Clinical Benefits in Patients With Psoriasis After Efalizumab Therapy: Clinical Trials Versus Practice

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Evaluations of efficacy of the new biologic therapies for psoriasis have used both physician-assessed endpoints and patient-reported outcome measures. The Psoriasis Area and Severity Index (PASI) is commonly used in clinical trials but is too labor intensive for clinical practice, which uses more subjective measures (physician global assessment [PGA] of change and Overall Lesion Severity [OLS] scale). Because psoriasis affects quality of life (QOL), patient-reported assessments of their satisfaction with treatment also are important.

The purpose of this study was to evaluate some of the measurement tools used in clinical trials to make them more applicable to the practicing dermatologist. We used results of a placebo-controlled clinical study of efalizumab for the treatment of patients with moderate to severe plaque psoriasis. After treatment, ratings of improvement in psoriasis as measured by the PASI and PGA were closely aligned. It was noted the latter tool could provide a more practical and user-friendly evaluation in clinical practice. After 12 weekly subcutaneous injections of efalizumab, patients who achieved ≥50% but <75% improvement in PASI had treatment responses rated as primarily good or excellent using the PGA; additionally, the patients treated with efalizumab had statistically significant improvements (P<.001) in all patient-reported QOL assessments compared with placebo-treated patients, as did patients who achieved a ≥75% improvement in PASI (PASI 75).

Cutis. 2004;74:193-200.

Psoriasis is a chronic inflammatory condition of the skin characterized by erythematous, sharply demarcated plaques covered by silvery-white scales. There is no cure for psoriasis, and patients may require long-term therapy, often over decades, to manage their condition. A new class of psoriasis therapies, the biologics, has been developed in response to the dissatisfaction of patients to traditional therapies,[1,2] the potential risk of long-term toxicity with current systemic modalities,[3] and the possibility of using agents specifically designed to act on the immunogenesis of psoriasis.[4] Activated memory T cells are central to the immunobiological basis of psoriasis.[5] One of the new biologics, efalizumab (anti-CD11a), has been shown to be efficacious and well tolerated in clinical trials for moderate to severe chronic plaque psoriasis.[6-11] Efalizumab is a recombinant humanized monoclonal antibody that binds to lymphocyte cell surface marker CD11a, the α chain of leukocyte function–associated antigen 1 (LFA-1), a marker expressed on the surface of T cells. Efalizumab prevents the interaction of LFA-1 and

the intercellular adhesion molecule 1 between T lymphocytes, antigen presenting cells, and vascular endothelial cells. This reversibly inhibits multiple steps in the immunologic cascade that result in the generation of psoriatic plaques, including T-cell activation, trafficking from the circulation into the dermal and epidermal tissue, and T-cell reactivation in the dermis and epidermis.

Traditionally, physicians have evaluated psoriasis on a somewhat subjective clinical basis. In clinical trials, the Psoriasis Area and Severity Index (PASI)[12,13] is the most common method used to assess drug efficacy. The US Food and Drug Administration has set a PASI 75 outcome (≥75% improvement in PASI score from baseline) as the primary efficacy endpoint for new therapeutic agents in psoriasis. However, in clinical practice, the PASI is not practical for routine use because it is too complicated and time-consuming. Other more amenable measures include the physician global assessment (PGA) of change (a dynamic measure categorizing responses with a 7-point severity scale)[14] and Overall Lesion Severity (OLS) scale (a static measure of disease severity; also called static PGA).[12,13] It is important for practicing clinicians to understand how evaluations reported in the clinical trial literature compare with their office assessments of disease presentation in patients and of treatment outcomes.

In addition to clinical responses to treatment, physicians and patients are concerned about the impact of psoriasis on quality of life (QOL).[2] Disease severity and health-related QOL are closely linked.[15,16] Questionnaires used to evaluate the impact of efalizumab on QOL have included the Dermatology Life Quality Index (DLQI),[17] the Visual Analog Scale (VAS) for assessment of itching,[18] and the Psoriasis Symptoms Assessment (PSA) scale.[18] Recent clinical reports have indicated that the new biologic therapies for psoriasis do improve QOL.[11,19] It is important to know how these patient-reported improvements in QOL coincide with physician assessments of psoriasis symptoms.

