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Cost-Effectiveness

A Comparison of the Clinical Effectiveness and Cost-Effectiveness of Treatments for Moderate to Severe Psoriasis

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This study investigated the clinical effectiveness and cost-effectiveness of treatments for moderate to severe psoriasis from a managed health care systems perspective. An analysis was conducted of randomized clinical trials evaluating biologic and oral systemic medications and phototherapy for patients with moderate to severe psoriasis. Of 22 trials, mean Psoriasis Area and Severity Index (PASI) improvement from baseline ranged from 33.4% to 97.3%. Annualized costs to achieve clinically meaningful outcomes (PASI 75) ranged from $2611 to $35,096. (Drug Benefit Trends. *2010;21:17-27)*

Psoriasis affects approximately 2% to 3% of the population in the United States[1-3] and is characterized by epidermal hyperproliferation, incomplete epidermal differentiation, vascular changes, and inflammation.[4] Current evidence implicates the immune system and inflammatory mechanisms, in particular T lymphocytes and inflammatory cytokines, in the pathogenesis of psoriasis.[5]

Psoriasis exerts a substantial clinical and economic toll. The degree of disability experienced by patients with psoriasis is comparable to that of patients with other major chronic medical conditions, such as diabetes, arthritis, and congestive heart failure.[6] In 2004, there were 36,400 inpatient stays, 158,000 outpatient hospital visits, 18,800 emergency department visits, and about 2.26 million physician outpatient visits attributable to psoriasis-related care in the United States.[7] Annual direct costs of psoriasis have been estimated at $700 million.[8,9] Of these direct costs, 23% were attributed to prescription medications, 13% to outpatient medical visits, 5% to hospitalization, 4% to phototherapy, and the remainder (55%) to over-the-counter medications.[8] Estimated indirect costs, due to lost productivity, were $1.2 billion in 2004.[7]

FDA-approved treatments for moderate to severe psoriasis, which affects approximately 33% of psoriasis patients,[2] have burgeoned since 2003, when only acitretin, cyclosporine, methotrexate, and phototherapy were available. As of June 2008, FDA-approved treatments for moderate to severe psoriasis included 3 oral systemic medications, 5 systemic biologic medications, and phototherapy. In addition, there are more than 20 treatments in clinical trials or under FDA review.[10]

Given the array of treatments for moderate to severe psoriasis and the lack of head-to-head comparative trials, dermatologists and health care insurers face a daunting task in making evidence-based decisions about the selection of treatments. To that end, we conducted an analysis of published clinical trials of treatments for moderate to severe psoriasis and applied these findings to compare their relative clinical effectiveness and cost-effectiveness.[11] Our goals were to create a transparent and flexible comparative-effectiveness methodology that could support current and future evidence-based clinical, as well as coverage and reimbursement, decisions for treatments of moderate to severe psoriasis[11,12] and to establish a benchmark against which to compare the clinical efficacy and costs of future treatments.

Methods

Selection of clinical trials for analysis. Randomized trials of treatments for moderate to severe psoriasis were identified through a MEDLINE search for clinical trials published in English from January 1966 through June 2008. On the basis of these results, a manual search was also conducted of reference lists for seminal clinical trials and review articles. Key word search terms included “psoriasis” and each of the following: acitretin (or etretin), adalimumab, alefacept, cyclosporine (or ciclosporin or ciclosporine), efalizumab, etanercept, infliximab, methotrexate, phototherapy, PUVA (or PUV-A or psoralen), or UVB (or UV-B or ultraviolet B).

One of the authors examined each article abstract for relevance. Articles that could not be ruled out as meeting the predefined inclusion or exclusion criteria were obtained while those that failed to meet one or more criteria were rejected. Next, each full article was closely examined to ensure that all inclusion or exclusion criteria were met. The following data from each article that was included were abstracted by a research associate under the supervision of 2 of the authors: citation; study design; treatment types, duration, and doses; participant inclusion or exclusion criteria; sample size; analytic approach; study end points; results; author conclusions; and reviewer comments.

