The Management of Psoriasis in the Age of Biologics: Clinical Update 2009

Jeffrey M. Weinberg MD[a] and Ellen H. Frankel MD[b]

[a]Columbia University College of Physicians and Surgeons, New York, NY; Department of Dermatology, St Luke's–Roosevelt Hospital Center and Beth Israel Medical Center, New York, NY
[b]Kent County Memorial Hospital, Warwick, RI; Clinical Partners, LLC, Johnston, RI

ABSTRACT

Psoriasis is a common, chronic, and costly condition that carries the potential for distressing medical and psychosocial consequences. The systemic treatment armamentarium for psoriasis includes traditional agents, such as methotrexate and cyclosporine, and biologic agents. The traditional medications tend to be less costly upfront and are often effective, but safety concerns limit their use, particularly over the long term. The biologics are initially more expensive, but once their high benefit-to-risk ratio is factored in, biologics may lower the economic expense of on-going treatment by reducing the direct and indirect costs of the disease. Much research has been conducted on the biologics with an abundance of clinical data generated. Study findings as well as clinical experience are noteworthy, demonstrating high efficacy rates with excellent safety profiles. Clinical trials of agents FDA-approved for treatment of psoriasis (etanercept, infliximab, adalimumab, alefacept) and one with approval expected shortly (ustekinumab) are comprehensively reviewed.

INTRODUCTION

Psoriasis affects as much as 2.2% of the United States population.[1] Epidemiologic data from 2004 show psoriasis accounting for 4.3% of ambulatory visits to the dermatologist;[2] in addition to an increased risk for other systemic conditions, such as psoriatic arthritis, Crohn's disease and cardiovascular disease. Patients with psoriasis often suffer psychosocial distress. Frequently, this is the driving force for the patient to visit a physician. A recent questionnaire further confirmed reports that, as psoriasis severity worsens, the negative impact on quality of life (QOL) increases.[3] A study of 1,006 patients revealed approximately one-third with moderate or severe psoriasis also reported suffering depression and/or anxiety.[4]

The indirect costs associated with psoriasis are staggering and far exceed total direct costs for the condition, with the annual cost of treating the disease potentially exceeding $3 billion annually.[1,5] Another analysis of the Internet-based survey of 1,006 patients with psoriasis revealed an average 4% absenteeism rate, 15% presenteeism rate (i.e., impairment at work), and 16% productivity loss among employed psoriasis sufferers. Severe disease correlated with higher rates of the aforementioned three variables compared with rates for patients with mild and moderate disease.[6]

For decades, traditional agents such as methotrexate and cyclosporine were used to treat psoriasis. Habit—or in some cases insurance demands—may dictate selection of these traditional agents as the initial systemic medication prescribed. Patients frequently benefit from administration of these agents, however safety issues can be limiting and worrisome. Drug savings may be offset by costly consequences of their use. Conversely, biologics, with seemingly high upfront costs, offer options with a high benefit-to-risk ratio for patients with moderate-to-severe disease.[7] In an era of rising healthcare costs coupled with arguments to control medically-related spending, selecting an effective treatment to manage symptoms may streamline expenses by reducing both direct medical costs (e.g., number of doctor visits) and indirect costs.[5] To increase understanding of the relevant biologics, this review summarizes anti-tumor necrosis factor (TNF; etanercept, infliximab, adalimumab) andT cell inhibitor (alefacept) data for agents with Food and Drug Administration (FDA) approval for the treatment of psoriasis. In addition, clinical trial data with ustekinumab, an interleukin (IL)-12/23 inhibitor expected to receive approval shortly, will be discussed.

Etanercept

Etanercept has been extensively studied in several clinical studies. The 2003 phase 3, 24-week, double-blind, placebo-controlled clinical trial conducted at 47 sites in the U.S. (n=672) evaluated the efficacy and safety of etanercept 50 mg twice weekly (BIW), 25 mg twice-daily (BID) and 25 mg weekly versus placebo in a population of adults with moderate-to-severe psoriasis. Psoriasis Area and Severity Index (PASI) 75 response rates for the three groups at week 12, which was the primary efficacy measure, were 49%, 34%, 15% and 4%, respectively, for the four groups in order of descending dose with the placebo group achieving a rate of 4% (P<0.001, all groups versus placebo). Statistically significant differences between the 50 mg BIW group and placebo were observed as early as week 4 and mean percentage improvements from baseline in PASI scores were statistically significant for all three etanercept treatment groups by week 2. Week 24 PASI 75 response rates were 59%, 44% and 25% for the etanercept 50 mg BIW, 25 mg BIW, and 25 mg weekly groups,

respectively. The analysis at week 24 did not include a placebo group because all patients in the original placebo group received etanercept after week 12.[8]

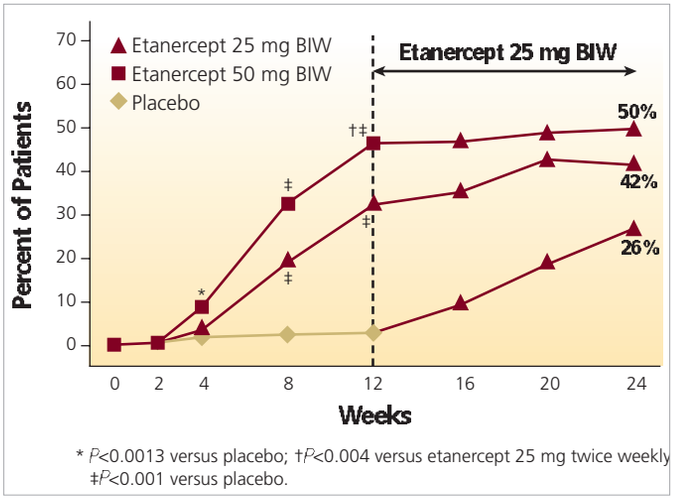
A 2005 double-blind, placebo-controlled, 24-week clinical trial (n=611) compared two etanercept dosing regimens: 50 mg BIW for 12 weeks followed by a step-down dose of 25 mg BIW for the remaining 12 weeks versus 25 mg BIW for the full 24-week period. Patients in the placebo group were given etanercept 25 mg BIW beginning at week 12. Results are illustrated in Figure 1 and demonstrate PASI 75 response rates were either sustained or improved, despite the reduction in dose for the 50 mg BIW group.[9]

