numbers of MS exacerbations compared to placebo as well as MS exacerbations that occurred earlier compared to placebo. Physicians should be wary of new-onset neurological symptoms in patients receiving etanercept treatment, and a good neurological history should be obtained before commencing therapy.

##### 9.2.4.4 *Autoimmunity*

Approximately 6% of patients with RA, psoriatic arthritis, ankylosing spondylitis, or plaque psoriasis developed non-neutralizing antibodies to the TNF receptor (package insert). Antinuclear antibodies develop in some patients receiving etanercept, but most typically this finding has no clinical significance. There have been rare cases of systemic and cutaneous lupus associated with etanercept use.

#### 9.2.4.5

##### **Congestive Heart Failure**

Etanercept and infliximab were evaluated for their use in patients with congestive heart failure (CHF), but the studies were terminated early due to lack of efficacy. One of the studies actually suggested a higher mortality rate in patients with CHF who received treatment with etanercept. In addition, there have been case reports describing new onset CHF in patients receiving etanercept who had no previous symptoms and were under the age of 50. Physicians should proceed with caution when prescribing etanercept for patients with a history of heart failure.

#### 9.2.5

##### **Off-Label Use**

Clinical studies have been performed to investigate the use of etanercept for other dermatological conditions. A small open-label study was conducted in patients with early stages of diffuse progressive systemic sclerosis, which found that 25 mg of etanercept subcutaneously provided improvement in skin symptoms as well as functional status. Also there have been numerous reports on the successful use of etanercept in the treatment of the following diseases: multicentric reticulohistiocytosis, erythroderma-associated pruritus, palmo-plantar and pustular psoriasis, pyoderma gangrenosum, alopecia areata, dermatomyositis, bullous pemphigoid, cicatricial pemphigoid, cutaneous sarcoidosis, erythema annulare, mixed connective tissue disease, recurrent aphthous stomatitis, refractory hidradenitis suppurativa, Behçet's disease, and Sweet's syndrome.

### 9.3

#### **Efalizumab**

##### 9.3.1

##### **Structure and Mode of Action**

Efalizumab (Raptiva, Genentech, Inc., South San Francisco, CA) is a recombinant, humanized, monoclonal IgG<sub>1</sub> antibody whose action affects several steps of the T-cell inflammatory cascade. The humanized version of the murine antihuman CD11a Mab, MHM24, was made by grafting the complementary-determining regions, or hypervariable region, from murine antibody to the human framework. Efalizumab binds to

CD11a, the  $\alpha$ -subunit of leukocyte-associated antigen (LFA-1). LFA-1 is a cell-surface glycoprotein of the integrin family that has been shown to promote intercellular adhesion of inflammatory cells, as well as play a role in T-cell activation. By binding with CD11a, efalizumab blocks the interaction between LFA-1 and the cell surface molecule, intracellular adhesion molecule 1 (ICAM-1), which is present on antigen-presenting cells (APCs), as well as endothelial cells and keratinocytes that are involved in psoriatic plaques. Research into the LFA-1/ICAM-1 interaction has found that the interaction is necessary for T-cell activation by activating the T-cell costimulatory pathways, as well as inhibiting the binding of T cells to endothelial cells and trafficking of inflammatory cells into the dermis (Lebwohl et al. 2004). Efalizumab is believed to act by inhibiting these reactions, thus decreasing the release of inflammatory mediators into the skin that cause the phenotypic features of psoriasis.

##### 9.3.2

##### **Pharmacokinetics and Pharmacodynamics**

The pharmacokinetic profile of subcutaneous efalizumab was described by Gottlieb, Miller et al. (2003) in a Phase 1, open-label, escalating dose study, in which it was found that peak efalizumab plasma concentrations were achieved in approximately 1–2 days following injection, and that efalizumab was detectable in the serum for 3–5 weeks following the final injection. Patients receiving efalizumab 0.5–1.0 mg/kg SC weekly had an average  $T_{1/2}$  of 4 days, whereas those receiving 1.0–2.0 mg/kg had a  $T_{1/2}$  of 6 days. Subcutaneous doses administered weekly gave peak plasma concentrations and efalizumab exposure of approximately one-third to one-half of the equivalent intravenous dose.