All study authors evaluated the abstracted information during an on-site 1-day Working Group meeting. The Working Group comprised 2 pharmacist formulary directors, 3 physician medical directors of health plans, and a health economist. Group consensus was required for all determinations. Reviewers were not blinded to authors, institutions, or journals because such methods do not appear to affect systematic review outcomes.[13] A board-certified dermatologist reviewed the findings to ensure that results were clinically meaningful and relevant.

Consistent with managed care coverage and reimbursement review procedures, we included information from trials of targeted treatments that had been published in peer-reviewed journals. Study inclusion and exclusion criteria were created to minimize the introduction of bias.[14] English-language studies that enrolled adults 18 years or older who had a diagnosis of predominantly plaque-type moderate to severe psoriasis were included. Efficacy analyses were based on the intent-to-treat sample or on samples with no dropouts. Efficacy was reported as either mean percentage improvement from baseline to end point on the Psoriasis Area and Severity Index (PASI); percentage of patients who achieved a mean PASI

improvement of at least 75%; or percentage of patients who achieved a 0 or 1 (clear or almost clear) score on the physician-completed patient global assessment at end point. Efficacy was also reported over a 6- to 14-week acute treatment period (as opposed to a maintenance or follow-up period).

Excluded studies were duplicates of other reviewed studies, did not include any of the treatments or outcomes of interest, or employed inappropriate treatment doses that exceeded or fell below the recommended dose or regimens. These studies did not specify the mean dose, treatment regimen, or duration, or they included fewer than 10 patients receiving active treatment. Also not included were studies with patients who had a limited range of skin types and studies that were potentially biased or of poor quality, such as having unaccounted dropouts or a flawed design. Studies that were not clinical trials, such as clinical case reports or review articles, were also not included. The predetermined inclusion and exclusion criteria were then further refined by the exclusion of all nonrandomized trials and those that did not report mean percentage PASI improvement from baseline to study end point.

Effectiveness end point. In psoriasis clinical trials, the FDA requires that the PASI be used as an efficacy end point[15]; the PASI is the most often cited measurement of psoriasis treatment efficacy.[16] This measure provides a composite score of a variety of physical signs of psoria-sis, including erythema, infiltration, desquamation, and body surface involvement.[17] Total scores range from 0 to 72, and higher scores denote greater severity of disease. In clinical trials, the PASI is usually assessed as the mean percentage change from baseline to end point. A 75% improvement in PASI (PASI 75) reflects a clinically meaningful outcome.[18,19]

Cost-effectiveness analysis. Cost-effectiveness was calculated as the sum of total annualized costs for each treatment divided by treatment efficacy. This yielded the cost to achieve a 1% PASI improvement (PASI 1). Because a PASI 75 reflects a clinically meaningful outcome,[18,19] we multiplied the cost to achieve PASI 1 by 75 to derive the annual cost to achieve PASI 75.

Where appropriate, total annualized costs included drug acquisition at the wholesale acquisition cost (WAC); clinical procedures, such as administration of intravenous infusion or administration of phototherapy at Medicare 2008 reimbursement rates; and screening and monitoring as recommended by the product label for drugs and in consensus statements for phototherapy at Medicare 2008 reimbursement rates. For systemic biologic medications that required clinician-administered procedures, such as alefacept intramuscular injection and infliximab intravenous infusion over 2 hours, the costs at Medicare 2008 reimbursement rates were included in total costs; all other systemic biologic agents were assumed to be patient-administered.

We annualized treatment regimens according to the following assumptions (as shown in **Table 1**):
• Daily doses of acitretin 25 and 50 mg and cyclosporine 1.25 and 3 mg/kg (365 doses per year).
• Weekly doses of methotrexate 7.5 and 15 mg and efalizumab 1 mg/kg (52 doses per year).
• Adalimumab 40 mg administered every other week (27 administrations per year).
• Two 12-week courses of intramuscular alefacept 15 mg (24 administrations per year).
• Efalizumab 75 mg weekly.
• Etanercept 25 and 50 mg administered twice weekly for 12 weeks, then once weekly (64 administrations per year).
• Intravenous infliximab 5 mg/kg administered at weeks 0, 2, and 6, then every 8 weeks (9 administrations per year).
• UVB received 2.5 times weekly for 8 weeks and twice weekly thereafter (108 administrations per

year).
• PUVA received 2.5 times weekly for 8 weeks and once weekly thereafter (64 administrations per year).