Our objective in this analysis was to determine how psoriasis evaluations used to establish efficacy in clinical trials might be related to assessments more appropriate to clinical practice. We used the database from a phase 3 clinical trial of efalizumab to determine the association between treatment responses assessed by the PASI and PGA of change. We wanted to determine whether PASI improvements relative to baseline at 3 levels of response (<50%, ≥50% but <75%, and ≥75%) are associated with clinically significant improvements in
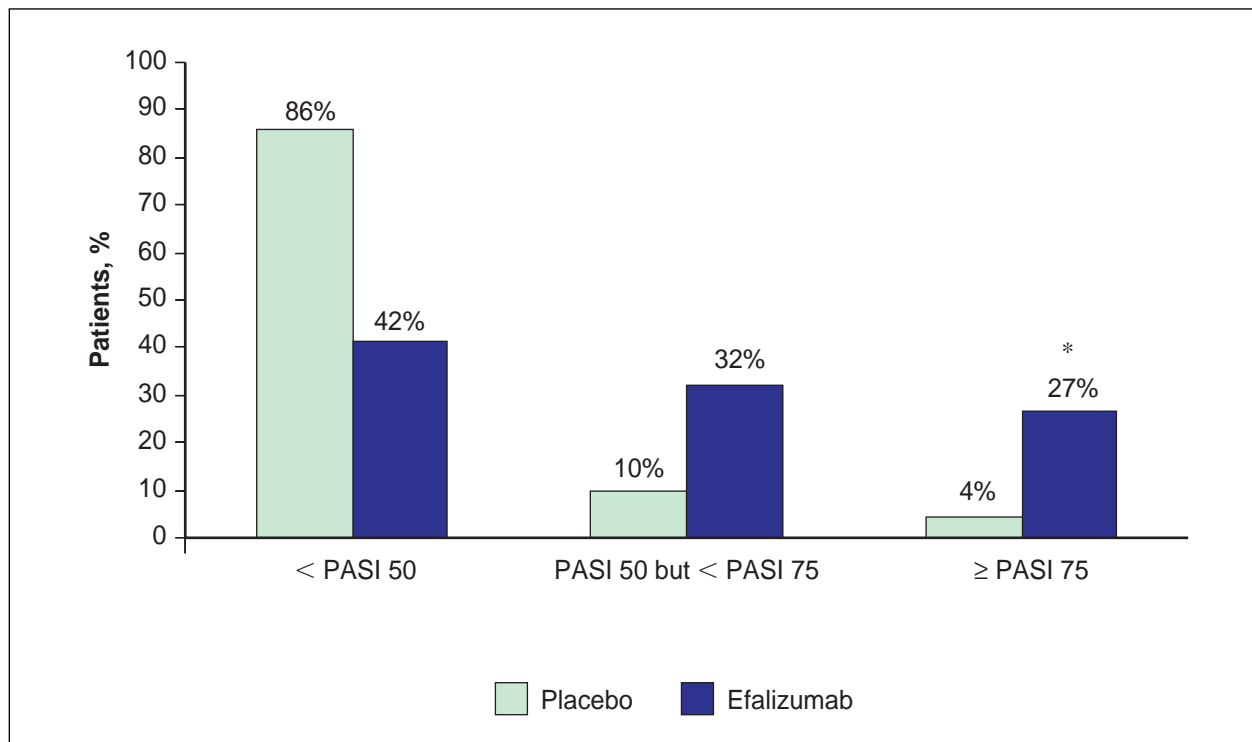