Two studies published in 2007 provide further insight for the practitioner about long-term patient management with etanercept. Moore and colleagues assessed the efficacy and safety of etanercept therapy (n=2,555) with ongoing, uninterrupted etanercept administration compared with a group of treatment responders whose therapy was discontinued and restarted upon symptomatic relapse. During the first 12 weeks of the 24-week study, all patients received etanercept 50 mg BIW. From weeks 12–24, the continuous group received etanercept 50 mg weekly while responders (i.e., physician global assessment [PGA] score of 2 or less) in the other group discontinued treatment until relapse at week 16 or 20 when etanercept was reinitiated. week 24 results revealed significant differences between the continuous treatment group (PGA=71%) and the interrupted treatment group (PGA=59.5%; *P*<0.0001). Once treatment was reinitiated in the interrupted group, most regained responder status. Mean time to relapse following etanercept discontinuation was 39.6 days; time to regain responder status once treatment was restarted was 35 days. It is suggested that continuous etanercept therapy is optimal but, should circumstances demand its discontinuation, etanercept may be stopped and restarted safely with the likelihood that the initial response will be reattained.[10]

The Tyring et al. study was a 12-week double-blind placebo-controlled trial followed by an open-label extension originally planned for 84 weeks but was extended to 132 weeks. An additional phase was subsequently included for up to 144 weeks of treatment. Patients were initially randomized (n=618) to receive etanercept 50 mg BIW or placebo for the first 12 weeks; at week 12 all patients were given the 50 mg BIW dose until week 132. The dose was decreased to 50 mg weekly for the final 12 weeks of the study. Patients unable to maintain efficacy with the lower dose were eligible to have their dose increased to 50 mg BIW.[11] PASI 75 response rates are shown in Figure 2. PASI scores for patients treated with etanercept 50 mg BIW for 144 weeks were 19 at baseline, 4.3 at week 96, 9 at week 120, and 7 at week 144.[12]

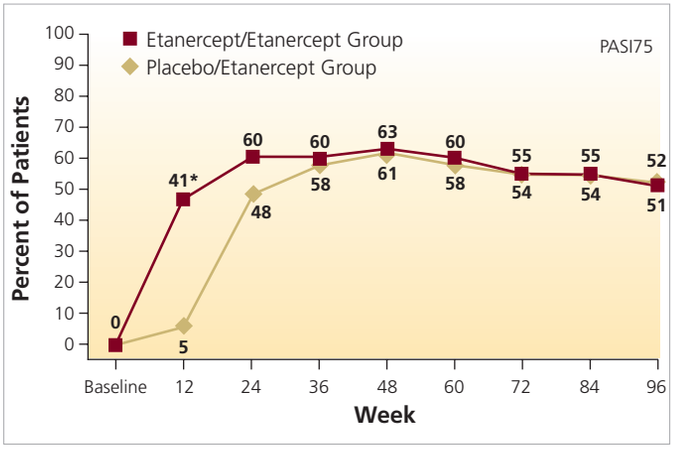
Details of the studies discussed above, and below, have previously been reported and are summarized in a review article published in the *Journal of Drugs in Dermatology*, June 2009.[13]

FIGURE 1. Psoriasis Area and Severity Index (PASI) 75 response rates across 24 weeks of treatment with etanercept: results of a double-blind, placebo-controlled clinical trial with step-down dosing.[9]



* *P*<0.0013 versus placebo; †*P*<0.004 versus etanercept 25 mg twice weekly ‡*P*<0.001 versus placebo.

FIGURE 2. Psoriasis Area and Severity Index (PASI) 75 response rates across 96 weeks of treatment with etanercept.[11]



Investigators at the 2009 American Academy of Dermatology meeting reported long-term study results from an extension study of Canadian adults with moderate-to-severe psoriasis from two precursor trials (n=383).[9,11,14,15] Patients were treated with etanercept between 2 and 4.2 years, for an accumulated exposure of 1169.5 patient-years. Etanercept doses in the extension phase were 50 mg weekly (n=32) or 50 mg BIW (n= 51). Primary efficacy end points were change in PGA, patient global assessment (PtGA), and change in Dermatology Life Quality Index (DLQI). PGA and PtGA results are presented in Figure 3. As noted by these and the DLQI results (not shown), patients treated with etanercept for up to 4.2 years experienced sustained efficacy with weekly or twice-weekly dosing.[16]

Infliximab

An abundance of clinical data about the efficacy and safety of infliximab for the treatment of psoriasis has been generated during

the last decade. In 2001, Chaudhari and colleagues performed a placebo-controlled, double-blind 10-week trial followed by an open-label phase-out period of 16 weeks in adults with moderate to severe psoriasis. Patients (n=33) were randomized to receive infliximab 5 mg/kg, 10 mg/kg, or placebo at weeks 0, 2 and 6. At week 10, 82% of patients in the 5 mg/kg group and 91% in the 10 mg/kg group compared with 18% in the placebo group achieved ratings of good, excellent or clear on the PGA (primary end point, *P*=0.0089, 5 mg/kg versus placebo; *P*=0.0019, 10 mg/kg versus placebo).[17] Thirty patients entered into the open-label extension. Nonresponders in the placebo group received infliximab 5 mg/kg or 10 mg/kg at weeks 10, 12 and 16 while responders were followed and offered infliximab upon relapse. Nonresponders in the 5 mg/kg group were offered one infusion at the 10 mg/kg dose. Nonresponders in the 10 mg/kg group were dropped from the study. Twenty-nine patients received infliximab 5 mg/kg or 10 mg/kg, while one patient in the placebo group did not require medication for the duration of the trial. PASI 75 response rates at weeks 16 and 26 were 82% and 33%, respectively, for the 5 mg/kg group and 73% and 67%, respectively, for the 10 mg/kg group, suggesting a dose-response for duration of clinical benefit.[18]