Assumptions. The PASI 75 achieved during the 6- to 14-week clinical trial was assumed to be maintained over the course of 1 year of treatment. We rounded doses to the nearest possible dose. For example, if the average weekly dose of methotrexate was 12.9 mg, we assumed the cost for a 15-mg dose of methotrexate. Finally, we assumed a patient weight of 75 kg (167 lb) for medication dosages based on weight.

Results

The initial study review process identified 46 studies as meeting inclusion/exclusion criteria. The Working Group review excluded 9 of these studies for the following reasons:
• Sample selection deficiencies (1 study).
• Mean dose was not provided (2 studies).
• Dose was not approved by the FDA (1 study).
• Study was presented as a poster only (1 study).
• Did not include treatment or outcomes of interest (2 studies).
• Poor quality (2 studies).

The final review of the 37 remaining studies excluded 12 studies for not reporting efficacy in terms of mean percentage improvement from baseline to end point on the PASI, 1 for reporting mean percentage improvement in PASI but including dropouts, and 3 for being nonrandomized. One previously excluded study had been incorrectly classified and was included in the final analysis. (A detailed table containing abstracted data and inclusion/exclusion determinations is available by contacting the primary author.)

Thus, 22 studies qualified for inclusion in the meta-analysis. **Table 1** shows the final studies selected and their number of patients, dosages, and reported effectiveness. When more than 1 study pertained to a given treatment, the weighted (by total number of patients) aver-age percentage change in PASI was calculated.

Comparative clinical effectiveness. The percentage change in PASI improvement from baseline ranged from 33.4% to 97.3% for cyclosporine 1.25 mg/d and combination therapy using psoralen with ultraviolet A plus acitretin 15 mg/d, respectively. Patients treated with cyclosporine, alefacept, or efalizumab did not achieve a PASI improvement from baseline of at least 50%, which is considered to represent a minimally clinically meaningful improvement.[18]

Comparative cost-effectiveness. Screening and monitoring recommendations per product labels, corresponding Current Procedural Terminology (CPT) codes, and 2008 Medicare reimbursement rates are shown in **Table 2**. **Table 3** displays the average dosage and the percentage improvement in PASI per treatment, drug cost (WAC), CPT for phototherapy and administration of systemic biologic agents, and screening and monitoring cost. These costs were summed to determine the total cost for each treatment; the total cost divided by the average percentage improvement in PASI yielded the cost to achieve a PASI 1 and PASI 75.

Discussion

In the absence of head-to-head trials, clinicians and health care insurers must find a way to compare the effectiveness and costs of treatments within a disease class. This is especially true for moderate to severe psoriasis, for which new market entries and treatment costs are on the rise. We found a wide range of annualized costs to achieve a PASI 75, from a low of $2611 for methotrexate 7.5 mg weekly to a high of $35,096 for alefacept 15 mg weekly.

This study represents an update of our previously conducted analysis, which was based on clinical trial data published from 1966 to 2004.[20] This study also indicates that the relative positioning of oral systemic medications, phototherapies, and systemic biologic agents has not substantially changed during the past 4 years. Our findings corroborate the results of a recent study that compared systemic biologic agents: alefacept 15 mg weekly, efalizumab 2 mg/kg weekly, and etanercept 50 mg twice weekly were the least cost-effective systemic biologic treatments in terms of cost per patient to achieve a PASI 75.[21]