A study examining the pharmacodynamic profile of subcutaneous efalizumab found that CD11a expression on circulating lymphocytes rapidly decreased to 15–30% of pretreatment levels and remained at this suppressed level until efalizumab was cleared from the plasma (Wellington and Perry 2005). Within 7–10 days of efalizumab clearance, CD11a expression returned to baseline. Following subcutaneous efalizumab administration of 1 mg/kg/week, CD11a expression is reduced within 1–2 days and is maintained with weekly administration. In addition, phase 2 studies evaluating SC efalizumab have noted histologically that epidermal thickness was reduced in the 0.3 mg/kg group com-

pared to placebo. This treatment group, 0.3 mg/kg efalizumab, also noted a reduction in the number of CD3+ T cells in skin biopsy specimens with a concurrent increase in circulating lymphocytes.

### 9.3.3 Efficacy

The efficacy of efalizumab for the treatment of adults with moderate to severe psoriasis was evaluated in three large phase 3 studies. Of these studies, two also had extension phases lasting an additional 12 weeks. In addition, an open-label study investigating the long-term efficacy over 3 years is ongoing. The phase 3 study by Lebwohl and colleagues was divided into three phases: a treatment phase from weeks 0 to 12, an extended treatment phase from weeks 13 to 24, and lastly a follow-up phase from weeks 25 to 36. In two of these studies, one by Lebwohl et al., the other by Leonardi and colleagues, subjects received efalizumab 1 or 2 mg/kg or placebo subcutaneously, after a first dose of 0.7 mg/kg to reduce first dose adverse events. In the other phase 3 study by Gordon et al., subjects received efalizumab 1.0 mg/kg subcutaneously or placebo. In the 3-year long term study, patients were randomized to receive 12 weeks of open-label efalizumab 2.0 mg/kg once weekly with or without topical fluocinolone ointment (0.025%) during weeks 9 through 12. After these 12 weeks, patients with a PASI score reduction of 50% (PASI-50) were then scheduled to receive efalizumab 1.0 mg/kg once weekly for up to 33 months. Patients who relapsed during the maintenance phase were switched to once weekly dosing of 2.0 mg/kg for 12 weeks or 4.0 mg/kg for 4 weeks. In the extension studies by Menter et al. (Menter et al. 2005), all the patients who finished the initial 12-week double-blind phase received efalizumab 1.0 mg/kg/week for a further 12 weeks. In another extension phase by Leonardi et al., patients who received efalizumab previously with PASI score reductions of less than 75% were then re-randomized to receive placebo or continue on their previously administered dose of efalizumab at 1.0 or 2.0 mg/kg/week.

All of the phase 3, double-blind studies used PASI score reductions of 75% (PASI-75) after 12 weeks of treatment as the primary efficacy endpoint. In the long-term study by Gottlieb et al. (2004), in addition to PASI-75, PASI-50 and PASI-90 scores were examined.

The study by Gordon and colleagues found that all efalizumab treated patients experienced statistically

significant improvement on all end points compared with those patients receiving placebo. Twenty-seven percent of patients receiving efalizumab achieved PASI-75 versus 4% of the placebo group. In addition, 95% of efalizumab treated patients achieved PASI-50 compared to 14% of those receiving placebo. With regard to patient reported outcomes, at week 12, patients treated with efalizumab had a greater mean percentage improvement in Dermatology Life Quality Index (DLQI) with 47% compared to 14% in the placebo group. Efalizumab treatment also produced a 38% improvement in Itching Visual Analog Score (VAS) compared to placebo. Lastly, efalizumab treated patients had a statistically significant improvement in Psoriasis Symptom Assessment (PSA), both frequency and severity subscales (48% vs. 18% and 46% vs. 17%, respectively), compared to placebo.