Figure 1. Psoriasis Area and Severity Index (PASI) scores in patients with moderate to severe chronic plaque psoriasis after 12 weeks of efalizumab therapy or placebo. Asterisk indicates *P*<.001. Data are from Gordon et al.[11]
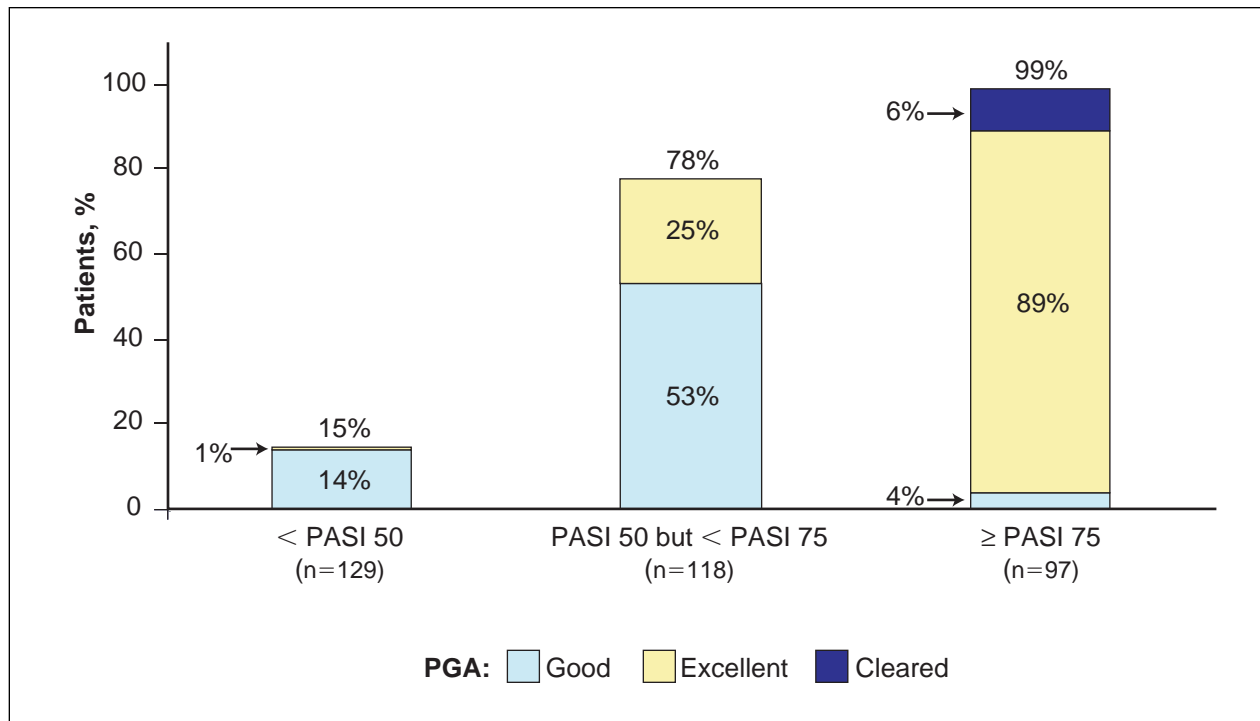
Figure 2. Association between Psoriasis Area and Severity Index (PASI) improvements and physician global assessment (PGA) of change in patients with responses to 12 weeks of efalizumab therapy. Data are from Gordon et al.[11]

QOL and to access whether the severity of a patient's psoriasis prior to treatment impacts the QOL benefits that can be achieved from treatment.

Methods

Study Design—A phase 3 randomized, double-blind, placebo-controlled study described in detail by Gordon and colleagues[11] was conducted to evaluate the efficacy, safety, and tolerability of 12 weeks of subcutaneous efalizumab (1 mg/kg per week) in adults with moderate to severe chronic plaque psoriasis. All patients signed informed consent and all sites received Institutional Review Board approval prior to study initiation. A total of 369 patients were randomized to receive efalizumab and 187 patients to receive placebo. Treatment was as a monotherapy, though bland emollients were permitted, as were tar and salicylic acid preparations for the scalp and low-potency topical corticosteroids. Systemic antipsoriasis therapies and phototherapy were excluded.[11]

Patient Population—Patients enrolled were predominantly white (aged 18–75 years) with plaque psoriasis of at least 6 months' duration with 10% or more body surface area involved. A minimum PASI score of 12 was required at screening, and patients were required to be candidates for systemic therapy.[11]

Efficacy Analysis—Several physician assessments of treatment outcomes were evaluated including the PASI, PGA of change, and OLS scale. The primary efficacy endpoint was the proportion of patients with PASI 75 at week 12 relative to baseline. In addition, patient responses were categorized either as < PASI 50, PASI 50 but < PASI 75, or ≥ PASI 75. Patient-reported assessments included the validated DLQI (a 10-item questionnaire measuring disease-related limitations; scores range from 0–30), patient global psoriasis assessment (PGPA), VAS for assessment of itching (scores range from 0–10), and PSA frequency and severity subscales (scores range from 0–24).[11]

The PASI 75 and the PASI 50 but < PASI 75 response rates after efalizumab treatment were compared with the response rate in the placebo group using a 2-sided Fisher exact test. The mean improvements in patient-reported outcomes were compared between the placebo group and the PASI 50 but < PASI 75 responders in the efalizumab-treated group using the *t* test.[11]

