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Et al.

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*This study of the efficacy and cost-effectiveness of moderate to severe psoriasis treatments compared phototherapy, oral systemic agents, and biologics from a managed health care systems perspective. A literature review was conducted to identify published studies reporting Psoriasis Area and Severity Index (PASI) percentage improvement from baseline (PASI%) for selected treatments. The researchers then calculated total annualized costs. For each treatment, annualized cost-effectiveness was calculated by dividing total annualized costs of treatment by PASI%. The costs necessary to achieve clinically meaningful outcomes (PASI50 and PASI75) were then calculated. Of 3886 articles examined, 16 studies met inclusion criteria. Oral systemic medications, UV therapy, and UV therapy combined with acitretin appear to be the most cost-effective therapies for moderate to severe psoriasis. (*Drug Benefit Trends. *2005;17:200-214)*

Key words: Cost-effectiveness • Psoriasis • Psoriasis Area and Severity Index

Psoriasis is a skin disorder that is characterized by scaly plaques, itching, and redness.[1] Of the nearly 8 million Americans who have psoriasis, an estimated 30% have symptoms severe enough to require treatment with phototherapy (UV-B or psoralen with UV-A [PUV-A]), oral systemic medications (acitretin, cyclosporine, and methotrexate), and/or biologic agents (alefacept, efalizumab, etanercept, and infliximab).[1,2]

Since 2003, the number of FDA-approved biologic treatments of psoriasis has increased 3-fold. Currently, there are more than a dozen biologic agents for the management of psoriasis either under FDA review or in development.[3,4] As demand for these newer and more costly drugs meets up with limited health systems resources, MCOs and other health care decision makers will need to better evaluate the effectiveness and costs of all therapies for moderate to severe psoriasis.

The Psoriasis Area and Severity Index (PASI) is the most frequently cited measure of treatment effectiveness for moderate to severe psoriasis and is accepted by the FDA as a primary end point in clinical trials.[5,6] Outcomes are often reported in terms of average percentage change in PASI score from baseline to end point (PASI%). Clinically meaningful outcomes are frequently reported as achievement of at least 50% or 75% improvement from baseline (PASI50 or PASI75).[6,7]

We sought to compare the cost-effectiveness of phototherapy, oral systemic medications, and biologic outpatient treatments of moderate to severe psoriasis. In the absence of head-to-head comparative trials, the PASI—a clinically meaningful metric—was used to measure treatment effectiveness. The primary study question was: From the perspective of the US health care system (ie, physicians, pharmacy and therapeutics committee members, medical directors, clinical pharmacists, and other health care professionals), what are the comparative annual costs to achieve PASI improvements of 1%, 50%, and 75% using these selected therapies for psoriasis?

Methods

A systematic review of the literature was conducted to identify studies reporting PASI% improvement for UV-B, PUV-A, acitretin, cyclosporine, methotrexate, alefacept, efalizumab, etanercept, and infliximab. Also identified were studies examining PASI% improvement for combined regimens of acitretin with PUV-A or UV-B. These treatments may have synergistic effects when combined, thereby reducing the overall number, duration, and cumulative doses required to achieve symptom improvement.[8]

The total annualized costs for each treatment were calculated, as was an annualized cost-effectiveness ratio—the total annualized cost of treatment divided by PASI% im-

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provement. The annualized cost-effectiveness ratio provides the cost to achieve a PASI score improvement of 1% (PASI1). To obtain more clinically meaningful outcomes, we multiplied the costs for PASI1 by 50 and 75 to estimate the costs to achieve PASI50 and PASI75 for each selected treatment.

Systematic review. A MEDLINE search from 1966 to August 2004 was performed for studies reported in English with the terms "psoriasis" and each of the following: acitretin, cyclosporine (including the spellings of ciclosporin and ciclosporine), methotrexate, alefacept, efalizumab, etanercept, infliximab, PUV-A, UV-B, UV-B and acitretin, and PUV-A and acitretin. Additional studies were obtained after being identified from citations in review articles.

One of the study authors assessed each citation for relevance. Of 3885 articles identified from MEDLINE and citation reviews, 84 were deemed preliminarily to meet inclusion criteria (described below) and were retrieved. For each retrieved article, the same study author noted the citation; study design; treatment type(s), duration, and dose(s); participant inclusion/exclusion criteria; sample size; analytic approach; study end points; results; and conclusions.