In the extension study published by Menter and colleagues, of the 342 subjects who received and completed the 12-week course of efalizumab treatment, 342 entered an open-label treatment period for an additional 12 weeks, receiving 1 mg/kg/week. In addition, 174 subjects who completed a 12-week course of placebo were scheduled to receive 12 weeks of efalizumab at the same dose. As the duration of treatment continued, PASI indexes continued to improve. At week 24, 66.6% of the previously efalizumab-treated patients achieved a PASI-50 response, and 43.8% achieved a PASI-75 response. The percentage of patients who achieved a static Physician's Global Assessment (sPGA) of minimal or clear increased from 25.7% to 35.9% from week 12 to week 24. For those subjects who received placebo followed by efalizumab, 28.7% achieved an sPGA rating of minimal or clear after 12 weeks. In addition to physician-assessed parameters, there was a statistically significant improvement after 12 weeks of efalizumab treatment in Dermatology Life Quality Index (DLQI), Itching scale, and Psoriasis Symptom Assessment (PSA) frequency and severity.

In a study by Lebwohl and colleagues, patients receiving 1 mg/kg of efalizumab per week achieved PASI-75 in 22% of the subjects and in 28% of those subjects receiving 2 mg/kg per week, compared to 5% of those subjects receiving placebo. In the extended treatment phase, those subjects achieving PASI-75 or PASI-50 were randomly assigned to continue receiving 2 mg/kg of efalizumab weekly or every other week or placebo. Those subjects not attaining at least PASI-50 were randomly assigned to either an increased dose of

4 mg/kg of efalizumab weekly or placebo. It was found in the extended treatment phase that of the efalizumab-treated subjects who initially achieved a PASI-75, a greater proportion of the subjects who received further treatment with efalizumab maintained a PASI-75 compared to those receiving placebo ( $p < 0.001$ ). Of those subjects who did not achieve a PASI-50 on initial efalizumab treatment, an improvement of 75 % or more was achieved in 40 % of those subjects receiving efalizumab 4 mg/kg per week, compared to 15 % in the placebo group ( $p = 0.02$ ).

At the 36-week follow-up, 12 weeks after the discontinuation of study treatment, it was found that in subjects who received at least 50 % improvement in their PASI index at week 24, the time to relapse (loss of at least 50 % of the improvement in the PASI index that had been achieved between base line and week 24) was approximately 84 days.

Leonardi and colleagues assessed short term and extended treatment efficacy and safety of efalizumab in another phase 3 study. The study was divided into three 12-week treatment periods, the first from weeks 1 to 12, and retreatment or extended treatment periods during weeks 13–24, with two observation periods, with subjects receiving an initial treatment of efalizumab 1 mg/kg/week, 2 mg/kg/week, or placebo. During the first treatment week after 12 weeks, significantly more patients receiving 1 mg/kg and 2 mg/kg achieved a PASI-75 (39 % and 27 %, respectively) compared with those subjects receiving placebo (2 %). Those efalizumab-treated subjects who did not achieve PASI-75 were re-randomized at week 12 to receive efalizumab or placebo for an extended 12-week period. At week 24, 20.3 % of subjects who received an additional 12 weeks of efalizumab achieved a PASI-75 compared to 6.7 % of those receiving placebo.