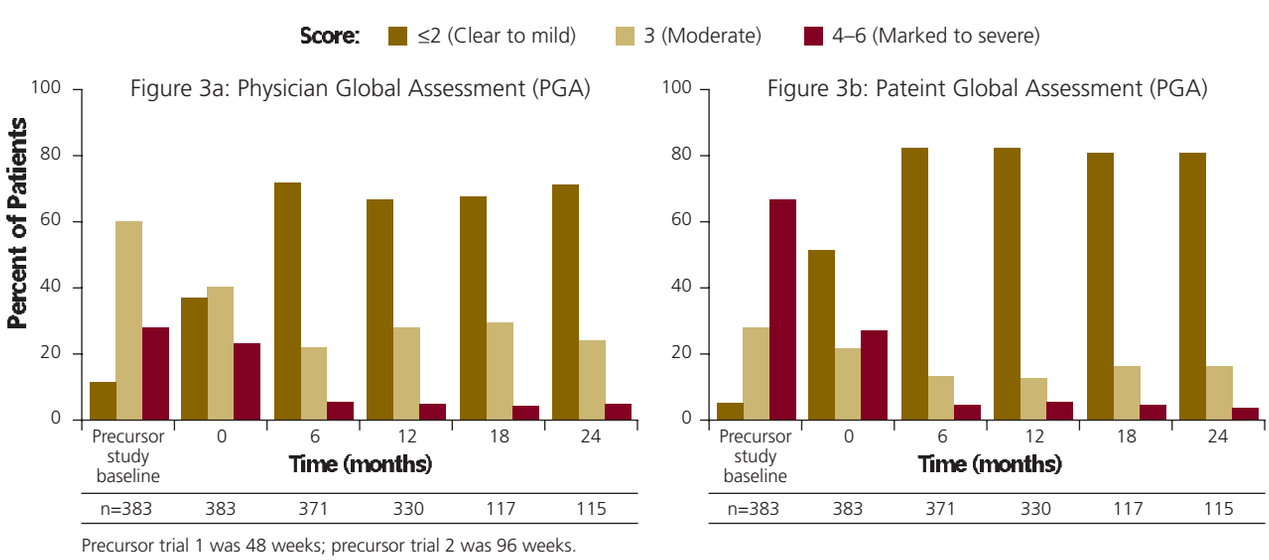
Reich and colleagues performed a large, long-term phase III, double-blind, placebo-controlled study that evaluated the 5 mg/kg infliximab dose. Patients were randomized to receive placebo (n=77) or infliximab 5 mg/kg (n=301) at weeks 0, 2, 6 and every eight weeks to week 46. At week 24, patients in the placebo group were switched to receive infliximab infusions at weeks 24, 26, 30 and every eight weeks to week 46. The primary efficacy variable of PASI 75 response at week 10 was achieved in 80% in the infliximab group and 3% in the placebo group (*P*<0.0001). Response rates were maintained through week 24, but declined to 61% by week 50. PASI 75 response was achieved at week 50 in 77% of patients in the original placebo group who switched at week 24 to infliximab 5 mg/kg.[19]

A 2007 study by Menter et al. provides guidance on dosing strategies for attaining the greatest benefits with infliximab administration. In the double-blind, placebo-controlled trial, patients (n=835) were randomly assigned to receive infusions of infliximab 3 mg/kg or 5 mg/kg either every eight weeks through week 46 (i.e., continuous dosing) or on an as-needed basis when improvement fell below PASI 75. In both groups, induction infusions at weeks 0, 2 and 6 were administered. During the initial randomization, 208 patients were assigned to the placebo group and received induction infusions of placebo following the same schedule as those in the active treatment groups. The 183 subjects in the placebo group who continued the study after week 14 were crossed over to active treatment with infliximab 5 mg/kg dosed at weeks 16, 18, and 22, and every eight weeks thereafter. PASI 75 response rates at week 10 were 70.3% in the infliximab 3 mg/kg group, 75.5% in the 10 mg/kg group, and 1.9% in the placebo group (*P*<0.001). PASI 75 response rates based on dosage and dosing schedule are illustrated in Figure 4 for weeks 26 and 50. The findings provide evidence that response is dose-related and administration at regular intervals is associated with greater beneficial response than an intermittent dosing schedule.[20]

Adalimumab

Approved in January 2008, clinical studies have demonstrated adalimumab to be an effective agent for the treatment of psoriasis. In 2006, Gordon et al. reported results from a long-term adalimumab study that consisted of a 12-week, double-blind, placebo-controlled phase followed by an extension to week 60.

FIGURE 3. Mean physician and patient global assessments, baseline to month 24.[16]



Precursor trial 1 was 48 weeks; precursor trial 2 was 96 weeks.

Patients were randomized (n=148) to receive placebo, adalimumab 80 mg at week 0 followed by 40 mg every other week (EOW), or adalimumab 80 mg at week 0 followed by 40 mg weekly. Patients in the placebo group were switched to adalimumab 80 mg at week 12 then 40 mg EOW beginning at week 13. Subjects who did not achieve a PASI 50 with the EOW dosing schedule could increase their dose to 40 mg weekly. A dose response was observed as measured by the primary efficacy measure of PASI 75 response rates at week 12: 53%, 80% and 4% for the adalimumab 40 mg EOW, 40 mg weekly and placebo groups, respectively (P<0.001). At week 60 there was a decline in the PASI 75 response rate to 64% in the weekly group; however, the response rate was maintained at 58% in the EOW group.[21]

Another year-long study was the large (n = 1212) and recent (2008) double-blind, placebo-controlled, phase 3 study by Menter and colleagues that evaluated adalimumab during three treatment periods as presented in Figure 5. PASI 75 response rates at week 16 were 71% for the adalimumab group and 7% for the placebo group (*P*<0.001). During the 17 weeks of the open-label second phase of the study, improvement from baseline was maintained. The final period of the study showed 28% of patients randomized to the placebo group lose adequate response (i.e., score less than PASI 50) compared with 5% of those who continued to receive adalimumab EOW.22 The PASI 75 response rate at the end of the 52-week study was 85%. An additional six-month treatment period was appended to the study for a total of 18 months of continuous adalimumab treatment. The PASI 75 response rate was maintained at 87% following 18 months of treatment with adalimumab.[23]

At the 2009 annual AAD meeting, investigators presented several noteworthy adalimumab studies that may also help guide treatment practices. A subanalysis of data from the Menter 2008 study discussed above evaluated the impact of treatment interruption and retreatment with adalimumab on outcomes in patients with prior PASI 75 responses. Patients who had their adalimumab administration interrupted experienced worsening of their symptoms while on placebo. Retreatment for 24 weeks improved psoriasis symptoms but not to the levels previously attained. PASI responses were minimally altered for patients given continuous, uninterrupted adalimumab treatment (Figure 6).[24]

Papp and colleagues analyzed data to determine the effect of adalimumab administration on the rate of progression from moderate-to-severe psoriasis. The primary outcome measure for the subanalysis was time to progression to severe psoriasis, defined as a follow-up visit with PASI >20 and DLQI >10. The re-