Extracted summaries prepared by the first author were evaluated for final selection by the other study authors. Consensus was achieved by reference to original articles, discussions during a day-long working-group session, and subsequent communications via telephone and e-mail. Reviewers were not blinded to articles' authors, institutions, or publication journal because such methods do not appear to affect systematic review outcomes.[9]

Study inclusion and exclusion criteria were designed to ensure that the systematic review was conducted to minimize the introduction of bias.[10] Consistent with formulary review processes typically conducted by US health care systems, we included only peer-reviewed, published studies. Priority was given to randomized, double-blind, placebo-controlled trials.

Only studies that reported mean PASI improvement from baseline and that specified time to the endpoint assessment were included. Other inclusion requirements were that the sample size of participants receiving active treatment was 10 or more, participants were adults (age 18 years or older) with a diagnosis of moderate to severe psoriasis or a baseline PASI score of at least 8 (signifying at least moderate severity), plaque psoriasis was the predominant subtype represented, and participant recruitment was not based on prior response to the targeted treatment. In addition, only studies were used that had a treatment duration of between 6 and 14 weeks, specified the mean dose of treatment (drug or number of phototherapy exposures), excluded as treatment ancillary concomitant systemic therapies or phototherapies, initiated treatment as de novo rather than as maintenance following stabilization, and adminstered medication in dose ranges within current product recommendations.

Excluded studies were those in which the targeted treatment was omitted and in which participants were not randomized to treatment conditions (for comparative trials). Studies that were duplicates of ones that we had already reviewed, that did not apply an intent-to-treat analysis, that did not include dropouts in the analysis, and that did not clarify the disposition of dropouts were eliminated.[11] Clinical case studies or retrospective case reviews, review articles, news articles, and letters were excluded as well.

Calculation of costs. Total annualized costs were calculated as the sum of costs for medication or phototherapy, treatment administration, monitoring for potential treatment-related adverse events, and treatment of adverse events. Average wholesale price (AWP) at January 2004 rates were used to calculate costs for oral systemic medications and biologic drugs.[12] Costs for phototherapy were calculated at 2004 Medicare reimbursement rates, using Evaluation and Management (E&M) codes 96910 for UV-B and 96912 for PUV-A.[13] For cyclosporine,[14] efalizumab[15], and infliximab[16] (the medications for which dosing is based on patient body weight), we assumed a weight of 75 kg (167 lb).

The following assumptions were made regarding annualized dosing regimens:

- For all oral systemics and efalizumab, therapy regimens reported in the targeted studies remained constant throughout the year.[15]
- For alefacept, based on product labeling, two 12-week courses of treatment were administered.[17]
- For etanercept, following an initial dose of 50 mg twice weekly, the dose was reduced to 25 mg twice weekly for the remainder of the year.[18]
- For infliximab, initial dosing occurred at 0, 2, and 6 weeks, followed by administration every 8 weeks thereafter (9 total annual administrations).[16]
- With regard to PUV-A, following the active treatment regimen specified by the study protocol, patients received 1 PUV-A treatment every week throughout the remainder of the year.[19]
- With regard to UV-B, patients received 2 UV-B treatments each week for the remaining year.[8,20]
- For PUV-A or UV-B therapy with acitretin, following the active treatment regimen specified by the

study protocol, patients received acitretin 25 mg every other day and UV-B or PUV-A once every other week (the equivalent of once weekly during autumn and winter months and no treatment during spring and summer).[21]

- For biologics that can be patient-injected, such as etanercept and efalizumab, there were no additional treatment administration costs.
- For biologics that require intravenous (IV) injection (alefacept), we applied the E&M code 90782 (subcutaneous injection) at 2004 Medicare reimbursement rates.[22]
- For biologics that require IV infusion over 2 hours (infliximab), we applied E&M codes 90780 (first hour IV infusion) and 90781 (second hour infusion).[22]

Because phototherapy, oral systemic medications, and biologic treatments are associated with the potential for adverse events, continued patient monitoring is required. Recommended monitoring regimens are specified in product labeling for oral systemic medications and biologic agents and in consensus statements for phototherapies. These recommendations were used to calculate annual costs of monitoring at 2004 Medicare reimbursement rates.