Gottlieb and colleagues assessed long term, continuous therapy with efalizumab in a multicenter, open-label, phase 3 study in patients with moderate to severe chronic plaque psoriasis. Preliminary data regarding the first 15 months of this 3-year-long study showed once weekly subcutaneous efalizumab maintains sustained efficacy without toxicity. Patients were randomized to receive 12 weeks open-label subcutaneous efalizumab 2.0 mg/kg/week with or without topical fluocinolone during weeks 9–12. After the 12th week, patients were then scheduled to receive efalizumab, 1.0 mg/kg/week for up to 33 weeks, if they received at least a PASI-50 during the first 12 weeks of treatment. If

a patient relapsed, therapy was increased to 2.0 mg/kg/week for 12 weeks or 4.0 mg/kg/week for 4 weeks. Concomitant topical corticosteroids and UVB phototherapy were also permitted. PASI improvement was maintained throughout the 15-month period.

### 9.3.4

#### Safety

Once weekly injections of efalizumab, 1 mg/kg, were generally well tolerated for 12 weeks to 15 months. In published clinical trials, between 3 % and 6 % of subjects withdrew due to adverse events of efalizumab compared to 1–3 % in the placebo groups. The most common adverse events seen in clinical trials included a first dose complex consisting of headache, nausea, myalgia, fever, and chills that typically developed within 2 days after the first two injections. After the third dose, these reactions diminished, with similar incidence in both efalizumab and placebo groups. These reactions were typically well managed with acetaminophen or nonsteroidal anti-inflammatory drugs. Serious adverse events were uncommon. In the three 12-week studies, 2 % of efalizumab-treated patients (1 mg/kg/week) had a serious adverse event during treatment. Withdrawals from the studies due to these adverse events were rare as well, with a total of 3.5 % of efalizumab (1 mg/kg/week) treated patients withdrawing from treatment due to adverse events in these same studies, whereas 2.1 % of placebo treated patients withdrew because of adverse events.

Long-term treatment with efalizumab, examined in the study by Gottlieb and colleagues, was not associated with an overall increased incidence of adverse events. Those events noted were similar in nature to those documented in short-term trials. There was no evidence of cumulative toxicity noted. Two serious adverse events that were determined by the investigator to be drug related included arthritis and gastrointestinal carcinoma.

### 9.3.4.1

#### Infections

In the phase 3 study by Gordon and colleagues, infections were present in 27 % of efalizumab treated patients compared to 23 % of those receiving placebo. Among these subjects, there was no increased susceptibility to any specific pathogen determined upon analy-

sis. In all three phase 3 studies by Gordon et al., Lebwohl et al. and Leonardi et al., no statistically significant increased risk of infection was found in the efalizumab treated patients compared to those subjects receiving placebo.

#### 9.3.4.2

##### **Malignancy**

There were two cases of malignancy in one clinical trial by Gordon and colleagues, which were determined not to be related to efalizumab secondary to the time line of drug initiation and identification of malignancy. According to company generated information, of the 2,762 patients who received efalizumab for a mean duration of 8 months, the incidence of malignancies of any kind was 1.8 per 100 patient-years with efalizumab and 1.6 per 100 patient-years with placebo.

#### 9.3.4.3

##### **Psoriasis Flare**

During clinical trials, 19 of 2,589 patients experienced worsening (past baseline) of their psoriasis during or after treatment with efalizumab. The worsening involved new plaques, as well as different forms of their psoriasis, including pustular and erythrodermic psoriasis. Some patients required hospitalization and alternate psoriasis treatments were administered.

#### 9.3.4.4

##### **Arthritis**

Clinical and post-marketing data have included reports of arthritis, including new onset as well as recurrent, severe arthritis. Joint pain was noted during treatment as well following discontinuation of efalizumab, and typically resolved after discontinuation of efalizumab and without other therapies.

#### 9.3.4.5

##### **Hematologic Complications**

Platelet counts at or below 52,000 cells/ $\mu$ l were observed in eight subjects during clinical trials. Seven (one patient was lost to follow-up) were treated with systemic corticosteroids, with resolution. Post-marketing surveillance has reported cases of severe thrombocytopenia as well, and physicians should monitor plate-

let count closely. Patients experiencing thrombocytopenia while taking efalizumab should discontinue treatment (Raptiva package insert, 2005). Hemolytic anemia, usually 4–6 months after the initiation of therapy, was noted, and treatment with efalizumab should be stopped if this develops.