FIGURE 4. Psoriasis Area and Severity Index (PASI) 75 response rates at weeks 26 and 50.[20]

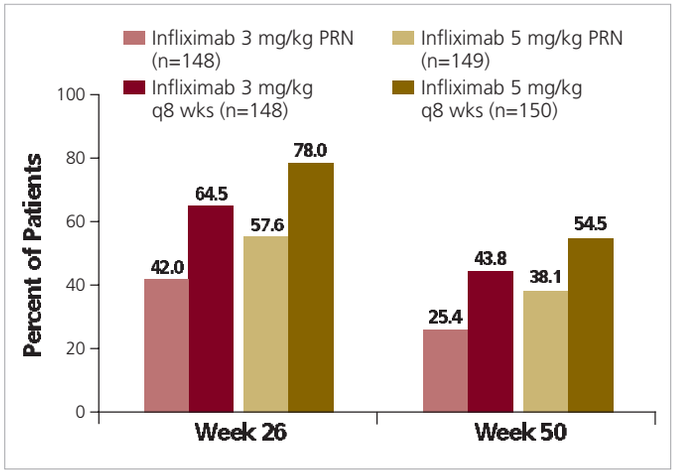
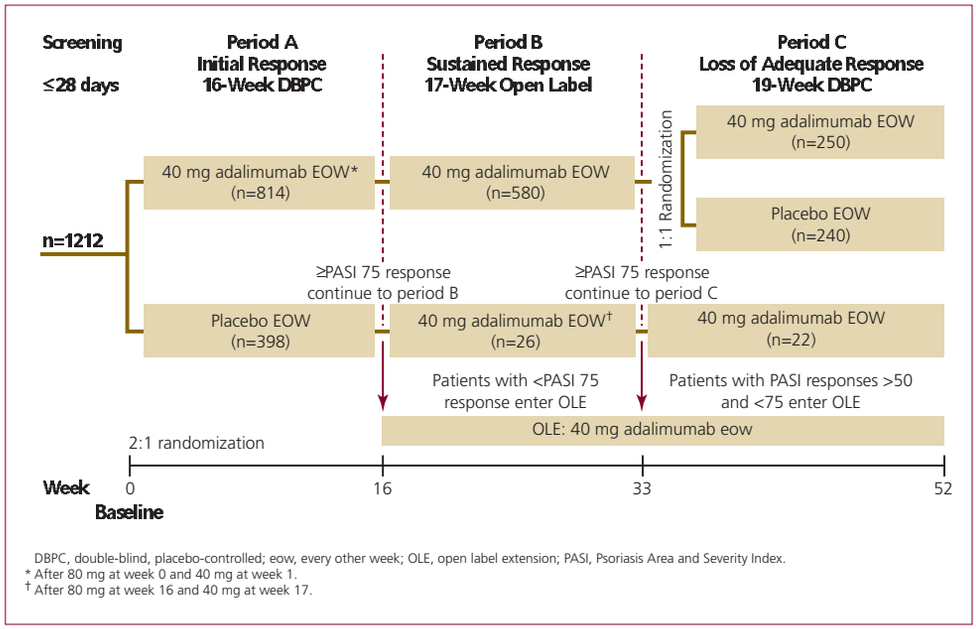


FIGURE 5. Study design for a double-blind, placebo-controlled, clinical trial with three treatment periods.[20,22]



DBPC, double-blind, placebo-controlled; eow, every other week; OLE, open label extension; PASI, Psoriasis Area and Severity Index.
* After 80 mg at week 0 and 40 mg at week 1.
† After 80 mg at week 16 and 40 mg at week 17.

searchers reported that patients treated with adalimumab had their risk of progression from moderate to severe psoriasis reduced by 94%. The 17-week risk for progression from moderate-to-severe psoriasis was 19% in the placebo group and 0.6% in the adalimumab 40 mg EOW group.[25]

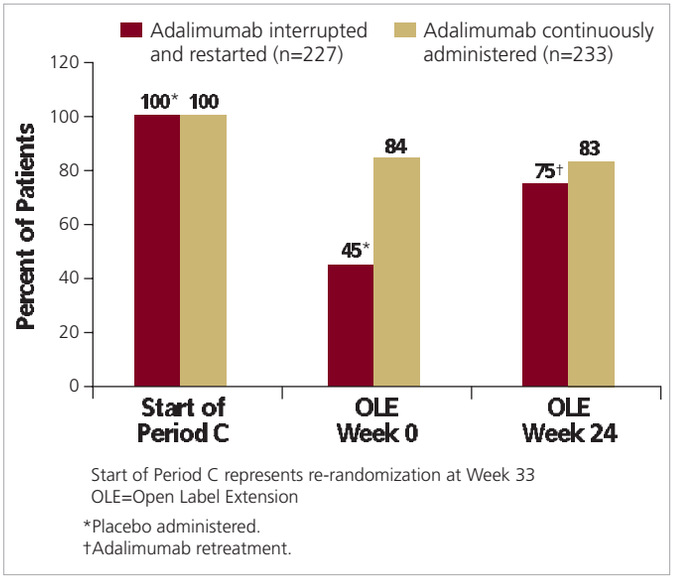
Alefacept

Until recently, the two T cell inhibitors alefacept and efalizumab were approved for the treatment of psoriasis; however, in June 2009 efalizumab was pulled from the U.S. market (see next section). Alefacept continues to be available with clinical data demonstrating its effectiveness in treating psoriasis. Krueger and colleagues performed a double-blind, placebo-controlled phase 3 study of patients (n=553) randomized to one of three treatment groups with drug administered intravenously (IV): two successive 12-week alefacept courses, one 12-week course with alefacept followed by a 12-week course with placebo, or one 12-week course with placebo followed by a 12-week course with alefacept. Results are presented in Table 1. Duration of response was notable with patients who achieved PASI 75 with a single course of alefacept maintaining at least a PASI 50 for more than seven months. Two courses provided longer duration of response but the time period was not quantified.[26]

A 10 mg weekly intramuscular (IM) dose and 15 mg weekly alefacept IM dose were evaluated in a double-blind, placebo-controlled clinical trial in which 507 patients were randomly assigned to a treatment or placebo group. Treatment was administered for 12 weeks and then followed by a 12-week post-dosing observational period. Improvements in PASI scores were observed in a dose-dependent manner, peaking 6 weeks after the end of treatment. Twelve weeks' post-treatment, mean PASI scores did not return to baseline. Maximum PASI reductions from baseline were 46%, 41% and 25% for the 15 mg, 10 mg and placebo groups, respectively.[27]