In addition, the literature was reviewed to identify risk factors for se-

Table 1. Summary of Symptom Improvement by PASI%

Treatment	Study	Specified Dose of Active Treatment	Sample Size	PASI%
Broadband UV-B	Ramsay[41]	3×/wk for 12 wk	164	80.1
	Woo[42]	3×/wk for 7 wk	50	83.7
	Walters[43]	3×/wk for 6 wk	11	47.0
Narrowband UV-B	Walters[43]	3×/wk for 6 wk	11	73.0
PUV-A	Caca-Biljanovska[55]	4×/wk for 6 wk, then 2×/wk for 2 wk	40	92.9
	Torras[56]	3×/wk for 10 wk	113	61.1
Acitretin	Gollnick[57]	48.2 mg/d	145	60.4
Cyclosporine	Ellis[58]	3 mg/kg/d	85	52.0
	Reitamo[59]	1.5 mg/kg/d	149	33.4
Methotrexate	Chladek[60]	7.5 mg/wk	24	58.4
		15 mg/wk	24	71.6
Alefacept	Lebwohl[23]	15 mg/wk	507	45.0
Efalizumab	Gordon[24]	1 mg/kg/wk	556	52.0
	Lebwohl[61]	1 mg/kg/wk	597	51.0
Etanercept	Leonardi[62]	50 mg 2×/wk	652	64.2
Infliximab	Chaudhari[63]	5 mg/kg at weeks 0, 2, and 6	33	82.8
UV-B* + acitretin	Carlin[64]	UV-B 5 - 7×/wk + acitretin 25 mg/d for 12 wk	17	80.7
PUV-A† + acitretin	Lauharanta[65]	Acitretin 40 mg/d for 2 wk, then acitretin 20 mg/d + PUV-A 3×/wk for 8 wk	34	97.3

PASI%, average percentage change in Psoriasis Area and Severity Index score from baseline to end point; PUV-A, psoralen with UV-A.
*UV-B obtained from commercial tanning beds.
†Administered by bath.

Table 2. Annualized Costs of Medication/UV Treatment

	Treatment Regimen		Annual Cost of Therapy		
Therapy	**Specified Active**	**Assumed Maintenance**	**Medication (AWP)[12]**	**UV[13,22]**	**Total**
Broadband UV-B*	3×/wk for 12 wk[41]	2×/wk for 40 wk	—	$4807	$4807
	3×/wk for 7 wk[42]	2×/wk for 45 wk	—	$4600	$4600
	3×/wk for 6 wk[43]	2×/wk for 46 wk	—	$4558	$4558
Narrowband UV-B*	3×/wk for 6 wk[43]	2×/wk for 46 wk	—	$4558	$4558
PUV-A†	4×/wk for 6 wk, then 2×/wk for 2 wk[55]	1×/wk for 44 wk	—	$3737	$3737
	3×/wk for 10 wk[56]	1×/wk for 42 wk	—	$3737	$3737
Acitretin	48.2 mg/d[57]	Constant daily dose (two 25-mg tablets)	$12,359	—	$12,359
Cyclosporine	3 mg/kg/d[58]	Constant daily dose (two 100-mg and one 25-mg tablets)	$5019	—	$5019
	1.5 mg/kg/d[59]	Constant daily dose (one 100-mg and one 25-mg tablets)	$2789	—	$2789
Methotrexate	7.5 mg/wk[60]	Constant dose (single tablet)	$595	—	$595
	15 mg/wk[60]	Constant dose (single tablet)	$1190	—	$1190
Alefacept	15 mg/wk[23]	Two 12-week courses (single dose)	$23,880	—	$23,880
Efalizumab	1 mg/kg/wk[24]	Constant dose (75 mg/wk, requiring 1 vial with 50 mg of waste)	$17,836	—	$17,836
Etanercept	50 mg 2×/wk for 12 wk[62]	25 mg 2×/wk for 40 wk (1 vial contains 25 mg)	$21,052	—	$21,052
Infliximab	5 mg/kg at wk 0, 2, and 6[63]	375 mg every 8 wk for 46 wk (6 administrations), requiring 4 vials with 25 mg of waste	$24,898	—	$24,898
UV-B‡ + acitretin	UV-B: 5 - 7×/wk for 12 wk; acitretin: 25 mg/d for 12 wk[64]	UV-B 0.5×/wk,§ acitretin reduced to 25 mg (single tablet) every other day for 40 wk	$3792	—	$3792
PUV-A + acitretin	Acitretin: 40 mg/d (one 25-mg, one 10-mg, and half 10-mg tablets) for 2 wk, then 20 mg/d plus PUV-A 3×/wk for 8 wk[65]	PUV-A 0.5×/wk§ + acitretin reduced to 25 mg every other day for 42 wk	$4437	$2336†	$6773

