Two considerations for patients with psoriasis and their clinicians:

What defines mild, moderate, and severe psoriasis?

What constitutes a clinically significant improvement when treating psoriasis?

The definitions of psoriasis severity and clinically significant improvement in psoriasis are used to classify treatments, obtain Food and Drug Administration approval, and determine product labeling and reimbursement. The Medical Advisory Board of the National Psoriasis Foundation has addressed these issues because of their importance in the clinical trials that are conducted to gain FDA approval of indications. Narrow indications, which are without a sound rational basis, will—in this era of constant oversight by third party payers—affect physicians’ ability to manage patients with psoriasis. Body surface area (BSA) is usually used to define severity for clinical trials. It is not optimal for defining psoriasis severity because there are some patients with low BSA involvement who have very severe psoriasis and some patients with high BSA involvement who have mild psoriasis. We conclude that a quality of life (QOL) standard is better than BSA measurement for identifying patients with severe psoriasis. The second issue is what defines clinically significant improvement for patients with psoriasis. Setting an arbitrarily high criterion of clinical efficacy for new psoriasis treatments will likely limit the development and approval of useful treatments. To maximize the availability of useful psoriasis treatments, it is our thesis that psoriasis treatments should be approved when they have been shown to produce a statistically significant level of improvement in well-designed clinical trials.
BACKGROUND TO A DEFINITION OF MILD, MODERATE, AND SEVERE PSORIASIS

Severity of psoriasis: A view from the clinic

Psoriasis vulgaris is a complex, multifaceted skin condition, the pathogenesis of which is still poorly understood.\(^1\) The characteristic scaly, red, indurated lesion of psoriasis typically varies as a function of time relative to the size of the lesion, the areas of involvement, the percentage of the body surface covered with disease, the complaint of pruritus, burning and/or pain in the lesions, and the associated arthropathy.\(^4\) Thus in any given patient severity will fluctuate and with it the impact of psoriasis on patients. These features make quantification of the severity of the disease difficult\(^6\) and raise the question: What are the key features that define the severity of psoriasis? Is it the redness, scale, or induration? Is it the extent of the disease, the percentage of body surface area affected? Is it the degree of itching? Is it the impact that it has on patients’ lives? Is it all of these?

The terms mild, moderate, and severe psoriasis are commonly used, but there are no standard criteria for them. How should they be defined? Can a specific definition be developed that is applicable in all settings? Definition of these terms is important in clinical care and in clinical research studies to identify and characterize new safe and efficacious treatments. Despite the lack of a uniformly accepted definition, these terms are used to classify treatments and to obtain FDA approval, product labeling, and, potentially, reimbursement. While regulatory agencies are considering this issue, one purpose of this position paper is to bring the issue to the attention of dermatologists and their patients. The Medical Advisory Board of the National Psoriasis Foundation does so with the goal of generating a definition of severity that is clinically relevant. Doing this makes outcomes of clinical trials transferable to clinical practice and brings consistency to the inclusion and exclusion criteria of patients in clinical trials. For patients and their physicians, severity is inexorably linked to the impact psoriasis has on QOL.\(^8\) Treatment decisions need to focus on the complex interplay between the severity of skin lesions and their impact on the patient and on the costs and risks to the patient relative to the expected benefits.\(^13\)

Severity of psoriasis: A view from the new drug approval process

To further appreciate the significance of this position paper, it is necessary to understand the current drug approval process for the treatment of psoriasis. First, there are preclinical studies that demonstrate a profile of activity (eg, anti-inflammatory properties, antiproliferative properties, antiangiogenesis properties) which suggests the drug may have an effect on any or all aspects of the clinical manifestations of psoriasis. Phase II safety and dose-ranging trials in normal people or patients with psoriasis ensue; a lack of significant toxicity and a potential for efficacy lead to dose-to-efficacy studies. If data from these trials indicate efficacy and acceptable toxicity, pivotal phase III studies are implemented. These compare a set dose(s) and duration of therapy with placebo in achieving predetermined end points. The severity of psoriasis required for patients entering these trials is determined in meetings with the FDA. Typically the pivotal study is conducted in patients with the same severity of disease as the phase II trials. If the new drug is to be administered systemically, the current FDA policy dictates that only patients with severe psoriasis be enrolled. For unknown reasons regulatory agencies and pharmaceutical companies have chosen to define psoriasis on the basis of percentage of body surface area (BSA) affected with psoriasis. Severe disease has frequently been defined as more than 20% BSA affected with psoriasis; more recently the Medical Advisory Board notes that occasionally the FDA has accepted 10% BSA as an indication of severe disease.