Patients from the two previously discussed studies who failed to improve with the initial course of therapy were entered into an extension study to receive up to five courses of alefacept, IM or

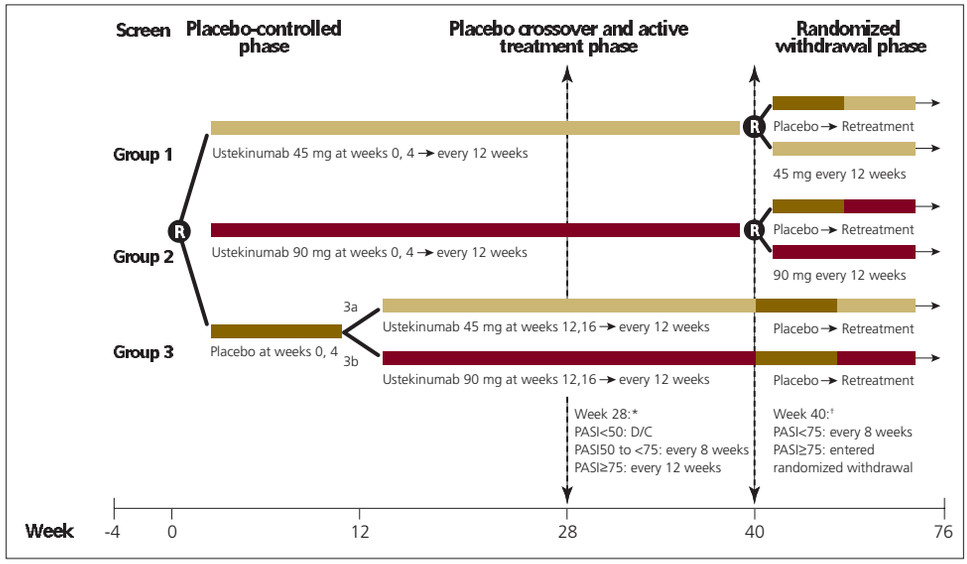
FIGURE 6. Psoriasis Area and Severity Index (PASI) 75 responses for patients whose adalimumab was interrupted and restarted versus patients treated continuously with adalimumab.[24]



Start of Period C represents re-randomization at Week 33
OLE=Open Label Extension

*Placebo administered.
†Adalimumab retreatment.

FIGURE 7. PHOENIX 1 study design.[39,40]



Study schema from week 0 through week 76 including the placebo-controlled phase (week 0–12), the placebo crossover and active treatment phase (weeks 12–40), and the randomized withdrawal phase (week 40–76).

D/C=discontinued. PASI=psoriasis area and severity index. R=randomization. *At week 28, in all groups, non-responders (PASI<50) discontinued study agent, partial responders (PASI 50 to <75) began dosing every 8 weeks, and PASI responders (PASI≥75) received dosing every 12 weeks. †At week 40, PASI responders to dosing every 12 weeks in groups 1 or 2 were randomized to either placebo or continued to receive ustekinumab every 12 weeks at their original dose. Individuals in group 3 received placebo. At loss of therapeutic effect patients receiving placebo began retreatment at their dosing regimen before withdrawal. In all groups, non-responders or partial responders were adjusted to dosing every eight weeks. Patients already receiving dosing every eight weeks continued this dosing schedule.

IV. Each successive treatment generated incremental improvements: 29% of patients achieved PASI 75 with the first course, 54% achieved the score with the fifth course.[28]

Effects of alefacept were analyzed in a retrospective chart review of 201 patients given 296 courses of alefacept treatment. Response to therapy as measured using the PGA was excellent in 17%, good in 18%, partial in 31%, and without response in 34% following the first course of therapy. Additional courses of treatment correlated with marked improvement in response. Average remission time for patients with an excellent response was seven months; 25% of the patients remained in remission for a year or more.[29]

Efalizumab

The decision to pull efalizumab from the U.S. market was based on three cases of progressive multifocal leukoencephalopathy (PML) identified in patients treated with efalizumab for more than 3 years. PML is a rare, progressive demyelinating disease of the central nervous system that is often fatal. Caused by activation of the John Cunningham (JC) virus, which sits latently in up to 80% of healthy adults, its activation in immunocompromised individuals is not fully understood. Due to the devastating consequences of PML for which there is no reliable treatment, and the newly found risk of its development associated with long-term efalizumab exposure, alternative therapy to manage psoriasis is advised.[31,32] Moreover, these findings further underscore the importance of constantly re-evaluating the safety profiles of medications and the need for long-term safety data.