Results

There were no significant differences in patient demographics, baseline disease characteristics, and severity between the 2 treatment groups. The
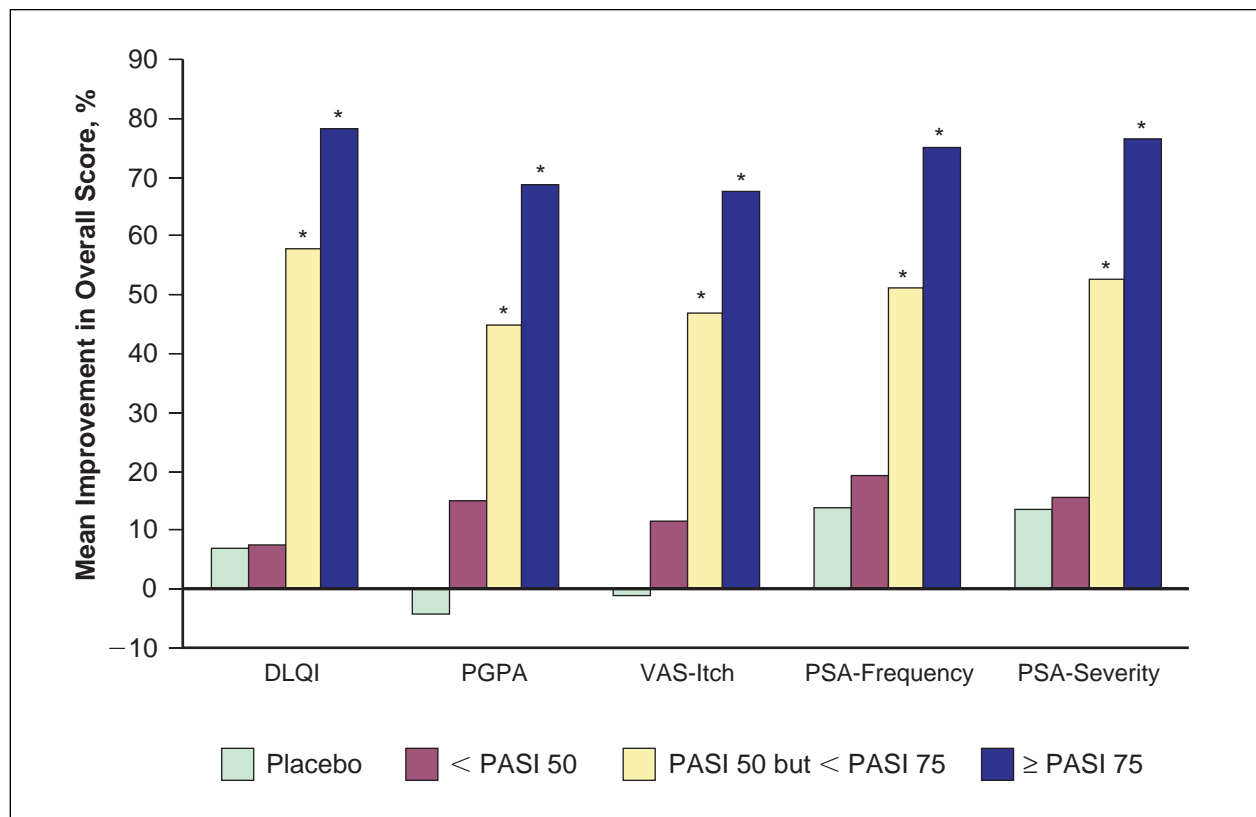
Figure 3. Mean improvement in patient-reported quality of life after 12 weeks of efalizumab therapy or placebo. Asterisk indicates $P<.001$ vs all placebo-treated patients and patients with < PASI 50; PASI, Psoriasis Area and Severity Index; DLQI, Dermatology Life Quality Index; PGPA, patient global psoriasis assessment; VAS, Visual Analog Scale; PSA, Psoriasis Symptoms Assessment. Data are from Gordon et al.[11]

patients with moderate to severe plaque psoriasis had a mean baseline PASI score of 19; the mean baseline body surface area involved for both the efalizumab and placebo groups was 28% and 27%, respectively. Using the PASI to assess outcomes after 12 weeks of therapy, 59% (216/369) of efalizumab-treated patients were scored as having had PASI 50 compared with 14% (26/187) of the placebo-treated patients ($P<.001$); 27% of patients achieved PASI 75 versus 4% of placebo-treated patients ($P<.001$)(Figure 1).[11]