At the end of the pivotal trial the data are analyzed. If the new drug is significantly better than the placebo relative to the predetermined end points and has an acceptable safety profile and potential in the marketplace, a New Drug Application (NDA) is filed with the FDA. An in-depth review process follows. Barring unexpected findings, the new drug is approved for the indication studied in the phase III trial.

Because denial of reimbursement for new drugs for indications outside the approved indication (eg, severe psoriasis) is now commonplace, the definition of severity becomes critically important. Strict BSA definitions are currently being recommended for studies of new biotechnology therapies for psoriasis. Envision that a new drug “XYZ” has been tested and approved using such a BSA criterion for “severe psoriasis.” The clinical trials have shown that it is very effective (ie, will produce 90% or more improvement in 50% of subjects who take it for the prescribed course) and that it has essentially no side effects. It is probable that “XYZ” is very expensive. A patient with 5% BSA learns about “XYZ” and its favorable therapeutic index and wants to try it. The consulting dermatologist believes “XYZ” is appropriate because the patient’s disease is disfiguring, painful, is having a negative impact on QOL, and has proven to be resistant to topical treatments. A prescription is written for “XYZ”; the patient takes it to the pharma-
cy and is told that the prescription cannot be filled without documentation of severity of disease. The records note that the patient has 5% BSA. This does not coincide with the definition of “severe” in the “package insert” (already BSA is listed as a criterion in the package insert information for use of topical tazarotene), and reimbursement is denied.

In this scenario the patient and then the doctor may become frustrated, disappointed, and angry, largely as a result of an inappropriate definition of severity. It is our position that BSA is not a rational definition of severity because there are some patients with low BSA involvement who have very severe psoriasis and some patients with high BSA involvement who have mild psoriasis. We conclude that a more rational definition of severity needs to be generated to facilitate the development and accessiblity of treatments for patients with psoriasis. After considerable and prolonged consideration, we conclude that the severity of psoriasis is, first and foremost, a QOL issue.

The complexity of determining what constitutes severe psoriasis: An illustration

This issue can be appreciated by considering which of the following 4 patients has severe psoriasis:

- Patient A: 20% BSA involved with psoriasis
- Patient B: 10% BSA involved with psoriasis
- Patient C: 5% BSA involved with psoriasis
- Patient D: 1% BSA involved with psoriasis

Consider each of these patients with the following caveats:

- Patient A has obvious widespread disease. This person’s disease is recognized by all as severe and therefore must alter the QOL. However, would it still be severe if it was not in the scalp, it was only on covered parts of the body, and the lesions were thin and did not itch?
- Patient B also has obvious disease, and most would consider it severe, especially if it is painful, bleeds frequently, and provokes constant itching.
- Patient C has less obvious disease; however, if the face and scalp have thick indurated plaques, most would consider this patient as having severe disease.
- Patient D has even less obvious disease; however, if it were all on the dominant hand, affecting daily activities, most would consider this patient as having severe disease.

Consider also the patient with essentially no skin lesions but who has arthritis that interferes with his or her performance in the workplace.

Conversely, consider patients who, on the basis of BSA, have severe disease but have modifying aspects that make it more appropriate to classify them as having moderate or perhaps even mild disease. The first example could be the unusual patient with 20% or more BSA affected with psoriasis who elects not to be treated; does this patient truly have severe disease? A second example could be a patient with 10% BSA affected who only wants treatments that have minimal to no side effects and is able to cope with significant residual disease after a course of such a treatment; does this patient truly have severe disease? These iterations, which are not uncommon, strengthen our thesis; the severity of psoriasis is, and actually always has been, a QOL issue.