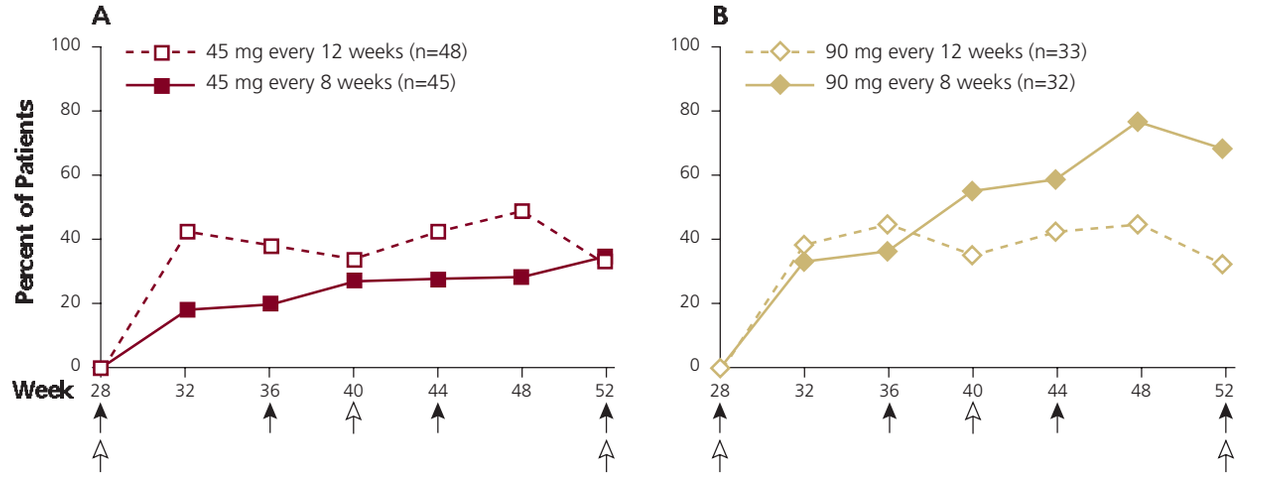
Safety

Review of the clinical data for incidence of adverse events with anti-TNF administration indicates generally comparable rates between active and placebo treatment cohorts. One of the few exceptions was the increased incidence of injection site reactions with etanercept and adalimumab compared with placebo and infusion reactions with infliximab relative to placebo. The key safety concerns with anti-TNF agents are the potentially serious complications that may arise as a consequence of the immunosuppressive nature of the medication, particularly infection and malignancy.[33] Demyelinating disease, lupus-like syndromes, and congestive heart failure are also worrisome—but infrequent—events. In addition, a warning for hepatitis B virus reactivation is included in the prescribing information for the three anti-TNF agents.[34–36]

Findings from an extensive review of published manuscripts and presentations of efficacy and safety studies in psoriasis that used the marketed dosages of anti-TNF agents were presented at the 2009 annual AAD meeting. Rates of serious adverse events (AEs) for the three agents were calculated and are summarized in Table 2. The authors comment that AE rates, which were generally low, may still be overestimated because the rates do not account for the endogenous risk of AEs owing to the disease itself, or for the sequelae associated with prior treatments with other therapeutics. Using comparisons of number needed to treat and number needed to harm, the investigators suggested that the three anti-TNF agents have a large benefit-risk ratio.[7]

Alefacept is generally well tolerated. The only AE with a 5% or higher incidence with alefacept treatment compared with placebo treatment was chills. During the placebo-controlled phase of alefacept clinical trials, incidence of malignancies was 1.3% for the alefacept group and 0.5% for the placebo group. Serious infection rates during the placebo-controlled phase were 0.9% and 0.2% for alefacept and placebo groups, respectively. Alefacept is contraindicated in

FIGURE 8. Clinical response of partial responders with ustekinumab dosed every eight weeks or every 12 weeks.



Proportion of partial responders achieving PASI 75 in the ustekinumab 45 mg (A) and 90 mg (B) groups. Arrows indicate the week that each corresponding treatment was administered (black arrow is every 8 weeks, white arrow is every 12 weeks).[40,41]

patients with human immunodeficiency virus positive patients and should also not be administered to patients with CD4T lymphocyte counts below normal due to the risk of further depletion.[37]

Ustekinumab: New Biologic on the Block

In June 2008 the Dermatologic and Ophthalmic Drugs Advisory Committee of the U.S. FDA recommended approval of ustekinumab for the treatment of adults with moderate-to-severe plaque psoriasis.[38] On May 26, 2009 it was announced that the FDA has extended the review timeline for the Biologic License Application by three months.[39] Ustekinumab is a human monoclonal antibody that binds to IL-12 and -23, blocking signaling to their cell surface receptors. The PHOENIX 1 and 2 studies were phase III studies designed to evaluate the efficacy and safety of ustekinumab for the treatment of moderate-to-severe psoriasis.

PHOENIX 1 was a 76-week, double-blind, placebo-controlled trial of adults with plaque psoriasis. The study design is illustrated in Figure 7. A total of 766 patients were randomized to one of three treatment groups: ustekinumab 45 mg every 12 weeks, 90 mg every 12 weeks, or placebo. PASI 75 response rates at week 12 (the primary efficacy end point) were: 67.1%, 66.4% and 3.1% for the 45 mg, 90 mg and placebo groups, respectively ($P<0.0001$). During the next 12 weeks, efficacy increased, peaking at week 24 with PASI 75 response rates of 76.1% in the ustekinumab 45 mg group and 85% in the 90 mg group. Overall, response rates were sustained through week 40 at which time patients were rerandomized to maintenance therapy or withdrawn from treatment. PASI 75 response rates remained stable in the maintenance therapy group to week 76; those in the withdrawal group experienced a decline in PASI improvements beginning at week 44 and accelerating after week 52. Ustekinumab reinitiation allowed for a PASI 75 response to be achieved in 85.6% of patients within 12 weeks of restarting the medication.[40]

PHOENIX 2 was also a double-blind, placebo-controlled trial of adults with plaque psoriasis performed during a 52-week period. The study was divided into three phases: placebo-controlled (weeks 0 to 12), crossover and active treatment (weeks 12 to 28), and randomized dose intensification (weeks 28 to 52). Patients were randomized (n=1230) at baseline to receive ustekinumab 45 mg or 90 mg at weeks 0, 4 and every 12 weeks, or to receive placebo at weeks 0 and 4 followed by rerandomization to ustekinumab 45 mg or 90 mg at weeks 12, 16 and every 12 weeks. The week 28 dose intensification portion was designed to rerandomize partial responders (i.e., score of >PASI 50 and <PASI 75) to receive a more intense ustekinumab dosing schedule of every 8 weeks or to continue every 12 weeks. Patients who did not achieve PASI 50 discontinued treatment; those who achieved PASI 75 continued on the 12-week dosing schedule. PASI 75 response rates (ie, primary efficacy variable) at week 12 were 66.7% in the ustekinumab 45 mg group, 75.7% in the 90 mg group and 3.7% in the placebo group. PASI 75 responders at week 28 who continued to receive their ustekinumab dose maintained their response to week 52. The partial responders tended to be patients with a higher body weight, greater disease severity, and higher incidence of psoriatic arthritis. When compared with those administered with every 12 week dosing, response rates for partial responders randomized to the every eight-week treatment regimen were greater for those receiving the 90 mg dose of ustekinumab, but not the 45 mg dose (Figure 8).[41]

AEs were generally mild and, therefore, not serious. Common AEs included upper respiratory tract infection, nasopharyngitis, arthralgia and headache. Overall, rates were comparable between the active treatment and placebo groups except for the incidence of headache in PHOENIX 1, where it was reported approximately twice as often with ustekinumab as with placebo.40 Serious AE rates in PHOENIX 1 were 0.8% for the ustekinumab 45 mg group and placebo group and 1.6% for the 90 mg group; PHOENIX 2 rates were 2%, 1.2% and 2% for the ustekinumab 45 mg, 90 mg and placebo groups, respectively.[40,41]

TABLE 1.