#### 9.3.5

##### **Off-Label Use**

Currently, efalizumab is approved only for the treatment of patients with chronic, moderate-to-severe plaque psoriasis. It has been used with success in the treatment of disseminated granuloma annulare. Besides this dermatologic condition, efalizumab is currently being studied for use in renal transplant patients for prevention of acute rejection, as well as in asthmatics as a possible agent to reduce the late asthmatic response in patients with mild allergic asthma.

### 9.4

#### **Alefacept**

Psoriasis is an inflammatory disorder mediated primarily by T cells and the number of inflammatory cytokines that are released. Specific steps in the inflammatory cascade that cause psoriasis targeted by biologics include reduction of specific disease causing T-cell populations, inhibition of T-cell activation, prevention of T-cell trafficking, or specific inhibition of inflammatory cytokine release in psoriatic plaques.

#### 9.4.1

##### **Structure and Mode of Action**

Alefacept (Biogen, Inc., Cambridge, MA) is a fully human lymphocyte function-associated antigen 3/immunoglobulin 1 (LFA-3/IgG<sub>1</sub>) fusion protein, which consists of the first extracellular domain of LFA-3, fused to the hinge, C<sub>H</sub>2 and C<sub>H</sub>3, domains of human IgG1. The LFA-3 domain of the drug binds CD2 on T cells, thereby blocking T-cell activation and proliferation of memory effector cells (CD4+CD45+RO+ and CD8+CD45+RO+ T cells). This action results in decreased release of cytokines and less inflammation. CD2 is upregulated on memory T cells and therefore alefacept selectively targets and reduces a population of cells specific for the pathogenesis of psoriasis. In addi-

tion, the IgG1 domain of alefacept interacts with Fc $\gamma$ RII receptors on natural killer cells and macrophages, leading to apoptosis of memory effector T cells.

#### 9.4.2

##### Pharmacokinetics and Pharmacodynamics

The pharmacokinetics of single and multiple dose intravenous alefacept were studied in healthy Caucasian and Japanese volunteers as well as Caucasian patients with chronic plaque psoriasis. The elimination half-life of IV alefacept was found to be 890 h or approximately 5 weeks. In healthy Caucasian and Japanese volunteers, the half-life of alefacept was found to be similar, 202 and 198 h, respectively. Also, the relative bioavailability of IM to IV infusion was approximately 60%. After IM absorption was complete, the rate of elimination from the serum was consistent with that of IV administration, approximately 12 days. An intramuscular dose of approximately 150–200% of the IV dose is an appropriate alternative for the IV dose.

Multiple phase III studies examining patients with moderate-to-severe psoriasis found that alefacept treatment consistently reduced total lymphocyte and circulating memory-effector T cells. Specifically, Ellis and Kreuger found that during treatment with intravenous alefacept, there was a dose-dependent reduction in peripheral blood CD4<sup>+</sup> memory cells (CD45RO<sup>+</sup>), but not in CD4<sup>+</sup> naïve cells (CD45RA<sup>+</sup>). These dose related reductions in memory T cells correlated with, but were not predictive of, clinical response. A similar study by Lebwohl and colleagues examining intramuscular alefacept provided consistent data, with similar memory T-cell subset reductions.