A QOL-based definition of the severity of psoriasis

Tables I to IV define psoriasis in a fashion that encompasses the patients’ perceptions (the varying ability of patients to accept side effects, the hassle of topical and ultraviolet light (UVL)–based treatments, the costs, and the lack of complete efficacy and toxicity of current treatments14,15) and the prescribing habits of physicians. It is important to note that if there were an oral medication that worked every time, did not have associated side effects, and did not have contraindications, we would have a much different attitude about what defines severity. Although such a treatment is not currently available, this concept does make it necessary to realize that any definition of severity could change. It is also very important to appreciate, as Tables I, II, and III demonstrate, that moderate for one patient may be mild or severe for another.
A treatment that causes an improvement of 90% or more in a global assessment in clinical trials (trials designed to achieve statistical significance and that are properly blinded) clearly provides sufficient CSI to justify regulatory approval. Unfortunately, such a criterion would be met by few, if any, of the current therapies. The second purpose of this position paper is to bring attention to another important issue: “What constitutes clinically significant improvement (CSI)” in psoriasis? This is important both in clinical practice (medications that do not provide a particular patient a CSI are deemed not effective for that patient) and in regulatory decision-making (the FDA will not approve a treatment that does not provide a CSI). An attempt to define a CSI for clinical trials is a concept that is past due. The definition of CSI will have an impact on the availability of treatments to patients and their clinicians. The Medical Advisory Board applauds the FDA and others for directing attention to this issue. However, if too high a CSI criterion hurdle is required by the FDA, treatments with positive but limited effectiveness will not be approved. Moreover, a high CSI standard criterion would discourage industry from even attempting the development of new psoriasis treatments.

**Table III.** A quality of life–based definition of severe psoriasis

- Disease alters the patient’s quality of life.
- Disease does not have a satisfactory response to treatments that have minimal risks.
- Patients are willing to accept life-altering side effects to achieve less disease or no disease.
- Generally more than 10% of body surface area is involved with disease.
- Other factors
  - Patient’s attitude about disease
  - Location of disease (eg, face, hands, fingernails, feet, genitals)
  - Symptoms (eg, pain, tightness, bleeding, or severe itching)
  - Arthralgias/arthritis

Dermatologists who offer a complete array of treatments for psoriasis (topical, UVL-based, and oral therapies) have learned how to assess the severity of disease; this assessment includes the needs of the patient, the time needed for treatment, the cost of treatment, the benefit of the treatment and the willingness of the patient to accept potential life-altering side effects to achieve a better QOL. We argue that it is unreasonable to base the severity issue solely on BSA, not only for clinical trials but in everyday clinical assessments. As Table IV illustrates, there are multiple factors that encompass a clinical definition of severity issue. Because of the nature of a disease that has physical, social, and psychologic components, elements in Table IV overlap.

Specific aspects of psoriasis whose impact on QOL have been quantitated include appearance of the skin, scales falling off, itching, burning sensations, joint pain, skin soreness, appearance of joints or bones, time it takes to care for psoriasis, monetary cost of treatment, stains on clothing or furniture, time lost from work, hair loss, medication side effects, unpleasant odors, doctors’ attitude toward psoriasis, people staring or reacting negatively, avoidance by people, self-consciousness about the skin, and inability to control the psoriasis.11,12,14

It would be useful to bring a quantitative scale to each of these; however, because each patient has different limits of tolerance, that would be difficult and perhaps impossible. Our objective is not to generate a new quantitative assessment of psoriasis. Rather, it is to cause practitioners, pharmacy-benefit managers, insurers, and regulatory agencies such as the FDA to realize that BSA is not an accurate reflection of severity but instead to use and approve agents on a QOL basis.

**Table IV.** Considerations in a clinically based definition of severe psoriasis

Psoriasis has a broad impact on health-related quality of life.11,12 Severity of psoriasis is linked to the ways in which the disease alters the many dimensions of quality of life in the following 3 broad categories. Note: These categories can and do overlap.