PUV-A, psoralen with UV-A.
*Current Procedural Terminology (CPT) code 96910 ($41.44).
†CPT code 96912 ($51.90).
‡Because UV-B was obtained from commercial tanning beds, there was no cost to the health care system.
§Signifies every other week dosing.

rious adverse events associated with each treatment. These costs were calculated as the product of each treatment's adverse event risk multiplied by the cost of care associated with the adverse event. The total costs of treatment and method for determining cost-effectiveness were calculated by dividing the total costs of care—drug or phototherapy costs, administrative costs, monitoring costs, and costs of adverse events—by clinical outcomes, or the average PASI% improvement.

Results

Among the 3886 articles identified from MEDLINE and citation reviews, we identified 16 articles, for which there were 18 outcomes, to include in our calculation of PASI improvement. A list of the citations, treatments, and PASI% improvement is presented in Table 1.

Cost analysis. Table 2 presents the costs associated with each treatment and assumptions regarding maintenance therapy. For efalizumab, there were nearly identical PASI findings of 51%[23] and 52%[24]; thus, the slightly higher findings were used to represent the efficacy for this drug. Table 3 presents monitoring regimens and associated costs for the targeted treatments, and Table 4 details costs associated with the administration of biologic agents.

Because each treatment may be associated with risk of serious adverse events, the literature was reviewed to provide guidance regarding 1-year risk-adjusted costs for adverse events for each treatment at dosages specified in Table 2.

Adverse events associated with broadband UV-B. Pasker-de Jong and associates[25] found that the risk of UV-B–associated nonmelanoma skin cancer (NMSC) is unlikely to exceed 2% per year. In 1995, annual costs for NMSC treatment among Medicare patients were estimated at $702.[26] In 2004 dollars ($875), the risk-adjusted cost of broadband UV-B–related NMSC was $18 ($875 × 2%).

Adverse events associated with narrowband UV-B. Given its limited availability, little is known about the safety of narrowband UV-B. Thus, we assumed equivalent risk and costs for broadband UV-B–related NMSC ($18, described above).

Adverse events associated with PUV-A. Compared with the general population, patients with exposure to high-dose PUV-A have a substantially increased risk of developing squamous cell carcinoma (SCC); this risk is approximately 4-fold at 5 years.[19] The risk of SCC among the general population is 0.3%.[27] Therefore, we assumed an SCC incidence of 1.2% (4-fold risk) occurring 5 years after initial PUV-A exposure. At an annual cost of $875 for NMSC treatment, the annual per-patient risk-adjusted cost of PUV-A–related NMSC was $11 ($875 × 1.2%). (We did not recalculate this 5-year estimate to a 2004 value because its contribution to total costs is negligible.)

Adverse events associated with acitretin. The most common acitretin-related adverse event is hyperlipidemia, which may occur in up to 33% of persons taking the drug.[28-30] Use of antilipid agents, weight loss, or changes in diet may improve lipid levels.[30] We assumed that hyperlipidemia would develop in 33% of patients receiving acitretin. We know of no studies describing the percentage of patients taking acitretin who have hyperlipidemia and who receive antilipid treatment; we conservatively assumed that 25% of such patients would require antilipid agents. This represents 8.25% (33% × 25%) of all patients receiving acitretin. We further assumed a daily cost of $2.76 for antilipids (20 mg atorvastatin at AWP).[12] Thus, the annual per-patient risk-adjusted cost of acitretin-related hyperlipidemia is $80 ($2.76 × 8.25% × 365 days).