#### 9.4.3

##### Efficacy

The efficacy of alefacept is now well known after several phase II and III studies. In a phase II, randomized, placebo-controlled, dose-response trial of alefacept in subjects with chronic plaque psoriasis, patients received a single course of alefacept at 0.025, 0.075, or 0.15 mg/kg as an IV bolus injection weekly for 12 weeks with a 12-week follow-up period. Two weeks after completion of treatment, the mean PASI scores were 38%, 53%, and 53% lower than the baseline groups, who received 0.025, 0.075, and 0.15 mg/kg alefacept, respectively, compared to 21% lower in the placebo group

( $p < 0.001$ ). At both 2 weeks and 12 weeks after treatment completion, the PASI-50 and PASI-75 scores were significantly higher in the alefacept treatment groups than in the placebo group. For example, 2 weeks after treatment, 36%, 60%, and 56% of the subjects receiving 0.025, 0.075, and 0.15 mg/kg alefacept achieved a PASI-50, compared to 27% in the placebo group. Two weeks after treatment completion, 21%, 33%, and 31% of subjects in the three-alefacept treatment groups achieved a PASI-75, whereas only 10% in the placebo achieved such a score.

A phase 3 intravenous study of alefacept consisted of two treatment courses, each with a 12-week treatment period followed by a 12-week treatment free period. There were three separate cohorts: cohort 1 received alefacept 7.5 mg IV in the first and second course of treatment; cohort 2 received alefacept in the first course and placebo in the second; and cohort 3 received placebo in the first course and alefacept in the second. The primary efficacy endpoint was the percentage of patients with a 75% reduction in PASI at 2 weeks after the last dose of course 1, as well as an overall response rate defined as the percentage of people achieving “clear” or “almost clear” by the Physician’s Global Assessment (PGA). A significantly higher percentage of patients in the combined alefacept group (cohorts 1 and 2) achieved at least a PASI-75 or greater 2 weeks after the last dose of course 1, with 14% in those receiving alefacept, versus 4% in the placebo group. In course 1, 28%, 56%, and 23% of the subjects achieved a PASI-50, PASI-75, and PGA of “clear” or “almost clear”, respectively, versus 8%, 24%, and 6% in the placebo group, respectively. In course 2, 37%, 64%, and 30% of subjects receiving alefacept achieved a PASI-75, PASI-50, and PGA of “clear” or “almost clear” respectively, versus 19%, 49%, and 30% in the placebo group, respectively. The response to alefacept was long lasting. The subjects who received one course of alefacept therapy (cohort 2) and achieved a PASI-75 during or after treatment preserved a PASI-50 or greater for a median duration of more than 7 months. For subjects achieving two courses of alefacept (cohort 1), the median duration of response could not be determined since more than 50% of these subjects maintained 50% or greater improvement at the final end point, which was a year after the first dose of alefacept.

An international, randomized, double-blind, placebo-controlled phase III trial of intramuscular alefacept in patients with chronic plaque psoriasis found similar

efficacy to the intravenous dosing method. In this study, placebo, 10 mg, or 15 mg of alefacept was administered once weekly for 12 weeks followed by 12 weeks of observation. Mean reductions in PASI in the 15 mg alefacept, 10 mg alefacept, and placebo groups were 46 %, 41 %, and 25 %, respectively, 6 weeks after dosing. The percentage of subjects achieving at least a PASI-50 was 57 % and 53 % in the 15 mg and 10 mg alefacept groups, respectively, compared to 35 % in the placebo group. As the intravenous study showed, the response to alefacept was durable. Of those subjects receiving 15 mg of alefacept and who achieved a PASI-75, 74 % maintained at least a PASI-50 during the 12-week follow-up period. The overall response rates for the Physicians Global Assessment (PGA) of clear or almost clear were 24 %, 22 % and 8 % of patients in the 15 mg alefacept, 10 mg alefacept, and placebo groups, respectively. In a follow-up extension study of the intramuscular alefacept trial, patients who achieved 75 % or more reduction in PASI with the first course of intramuscular alefacept 15 mg maintained a PASI-50 for a median duration of 209 days. In addition, two courses of 15 mg intramuscular alefacept produced a PASI-50 overall response rate of 69 %, whereas only 57 % did so with a single course.