Results of Several Efficacy Outcome Measures With One or Two Courses of Alefacept Treatment or Placebo[26]

Treatment Cohort	Outcome (%)
One course of alefacept 7.5 mg	PASI 50: 56 PASI 75: 28 PGA clear or almost clear: 23
Two courses of alefacept 7.5 mg	PASI 50: 71 PASI 75: 40 PGA clear or almost clear: 32
Placebo	PASI 50: 24 PASI 75: 8 PGA clear or almost clear: 6

PASI = Psoriasis Area and Severity Index;
PGA = Physician's Global Assessment.

DISCUSSION

Many patients suffer greatly with psoriasis; however, available treatments can dramatically impact their symptoms and improve overall well being. Data and experience with biologics strongly suggest the class is highly effective in managing symptoms of psoriasis, offering a considerable benefit-risk ratio. Although it has been a decade since the first agent was introduced, many clinicians appear to shy away from their use. Recent data collected on patterns of care among 1,006 patients with psoriasis found biologics were prescribed approximately 2.5 years after first-line therapy. Biologics were used as first-line therapy for 9% of patients. Among those who progressed to second-line therapy, biologics were prescribed for 10%. Biologics accounted for 20% of third-line, 33% of fourth-line and 34% of fifth-line therapies.[42] It remains speculative as to why biologics are often not considered until late in the treatment paradigm when early inclusion of biologics into the clinicians' therapeutic approach may provide rapid and dramatic symptomatic relief to patients. Familiarity with the data may provide an increased level of comfort, prompting practitioners to con-

sider biologics as an upfront choice when managing patients with moderate-to-severe psoriasis.

REFERENCES

1. National Psoriasis Foundation. About psoriasis, statistics. Available at: http://www.psoriasis.org/netcommunity/learn_statistics. Accessed May 29, 2009.
2. Thiers BH, Lang PG Jr. Year Book of Dermatology and Dermatologic Surgery 2007. St Louis, Mo: Elsevier Mosby; 2007:49.
3. Carneiro SC, Japiassu MA, Darcier B, et al. Quality of life in psoriasis: evaluation of 200 patients at a Brazilian university hospital. Poster presented at: American Academy of Dermatology 67th Annual Meeting; March 6-10, 2009; San Francisco, CA. Poster P3353.
4. Waters HC, Carter C, Annunziata K, Piech CT. The impact of psoriasis on psychological functioning and quality of life. Poster presented at: American Academy of Dermatology 67th Annual Meeting; March 6-10, 2009; San Francisco, CA. Poster P3386.
5. Schmitt JM, Ford DE. Work limitations and productivity loss are associated with health-related quality of life but not with clinical severity in patients with psoriasis. *Dermatology*. 2006;213:102-110.
6. Naim AB, Carter CT, Annunziata K, Piech CT. Assessing work productivity loss, absenteeism, and presenteeism among psoriasis sufferers in the United States. Poster presented at: American Academy of Dermatology 67th Annual Meeting; March 6-10, 2009; San Francisco, CA. Poster P3374.
7. Langley RG, Strober B, Gu Y, et al. An evidence-based risk-benefit assessment of adalimumab, etanercept, and infliximab in psoriasis. Poster presented at: American Academy of Dermatology 67th Annual Meeting; March 6-10, 2009; San Francisco, CA. Poster P3323.
8. Leonardi CL, Powers JL, Matheson RT, et al. Etanercept as monotherapy in patients with psoriasis. *N Engl J Med*. 2003;349:2014-2022.
9. Papp KA, Tyring S, Lahfa M, et al. A global phase III randomized controlled trial of etanercept in psoriasis: Safety, efficacy, and effect of dose reduction. *Br J Dermatol*. 2005;152(6):1304-1312.
10. Moore A, Gordon KB, Kang S, et al. A randomized, open-label trial of continuous versus interrupted etanercept therapy in the treatment of psoriasis. *J Am Acad Dermatol*. 2007;56:598-603.
11. Tyring S, Gordon KB, Poulin Y, et al. Long-term safety and efficacy of 50 mg of etanercept twice weekly in patients with psoriasis. *Arch Dermatol*. 2007;143:719-726.
12. Tyring S, Langley R, Gordon KB, Poulin Y. Efficacy and safety profiles of etanercept 50 mg twice weekly for up to 144 weeks in patients with moderate to severe plaque psoriasis. Poster presented at: American Academy of Dermatology 65th Annual Meeting; February 2-6, 2007; Washington DC. Poster P2731.
13. Kircik LH, Del Rosso JQ. Anti-TNF agents for the treatment of psoriasis. *J Drugs Dermatol*. 2009;8(6):546-559.
14. Elewski B, Leonardi C, Gottlieb A, et al. Sustained long-term clinical efficacy and safety for up to 2.5 years of etanercept in patients with psoriasis. Poster presented at: American Academy of Dermatology 64th

TABLE 2.

Serious Adverse Event Rates for Etanercept, Infliximab, and Adalimumab in Clinical Trials for Psoriasis[7]

	Etanercept Various Dosages		Infliximab (3mg/kg and 5 mg/kg dosing)		Adalimumab 40 mg eow	
Patients, n	4,410		1,564		1,403	
Duration of exposure, PYs	4,090		1,013		1,286	
Duration of exposure per patient, months	11.1		7.8		11.0	
	Rate (events)	**NPY (95% CI)**	**Rate (events)**	**NPY (95% CI)**	**Rate (events)**	**NPY (95% CI)**
Serious infections	0.014 (56)†	73† (56, 95)	0.018 (18)	56 (35, 89)	0.015 (19)	68 (43, 106)
Malignancies, excluding NMSC and lymphoma	0.006 (25)	164 (111, 242)	0.002 (2)	507 (127, 2025)	0.004 (5)	257 (107, 618)
NMSC	0.010 (21)‡	98 (64, 150)	0.017 (17)	60 (37,96)	0.007 (9)	143 (74, 275)
Tuberculosis	0	∞	0.002 (2)	507 (127, 2025)	0.002 (3)	429 (138, 1329)
Congestive heart failure	0.001 (5)	818 (340, 1965)	N/A	N/A	0.001 (1)	1286 (181, 9129)
Lymphomas	<0.001 (2)	2045 (51, 8177)	0.001 (1)	1013 (143, 7191)	0	∞
Demylinating disease	<0.001 (1)	4090 (576, 29035)	N/A	N/A	0	∞
Systemic lupus erythematosus/ lupus-like syndrome	0	∞	0.007 (7)	145 (69, 304)	0	∞

N/A = not available.