In patients treated with efalizumab for 12 weeks, a comparison was made between the physician-rated measures—PASI score and categorical PGA of change (Figure 2). Patient responses evaluated by PGA of change were closely aligned with the PASI improvements. A total of 78% of patients who achieved PASI 50 but < PASI 75 responses were characterized as good/excellent by PGA of change, and the PASI 75 responses were primarily excellent (89%). A few patients (14%) with < PASI 50 did have outcomes that were rated as good. Although the number of placebo-treated patients

with ≥ PASI 50 was small (26/187), evaluations of response by PGA showed a similar strong association with PASI.[11]

Post hoc analyses demonstrated that patients who achieved a treatment response of PASI 75, as well as those who achieved PASI 50 but < PASI 75, had significant improvements in all patient-reported QOL measures (DLQI, PGPA, VAS for assessment of itching, and PSA frequency and severity subscales) compared with all placebo-treated patients and patients with < PASI 50 ($P<.001$)(Figure 3). Patients with < PASI 50 after treatment reported modest improvements in itching and PGPA. Thus, the QOL improvements closely reflected the improvements patients experienced in psoriatic skin symptoms. The association between improved PASI scores and improved QOL also was seen in the small group of placebo-treated patients who achieved ≥ PASI 50. Assessments also were made of the individual components of the DLQI, which are indicative of the dermatology-related limitations and impact of disease on emotional and social functioning. Patients who achieved ≥ PASI 50 after
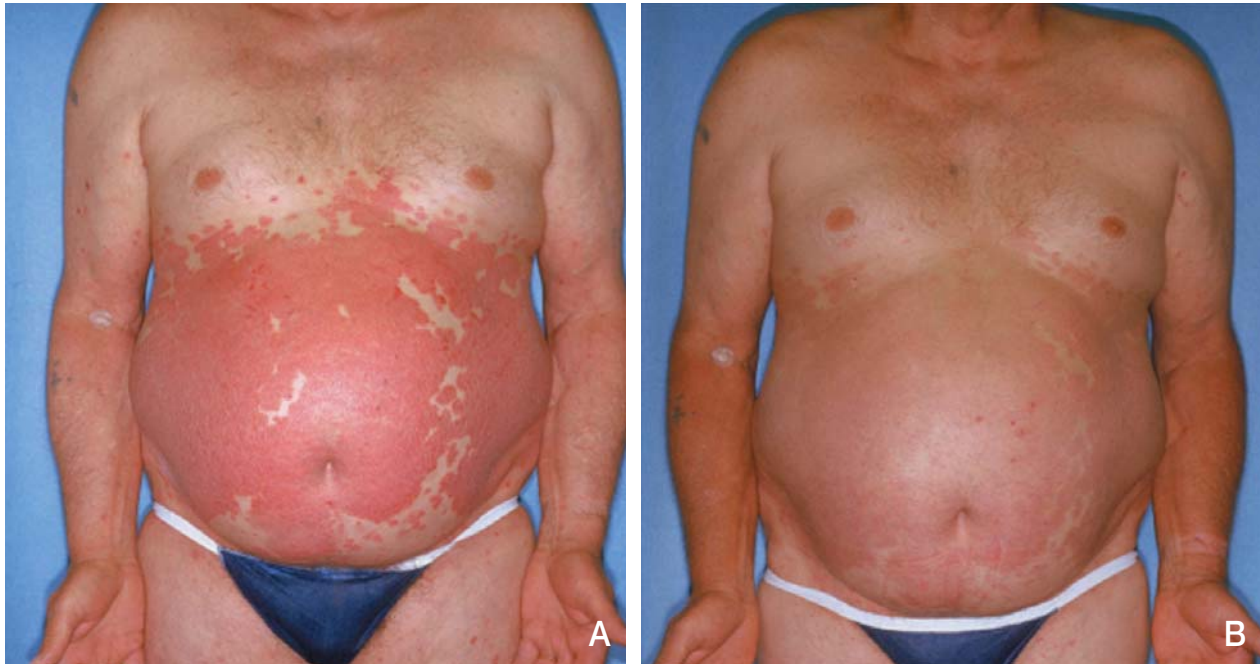
Figure 4. A patient with severe chronic plaque psoriasis at baseline (A) with a Psoriasis Area and Severity Index (PASI) score of 22. After 12 weeks of subcutaneous efalizumab therapy (B), the patient achieved PASI 50 but < PASI 75 response (57% improvement) and a physician global assessment of change score of good. Dermatology Life Quality Index and Psoriasis Symptoms Assessment frequency and severity subscales improved by ≥65% (range, 65%–100%); Visual Analog Scale for assessment of itching and patient global psoriasis assessment were improved by 10%–30%.

