

Long-term Treatment for Severe Psoriasis

We're Halfway There, With a Long Way to Go

OVER THE LAST 30 YEARS, THE LANDMARK PUVA [psoralen-UV-A] Follow-up Study has demonstrated the importance of clinical epidemiology research in making informed treatment decisions for patients with psoriasis. When PUVA was first introduced, psoriasis was widely believed to be an epidermal cell proliferation disorder, and there were few systemic treatment options available at that time.¹ Thirty years later, psoriasis is believed to be an immunologic disorder, and more new systemic therapies have been approved to treat it in the last 4 years than in the previous 30 years combined.²⁻⁸ Our objective criterion regarding which patients have severe psoriasis and therefore are candidates for systemic therapy has also evolved during this period, declining from 20% to 30% body surface area (BSA) in the 1970s to 1990s to 5% more recently.^{9,10} With the increasing recognition of the impact of psoriasis on health-related quality of life and the advent of novel therapies targeting its immunopathogenesis, the treatment of psoriasis is undergoing a revolution. As patients with psoriasis are increasingly being treated with systemic agents on a long-term basis, the PUVA study provides an important reminder of the challenge involved in making clinical decisions based on a scientific understanding of the disease's natural history and the robust long-term safety and efficacy data of its treatments.

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First, the PUVA experience exemplifies the critical importance of long-term studies to fully define the risks and benefits of a novel treatment. In 1974, years before the importance of PUVA in targeting T cells and dendritic cells was recognized, this treatment was first shown to be effective for severe psoriasis in 21 patients who had at least 50% BSA involvement.^{1,11} The use of PUVA for treating very severe psoriasis was a major development, as all patients in the trial achieved complete clearance and reported adverse effects were minimal. In 1977, a large multicenter clinical trial involving more than 1300 patients who received more than 45 000 treatments demonstrated that only 3% of patients failed to achieve clearance with this regimen and that adverse effects due to PUVA therapy were uncommon, temporary, and generally mild.¹² Although PUVA therapy was considered an experimental technique, with limited long-term safety data, it was widely used in the United States, with an estimated 35 000 patients being treated in 1978 alone.¹³ In

1979, the first observations of cutaneous carcinoma were reported in the cohort; however, it was not clear if PUVA therapy was responsible for the excess number of skin cancers, as affected patients had a history of treatment with ionizing radiation or a history of skin cancer.¹³ In 1984, about 2 years after being approved by the Food and Drug Administration, PUVA was definitively linked to an excess risk of squamous cell carcinoma when the cohort had an average follow-up of 5.7 years.¹⁴ In 1997, when the median follow-up of patients reached 19 years, PUVA use was associated with an increased risk of melanoma, a finding that remains controversial.¹⁵

Although it took 10 years to clearly demonstrate the risk of squamous cell carcinoma from PUVA therapy and even longer to detect a potential association with melanoma, the PUVA study represents a success in defining the long-term safety of a systemic psoriasis treatment. Currently, the most robust safety data for psoriasis treatments are derived predominantly from randomized controlled clinical trials. However, these trials are generally of short duration, measured in weeks to months, whereas psoriasis is a lifelong disease that requires several decades of treatment for control.¹⁶ Although clinical trials are well suited to define the efficacy of an agent, they are particularly prone to miss the effects of drugs that are delayed and/or uncommon (eg, cancer, cardiovascular disease, and serious infections).¹⁷ The current drug approval process leaves us with wide gaps in our knowledge of treatment safety, which is particularly problematic when the therapy is to be used in large populations of patients on a long-term basis.¹⁸ In particular, existing safety data of systemic therapies for severe psoriasis are limited in the duration of drug exposure and in the number of patients who are receiving follow-up. Therefore, the potential risks associated with truly long-term treatment of psoriasis remain to be further defined for serious end points such as malignancy.¹⁹