Value for patient-years calculated from mean exposure per patient and number of patients. Analysis included 200 patients from the IMPACT 2 PsA trial. IMPACT 2 did not contribute any of the listed AEs20.

†Number of events estimated fromt he rate. Possible number of cases consistent with this reported rate ranges from 56 to 59, corresponding to NYP (95% CI) ranging from 69 (54, 89) to 73 (56, 95).

‡The NMSC rate for etanercept is based on 21 cases during 2052.4 PYs

Annual Meeting; March 3-7, 2006; San Francisco, CA. Poster P2908.
15. Tyring S, Gottlieb A, Papp K, et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: Double-blind, placebo-controlled randomized phase III trial. *Lancet*. 2006;367:29-35.
16. Papp K, Poulin Y, Bissonnette R, et al. Assessment of the long-term safety and efficacy of etanercept for the treatment of psoriasis in an adult Canadian population. Poster presented at: American Academy of Dermatology 67th Annual Meeting; March 6-10, 2009; San Francisco, CA. Poster P3314.
17. Chaudhari U, Romano P, Mulcahy LD, Dooley LT, Baker DG, Gottlieb AB. Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: A randomized trial. *Lancet*. 2001;357:1842-1847.
18. Gottlieb AB, Chaudhari U, Mulcahy LD, et al. Infliximab monotherapy provides rapid and sustained benefit for plaque-type psoriasis. *J Am Acad Dermatol*. 2003;48:829-835.
19. Reich K, Nestle FO, Papp K, et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: A phase III, multicentre, double-blind trial. *Lancet*. 2005;366:1367-1374.
20. Menter A, Feldman SR, Weinstein GD, et al. A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. *J Am Acad Dermatol*. 2007;56:31.e1-e15.
21. Gordon KB, Langley RG, Leonardi C, et al. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: Double-blind, randomized controlled trial and open-label extension study. *J Am Acad Dermatol*. 2006;55:598-606.
22. Menter A, Tyring SK, Gordon K, et al. Adalimumab therapy for moderate to severe psoriasis: A randomized, controlled phase III trial. *J Am Acad Dermatol*. 2008;58:106-115.
23. Gordon K, Tyring S, Gu Y, Okun M. Psoriasis patients treated continuously with adalimumab: efficacy and safety results from months 12 to 18. *J Am Acad Dermatol*. 2008;58(2):AB129.
24. Menter A, Gu Y, Sasso EH. Relationship between effectiveness of restarting adalimumab and degree of psoriasis activity after a period of discontinuation. Poster presented at: American Academy of Dermatology 67th Annual Meeting; March 6-10, 2009; San Francisco, CA. Poster P3387.
25. Papp K, Signorovitch J, Gupta S, Mulani P. Adalimumab treatment for moderate psoriasis reduces the risk of transitioning to severe psoriasis. Poster presented at: American Academy of Dermatology 67th Annual Meeting; March 6-10, 2009; San Francisco, CA. Poster P3378.
26. Krueger GG, Papp KA, Stough DB, et al. A randomized, double-blind, placebo-controlled phase III study evaluating efficacy and tolerability of 2 courses of alefacept in patients with chronic plaque psoriasis. *J Am Acad Dermatol*. 2002;47:821-833.
27. Lebwohl M, Christophers E, Langley R, et al. An international randomized double-blind, placebo-controlled phase 3 trial of intramuscular alefacept in patients with chronic plaque psoriasis. *Arch Dermatol*. 2003;139:719-727.
28. Menter A, Leonardi CL, Sterry W, Bos JD, Papp KA. Long-term management of plaque psoriasis with continuous efalizumab therapy. *J Am Acad Dermatol*. 2006;43(suppl):s182-s188.
29. Perlmutter A, Cather J, Franks B, et al. Alefacept revisited: Our 3-year clinical experience in 200 patients with chronic plaque psoriasis. *J Am Acad Dermatol*. 2008;58:116-124.
30. Kircik LH, Weinberg JM. Critical reviews of clinical data: Focus on T cell agents for the treatment of psoriasis. *J Drugs Dermatol*. 2009;8(5 Suppl).
31. Genentech, Inc. Important drug warning regarding Raptiva® (efalizumab) Available at: http://www.gene.com/gene/products/information/pdf/raptiva_dhcp_pml2.pdf. November 2009. Accessed June 5, 2009.
32. Genentech, Inc. Dear health care professional letter. Available at: http://www.gene.com/gene/products/information/pdf/raptiva_dhcp_pml3.pdf. February 10, 2009. Accessed June 5, 2009.
33. Patel RV, Clark LN, Lebwohl M, Weinberg JM. Treatments for psoriasis and the risk of malignancy. *J Am Acad Dermatol*. 2009;60:1001-1017.
34. Enbrel [package insert]. Thousand Oaks, CA: Amgen and Wyeth; 2009.
35. Remicade [package insert]. Malvern, PA: Centocor, Inc; 2009.
36. Humira [package insert]. North Chicago, IL: Abbott Laboratories; 2009.
37. Amevive [package insert]. Deerfield, IL: Astellas Pharma US, Inc. 2009.
38. Drugs.com. Treatment for psoriasis. Available at: http://www.drugs.com/nda/ustekinumab_080618.html. Accessed May 27, 2009.
39. redOrbit. FDA extends review timeline for STELARA™ (ustekinumab) biologic license application by three months. Available at: http://www.redorbit.com/news/health/1695098/fda_extends_review_timeline_for_stelaratm_ustekinumab_biologic_license_application/index.html?source=r_health. Accessed May 28, 2009.
40. Leonardi CL, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomized, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet*. 2008;371:1665-1674.
41. Papp KA, Langley RG, Lebwohl M, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomized, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet*. 2008;371:1675-1684.
42. Carter CT, Waters HC, Annunziata K, Piech CT. Patient-reported pattern of care in psoriasis. Poster presented at: American Academy of Dermatology 67th Annual Meeting; March 6-10, 2009; San Francisco, CA. Poster P3345.

ADDRESS FOR CORRESPONDENCE

Jeffrey M. Weinberg, MD
St. Luke's-Roosevelt Hospital Center
Department of Dermatology
1090 Amsterdam Ave, Suite 11-D
New York, NY 10025-1737
Phone: ..... (212) 523-4366
E-mail: ..... jweinberg3@nyc.rr.com