12 weeks of efalizumab therapy reported substantial improvements in all aspects of QOL compared with all placebo-treated patients. Examples of patients' responses to efalizumab therapy, including both psoriasis symptoms and QOL outcomes, are shown and discussed in Figures 4 and 5.[11]

The severity of psoriasis before treatment, as rated by the OLS scale, had little or no impact on whether patients would attain meaningful therapeutic benefits. After 12 weeks of efalizumab treatment, patients with psoriasis that was characterized as severe or very severe before treatment achieved similar degrees of improvement in all patient-reported QOL measures as did patients who entered the study with less severe psoriasis (Figure 6).[11]

Comprehensive safety and tolerability results are reported elsewhere.[11] However, once-weekly efalizumab therapy was well tolerated without any evidence of end organ toxicity. Infection and malignancy rates after 12 weeks of therapy were comparable with those in the placebo-treated group.[11]

Comment

The PASI remains the most widely used tool for evaluating psoriasis severity in clinical studies of new antipsoriasis therapeutics. PASI scores are based on the quantitative assessment of degree of erythema, scaling, and induration of the plaque, weighted by the body surface area involved. The PASI is not practical for use in clinical practice. The measures are time-consuming, have high interobserver variability in the calculation of involved area, and are not a linear measure of severity.[20] Interpretation of the PASI scores reported in the literature can be difficult for the practicing dermatologist. The PGA of change is a simpler measure of disease severity, providing a categorical description of disease presentation and response to treatment (eg, worse, unchanged, slight, fair, good, excellent, clear).

We compared the PASI and PGA of change assessments conducted during the 12-week efalizumab clinical trial. These clinical metrics were found to be closely associated. Of the efalizumab-treated patients who achieved PASI 75, 99% were rated with PGA scores of good, excellent, or clear. A total of 78% of patients with PASI 50 but < PASI 75 received PGA scores of good or excellent. This analysis illustrates that although PASI 75 is the primary endpoint mandated by the US Food and Drug Administration, a response of PASI 50 but < PASI 75 had a significant clinical impact on patients for amelioration of psoriasis

Figure 5. A patient with severe chronic plaque psoriasis at baseline (A) with a Psoriasis Area and Severity Index (PASI) score of 45.2. After 12 weeks of subcutaneous efalizumab therapy (B), the patient achieved a PASI 75 response (95% improvement) and a physician global assessment of change score of excellent. All patient-reported assessments, including Dermatology Life Quality Index and Psoriasis Symptoms Assessment frequency and severity subscales, Visual Analog Scale for assessment of itching, and patient global psoriasis assessment, were improved by ≥60% (range, 61%–88%).

symptoms, improved dermatologic-related functionality, and patient well-being.

It is anticipated that clinically meaningful improvements in QOL would be incremental with improvements in PASI scores. After treatment with efalizumab, patients with psoriasis with ≥ PASI 75 had improvements ranging from approximately 70% to 80% in all patient-reported QOL assessments. Each of the measures (DLQI, VAS for assessment of itching, PSA frequency and severity subscales, and PGPA) was significantly better (P<.001) compared with outcomes for placebo-treated patients. Patients who attained PASI 50 but < PASI 75 after efalizumab therapy also had substantial (approximately ≥50%) improvements in their psoriasis severity and symptoms, as well as in their emotional life and social functioning. These improvements were significantly better (P<.001) compared with the placebo group. When

the individual components of the DLQI related to function limitations caused by psoriasis were examined, there was confirmation that ≥ PASI 50 (including PASI 50 but < PASI 75 and PASI 75) after efalizumab therapy resulted in substantial improvements in QOL compared with placebo.[11]