#### 9.4.4 Safety

The safety of alefacept has been evaluated in two placebo-controlled phase 3 clinical trials that enrolled over 1,000 patients. In course 1, 186 subjects received placebo, and 367 received 7.5 mg IV alefacept. In the second course, 142 subjects received placebo and 307 received alefacept. In the phase 3 intramuscular study, 173 subjects received 10 mg alefacept, 166 received 15 mg alefacept, and 169 received placebo.

Both studies required weekly monitoring of CD4+ T-cell counts as alefacept acts by binding to CD2 receptors, therefore affecting the activity and quantity of cells expressing these receptors. In course 1, 38 patients (10 %) in cohorts 1 and 2 had at least one placebo substitution due to CD4+ lymphocyte counts below 250 cells/ $\mu$ l. There were seven permanent placebo substitutions due to four consecutive CD4+ T-cell counts below 250 cells/ $\mu$ l. In the second course, there was placebo substitution in 14 patients (9 %) in cohort 1 (2nd course 7.5 mg alefacept) and 8 patients (5 %) in cohort 3 (alefacept during 2nd course of therapy), while there was

only one permanent substitution in course 2. Throughout the study, no opportunistic infections and no associated infections were noted with CD4+ T-cell counts below 250 cells/ $\mu$ l. In the IM study, 4 % of patients had at least one placebo substitution for CD4+ T-cell counts below 250 cells/ $\mu$ l, and there were no permanent substitutions. At the end of treatment in both studies, T-cell counts recovered to normal levels. Also at the end of the 12-week observation period, 98 % of patients in both the IV and IM studies had total lymphocyte counts that were above the lower limit of normal.

In all, alefacept therapy was well tolerated. For patients in the two course intravenous study, relative to the first course of therapy received in those patients in cohort 1, the incidence of each adverse event was similar or lower in the 2nd cohort. In the IV study, the only adverse event in course 1 that had a greater than or equal to 5 % higher incidence in the combined alefacept group (cohorts 1 and 2) versus placebo (cohort 3) was chills (10 % vs. 1 %). For subjects who received two courses of alefacept (cohort 1), this frequency substantially decreased in the 2nd course of therapy compared to the first (< 1 % vs. 13 %, respectively). Adverse events experienced in greater than 10 % of patients receiving a single course and two courses are shown in Table 9.1.

Other commonly reported events were headache, pharyngitis, flu syndrome, and infection, which most frequently referred to the common cold.

In the IM study, alefacept was also found to be well tolerated. Adverse events occurring at an incidence of 5 % or greater in the alefacept group compared to placebo were observed for pruritus, injection-site pain, and injection-site inflammation. The incidence of infections was monitored by CD4+ T-cell counts lower than 250 and at least 250 cells/ $\mu$ l. No relationship between the incidence of infections and decreased CD4+ T-cell counts was observed. In both studies, there was no single event that contributed significantly to drug discontinuation. In the IV study, 2 % of patients receiving alefacept, compared to 1 % in the placebo group, discontinued the study drug. Similarly in the IM study, 2 %, 2 %, and 1 % of patients in the placebo, 10 mg, and 15 mg alefacept groups, respectively, discontinued the drug. In addition, a study by Gottlieb and colleagues examined the effect of alefacept on T-cell-dependent humoral responses to a neoantigen and recall antigen (tetanus toxoid). The study found that alefacept did not alter primary or secondary antibody responses to a neoantigen or memory responses to a recall antigen.

### 9.4.5

#### Off-Label Use

Alefacept is currently approved for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy. There have been numerous case reports and small case series regarding the use of alefacept for the management of diseases such as palmoplantar psoriasis, psoriasis affecting the nails, and erythema nodosum, lichen planus, pyoderma gangrenosum, and scalp psoriasis.