The current PUVA Follow-up Study, as analyzed by Nijsten et al,²⁰ also provides unique data regarding the effectiveness of long-term treatment of severe psoriasis. During the follow-up of 815 patients who underwent 2378 skin examinations from 1985 to 2005, approximately 50% of such examinations demonstrated that patients had mild to no skin disease. Moreover, Nijsten and coauthors note that the likelihood that the extent of psoriasis will change more than 1 physician global assessment level over 1 year and over 10 years is relatively small. These observations suggest that our treatment approach is about 50% effective over the long term, given that the average BSA of patients who initially entered the multicenter PUVA trial

was 33%. Based on the ecological design used for the PUVA study, in which treatment use and psoriasis severity were not linked at the individual level, it is unclear if these patients had mild or no psoriasis because of the natural history of psoriasis or because of the use of psoriasis treatments. The natural history and determinants of psoriasis remission and flare remain poorly understood as reviewed by Nijsten and colleagues. This study therefore underscores the need for further prospective epidemiological investigations to determine the true rate and determinants of spontaneous psoriasis improvement and flare, as well as how psoriasis may lead to other disease states that are associated with chronic T_H1 inflammation, such as psoriatic arthritis, metabolic disease, atherosclerosis, and myocardial infarction.²¹⁻²⁴ Such information would better inform patients about the natural history of their psoriasis, would improve clinical trial designs and the interpretation of safety data, and would allow clinicians and patients to make more informed decisions about long-term vs intermittent therapy.

Remarkably, Nijsten et al²⁰ report that despite having access to a wide array of dermatologic therapeutic modalities, including extensive use of phototherapy and methotrexate in the study population, about 50% of patients continued to have moderate to severe psoriasis on their follow-up examinations. This observation demonstrates that we still have a long way to go when it comes to consistently controlling severe psoriasis. For example, a recent study of 1657 contacts of the National Psoriasis Foundation demonstrated that 37% of patients with moderate psoriasis (defined as 3%-10% BSA) and 39% of patients with severe disease (>10% BSA) were not receiving any therapy.²⁵ Furthermore, more than 80% of patients with severe psoriasis were not receiving systemic therapy or phototherapy. These data suggest that severe psoriasis remains uncontrolled in the majority of patients affected. Further studies are necessary to determine the degree to which this is attributable to patient factors (such as changing treatment preference, adherence, or access to therapies) or to factors related to treatment failure over time. Although short-term clinical trials in highly selected patient populations have shown the efficacy of systemic therapies for psoriasis, we have large gaps in our knowledge of the long-term effectiveness of these treatments when they are used on a long-term basis in a broader population of patients with psoriasis. For example, the limited data we have on methotrexate suggest that the drug is highly efficacious over the short term (16 weeks) but that over 1 year of follow-up about 25% of patients discontinue therapy because of adverse effects, indicating that long-term effectiveness is well below short-term efficacy.²⁶ Similarly, long-term studies of biologic antibody therapy (chimeric and humanized) for inflammatory diseases show high short-term efficacy but lower long-term effectiveness as a result of drug discontinuation associated with adverse effects or loss of treatment response during extended periods of treatment.^{7,27,28}

Dermatologists and patients have scant data to make head-to-head comparisons of systemic therapies, and our general assumptions about which treatments are most safe, efficacious, and cost-effective based on short-term trial

data may not be valid when the end point is more clinically relevant (eg, long-term effectiveness). The burden of treatment success and failure over the patient's lifetime is eloquently described by John Updike,²⁹ who wrote, ". . . when I am at last too ill for all of these demanding and perilous palliatives, the psoriasis like a smoldering fire in damp peat will break out and spread triumphantly; in my dying I will become hideous, I will become what I am."

Over the last 30 years, tremendous progress has been made in our knowledge of the pathogenesis of psoriasis and in the development of systemic therapies to treat this disease. This progress has been well documented by the more than 20 000 medical publications related to psoriasis since PUVA was introduced. Despite this progress, we still have major gaps in our basic knowledge of the natural history of psoriasis, and a large percentage of patients with extensive psoriasis will continue to suffer from the burden of this disease for decades.

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