In summary, once-weekly subcutaneous efalizumab therapy is a novel psoriasis therapy that provides statistically significant improvements in moderate to severe chronic plaque psoriasis. The outcomes of treatment, rated using the clinical trial or clinical practice measures of the PASI and PGA of change, respectively, were closely associated with attainment of clinically significant patient benefits reflected in all patient-reported QOL measures. We suggest that the categorical PGA of change is a tool that could be easily used in clinical practice for assessing patients' response to therapy. The PGA aligns with PASI outcomes and
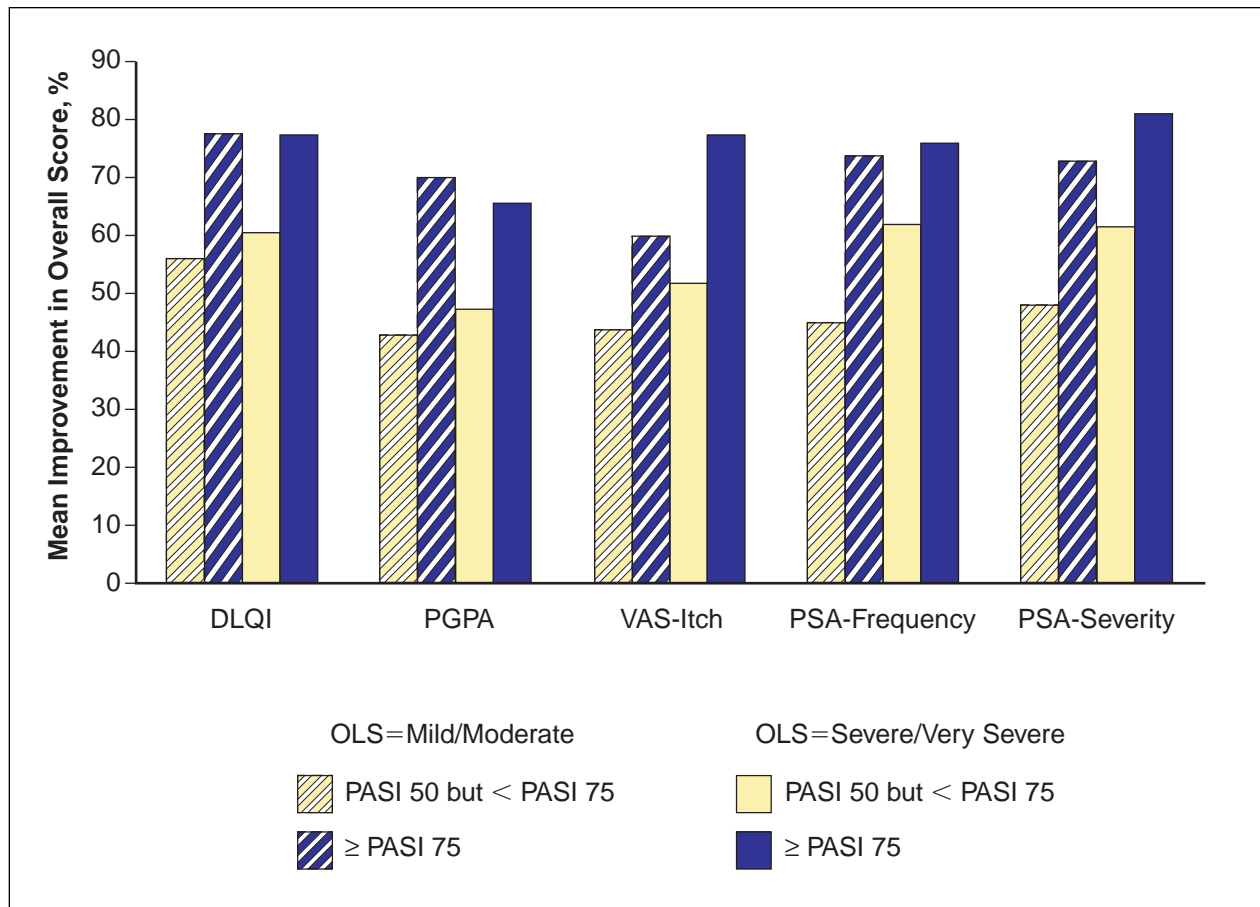
Figure 6. Mean improvements in quality-of-life measures based on Overall Lesion Severity (OLS) of psoriasis in patients before efalizumab therapy. PASI indicates Psoriasis Area and Severity Index; DLQI, Dermatology Life Quality Index; PGPA, patient global psoriasis assessment; VAS, Visual Analog Scale; PSA, Psoriasis Symptoms Assessment. Data are from Gordon et al.[11]

thus allows clinicians a comparator for applying their clinical findings to clinical study results.

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