There are several limitations to the current study. First, all treatments for moderate to severe psoriasis may cause serious adverse effects: there is an increased risk of skin cancer with phototherapy; renal impairment and hypertension with cyclosporine; bone marrow toxicity, miscarriage, hepatic fibrosis, and cirrhosis with methotrexate; and birth defects with acitretin, which is highly teratogenic.[22] Systemic biologic agents carry an increased risk of serious infection.[22] In addition, there is an increased risk of lymphopenia and malignancy with alefacept; malignancy and thrombocytopenia with efalizumab; CNS demyelinating disorders with etanercept, infliximab, and adalimumab; lupus-like syndrome and lymphoma with infliximab and adalimumab; and exacerbation of congestive heart failure with etanercept and infliximab.[23-26]

New information about the safety of treatments for moderate to severe psoriasis—particularly treatments that were introduced more recently—may continue to emerge. For example, the FDA recently added a black box warning for etanercept regarding the risk of tuberculosis and other infections.[25] The warning states that health care professionals should screen patients for latent tuberculosis infection before etanercept therapy is started. The requirement for a tuberculosis test before initiating treatment with etanercept was made after our meta-analysis had been completed, and therefore it was not included in the estimate of annualized costs for this drug. Also, we extrapolated the short-term efficacy outcomes to 1 year because of the dearth of available, methodologically sound, long-term efficacy data for oral systemic medications and systemic biologic agents.[27,28] Short-term efficacy results associated with treatments for moderate to severe psoriasis may not be equivalently maintained over longer-term treatment periods.

Because serious adverse events are extremely rare and are unlikely to occur within the 1-year time frame of our analysis, we used screening and monitoring recommendations from product inserts to reflect risk. Given this approach, our estimates may understate actual long-term costs of these treatments. In addition, we assumed that outcomes reported at the end of trials were sustained over the 1-year study horizon, provided that patients continued maintenance treatments. Therefore, our analysis does not reflect fluctuations in outcomes that may be affected by factors such as patient adherence and the potential need to switch or rotate treatments because of changes in tolerance and efficacy.

We did not require that studies include a placebo arm because this is not feasible for phototherapy trials, in which active UV treatment is selected for half of the body while the other half is shielded. Inclusion of a placebo arm was also uncommon in early trials of oral systemic medications. As a result, we cannot

report incremental cost-effectiveness ratios (the incremental benefit of treatment over placebo). However, this is not to say that earlier, open-label studies were poorly controlled. In fact, criteria for patient selection and PASI scoring in these open-label trials were often more rigorous than those that used placebo controls.

Finally, doses reported in this analysis of clinical trials may not reflect those used in actual practice. Cather and colleagues[29] found that patients who received acitretin 10 mg daily achieved a PASI improvement that was similar to that achieved by those who received 25 mg daily; our current analysis revealed that the clinical effectiveness associated with the 25-mg daily dose of acitretin exceeded that with the 50-mg daily dose. Consequently, comparable or superior clinical effectiveness and cost-effectiveness of acitretin may be achieved at lower doses.

In a retrospective analysis of adult enrollees in Florida Medicaid from 1997 to 2007, Hankin and associates[30] reported that patients with a diagnosis of psoriasis received median dosages of acitretin (25 mg/d), cyclosporine (100 mg/d, the equivalent of 1.1 mg/kg/d for the average man and 1.3 mg/kg/d for the average woman),[31] methotrexate (14.7 mg/wk), and etanercept (49.7 mg/wk). Data for alefacept, efalizumab, and infliximab were insufficient for analysis. Eighty-one percent of patients received a mean daily dose of acitretin of 25 mg or less, 67% received an average daily dose of cyclosporine of 100 mg or less, 72% received an average weekly dose of methotrexate of 17.5 mg or less, and 54.5% received an average weekly dose of etanercept of 50 mg or less.

Despite the research limitations noted above, our study is the only clinical effectiveness and cost-effectiveness analysis that has considered the full range of treatments for moderate to severe psoriasis using a clinically meaningful outcome. We sought to create a sufficiently transparent and flexible methodology that can be used by dermatologists and health care insurers to help make informed clinical, and coverage and reimbursement, decisions, respectively, for treatments of moderate to severe psoriasis. We also sought to establish a cost-effectiveness benchmark against which to compare future treatments.

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