### 9.5

#### Infliximab

Infliximab is a chimeric anti-TNF- $\alpha$  monoclonal antibody that is given by intravenous infusion. It was the first anti-TNF therapy studied for the treatment of psoriasis, and is currently 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 who have rheumatoid arthritis or Crohn's disease and have failed previous conventional treatments, as well as psoriatic arthritis. A double-blind study by Chaudhari and colleagues showed that infliximab provides substantial clinical efficacy with high tolerability. Specifically, 82% and 73% of patients with psoriasis receiving 5 and 10 mg/kg of infliximab, respectively, achieved a PASI-75 at week 10. An open-label phase of the same study showed that at week 26, PASI response was maintained in 40% and 73% of patients receiving 5 and 10 mg/kg of infliximab, respectively. A double blind, placebo-controlled, phase 2 trial conducted by Gottlieb and colleagues found that at week 10 (intravenous infusions of placebo or infliximab at either 3 or 5 mg/kg given at weeks 0, 2, and 6), 72% of patients treated with infliximab (3 mg/kg) and 88% of patients treated with infliximab, 5 mg/kg, achieved a PASI-75 or greater, compared to only 6% of those receiving placebo. These improvements were seen as early as 2 weeks. More recently a phase 3, double-blind study examined the utility of infliximab as an induction and maintenance therapy to moderate to severe psoriasis. Patients were randomized to receive infliximab 5 mg/kg or placebo at weeks 0, 2, and 6, and then every 8 weeks until week 46. Those patients receiving placebo were crossed

over to receive infliximab at week 24. At week 10, 80% of patients treated with infliximab achieved a PASI-75 and 57% achieved a PASI-90, compared to 3% and 1%, respectively, in the placebo group. PASI-75 scores were maintained at week 24 as well (82% for infliximab compared to 4% for placebo). At week 50, 61% of the infliximab treated patients achieved a PASI-75 and 45% achieved a PASI-90, showing a sustained effect.

Overall, infliximab has been well tolerated in clinical trials. The most common adverse events reported in 10% or more of infliximab treated patients include headache, nausea, and upper respiratory tract infection (Winterfield and Menter 2004). Similar safety issues are seen in patients receiving infliximab as are seen in etanercept treated patients including infections and reactivation of tuberculosis (with mandatory PPD testing), demyelinating conditions, congestive heart failure, malignancy, and autoimmunity.

Infliximab is approved by the EMEA and is filed at the FDA for treatment of moderate to severe psoriasis. Its use in the treatment of many other dermatological conditions has been reported and includes the following: Behçet's, graft versus host disease, hidradenitis suppurativa, panniculitis, pyoderma gangrenosum, SAPHO (synovitis, acne, hyperostosis, and osteitis), sarcoidosis, subcorneal pustular dermatosis, Sweet's syndrome, toxic epidermal necrolysis, and Wegener's syndrome.

### 9.6

#### Adalimumab

Adalimumab is a fully human anti-TNF- $\alpha$  monoclonal antibody currently in phase 2 studies for the treatment of moderate to severe psoriasis. It is currently approved for the treatment of rheumatoid arthritis as a second-line agent, alone or in combination with a disease-modifying anti-rheumatic drug (DMARD) and psoriatic arthritis. Adalimumab is given as a 40 mg subcutaneous injection every 2 weeks. A phase 2 trial by Chen and colleagues found that 53% of study patients receiving 40 mg every other week achieved a PASI-75, and 80% of patients receiving 40 mg weekly achieved a PASI-75. The percentages of patients achieving a PASI-75 were statistically significantly greater than placebo as early as 4 weeks. As discussed with etanercept and infliximab, adalimumab has the same important side effects as the other TNF- $\alpha$  inhibitors exhibit.

Adalimumab is currently undergoing a phase 3 investigational study for the treatment of moderate to severe psoriasis. In addition to psoriasis, there have been case reports on the successful use of adalimumab in the treatment of recalcitrant acrodermatitis continua of Hallopeau (with acitretin), psoriatic onychopachydermo periostitis (POPP), pyoderma gangrenosum, and refractory rheumatoid arthritis-associated leg ulcerations.

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