- Impact on daily physical activities; the role of psoriasis on routine activities at work, school and home. Included in this are performance on the job, school, or home; time away from work, school, or home; and the amount of discomfort (eg, pain, itching, arthritis, interruption of sleep) while doing these activities.
- Impact on social activities; the role of psoriasis on effective interaction in the routine activities of work, school, and home. Included in this are attitudes of others at work, school, or home about psoriasis (eg, the idea that psoriasis is contagious; the appearance of skin, nails, and joints; the constant scaling) and the attitude of the patient toward these same aspects.
- Impact on psychologic aspects; the role of psoriasis on the patient’s mental health. Included in this are the effects of a diminished body image caused by psoriasis, which results in withdrawal, depression, anxiety, feelings of inadequacy, and being sexually unappealing.

**BACKGROUND TO WHAT CONSTITUTES CLINICALLY SIGNIFICANT IMPROVEMENT**

The second purpose of this position paper is to bring attention to another important issue: “What constitutes clinically significant improvement (CSI)” in psoriasis? This is important both in clinical practice (medications that do not provide a particular patient a CSI are deemed not effective for that patient) and in regulatory decision-making (the FDA will not approve a treatment that does not provide a CSI). An attempt to define a CSI for clinical trials is a concept that is past due. The definition of CSI will have an impact on the availability of treatments to patients and their clinicians. The Medical Advisory Board applauds the FDA and others for directing attention to this issue. However, if too high a CSI criterion hurdle is required by the FDA, treatments with positive but limited effectiveness will not be approved. Moreover, a high CSI standard criterion would discourage industry from even attempting the development of new psoriasis treatments.

**A working definition of CSI**

A treatment that causes an improvement of 90% or more in a global assessment in clinical trials (trials designed to achieve statistical significance and that are properly blinded) clearly provides sufficient CSI to justify regulatory approval. Unfortunately, such a criterion would be met by few, if any, of the current...
psoriasis treatments. Some treatments may provide limited clearing of psoriasis in a broad range of patients or more extensive clearance in a few patients. Because of our desire to make effective psoriasis treatments accessible to patients, the Medical Advisory Board now concludes that an appropriate definition for CSI in clinical trials is any degree of improvement in a primary end point that achieves significance at a P value of .05 or less, compared with placebo, in clinical trials designed to achieve statistical significance and which are properly blinded.

Psoriasis is a multigenic disease. Thus it is likely that responses to agents will be selective, that is, some patients will have a constant response and others will not. Any treatment that consistently leads to clearing provides a CSI, even if it occurs in fewer than 5% of subjects, and would be a valuable clinical tool. The Medical Advisory Board feels strongly that such treatments should be available to the patients who would benefit from them.

Consistent, predictable, and statistically significant responses, short of complete clearing with minimal or no side effects, are CSI. Approving treatments with limited but proven efficacy will permit clinicians the latitude to determine what is most effective for their patients. For example, drugs that cause modest improvement as a monotherapy may be much more effective when combined with another agent (eg, retinoids, UVL). Moreover, any agent that predictably enhances QOL in a statistically significant fashion is providing a CSI. Examples would include agents that decrease itching or scaling. Finally, a drug that does not cause significant improvement may provide a CSI if it maintains patients in a disease-free state when used after psoriasis is brought to remission with another treatment approach.

CONCLUSION

Until we understand the molecular basis of psoriasis and have specific curative or consistently remitting therapies, the approving agencies should continue to assess new drug applications and approve those that are safe and demonstrate CSI in one or more end points. It is recognized that this invites approval of agents that will have limited beneficial effects. Perhaps the marketplace will effectively sort out those that are worthwhile from those that are not, but the current health care “market” may not be entirely effective in distinguishing cost from cost/benefit. Because many treatments for psoriasis can be combined to work in an augmentative fashion in this life-altering disease, all therapeutic options need to be available.

REFERENCES