Adverse events associated with cyclosporine. The most common cyclosporine-related adverse event at doses of less than 5 mg/kg/d is hypertension, which occurs among 8.5% to 27% of persons treated.[31] Persons who have cyclosporine-induced hypertension best respond to calcium channel antagonists for lowering blood pressure levels.[31] We selected a midpoint of 17.75% as the cyclosporine-related hypertension risk. At a daily cost of $2.10 for calcium channel antagonists (300 mg long-acting diltiazem at AWP),[12] the annual per-patient risk-adjusted cost of cyclosporine-related hypertension is $136 ($2.10 × 17.75% × 365 days).

Adverse events associated with methotrexate. Bone marrow suppression and lymphoma, the most worrisome methotrexate-related adverse effects, are rare among psoriasis patients.[29] Whereas hematologic toxicity risk varies from 3% to 9%, supplementation with folic acid, 1 to 5 mg/d, dramatically reduces this risk.[29] The most consistent evidence of methotrexate-related side effects pertains to hepatic function.[32-35] However, we are not aware of any research regarding risk after only 1 year of methotrexate use at dosages of less than 20 mg/wk. Therefore, we assume no risk-adjusted costs for methotrexate-related adverse events.

Adverse events associated with combined phototherapy and acitretin. Acitretin dosages are commonly reduced by half when administered in combination with phototherapy.[36] Therefore, we halved our previous 33% estimate for acitretin-related hyperlipidemia to 16.5% when acitretin was administered in combination with phototherapy. Of those patients receiving combined treatment, we further assumed that 25% would require lipid level–lowering agents. Thus, 4.13% (16.5% × 25%) of pa-

tients who received phototherapy and acitretin in combination would require an antilipid medication. At a cost of $2.76 per day for antilipids (20 mg atorvastatin at AWP), the annual per-patient risk-adjusted cost of hyperlipidemia related to combination therapy was $42 ($2.76 × 4.13% × 365 days).

Acitretin has been documented to have tumor-suppressive characteristics[37,38]; acitretin used in combination with PUV-A is associated with a 30% reduction in risk of NMSC developing, compared with use of PUV-A alone.[39] Consequently, we assumed an incidence of NMSC occurring 4 years after exposure to PUV-A and acitretin of 0.8% (70% of the 1.2% risk associated with PUV-A monotherapy), with an annual per-patient risk-adjusted cost of $7 ($875 × 0.8%). For combined UV-B and acitretin therapy, the annual per-patient risk-adjusted cost of NMSC was $12 ($875 × [2% × 70%]). Thus, the risk-adjusted costs of adverse events were estimated to be $54 for combined UV-B and acitretin and $49 for PUV-A plus acitretin.

Adverse events associated with biologics. Experts caution that given the immunosuppressive action of some biologics, there is the possibility of increased risk of long-term carcinogenicity.[40] Because biologics have not

Table 3. Monitoring Regimens per Product Labeling (Medications) or Consensus Statements (Phototherapies)

Therapy	Monitoring Regimen for 1 Year of Treatment	Total Annual Cost*
Broadband UV-B[18]	Complete physical, 1	$106
Narrowband UV-B[18]	Complete physical, 1	$106
Psoralen with UV-A[19]	Complete physical, 1	$106
Acitretin[28]	Complete physical, 1; Liver function, 15; Lipid panel, 15	$618
Cyclosporine[14]	Complete physical, 1; Brief examination, 16; Liver function, 13; Lipid panel, 16; Serum creatinine, 17; Electrolytes, 16; Magnesium, 16; Blood urea nitrogen, 16; Uric acid, 13; CBC count, 16	$1794
Methotrexate[66]	Complete physical, 1; Liver function, 13; CBC count, 13; Renal function, 13; Chest x-ray, 1; Liver biopsy, 0.5 (recommended every other year)	$1188
Alefacept[17]	Complete physical, 1; CD4 T-lymphocyte, 26	$2412
Efalizumab[15]	Complete physical, 1; Red blood cell count, automated, 7	$163
Etanercept[21]	Complete physical, 1	$106
Infliximab[16]	Complete physical, 1; Tuberculosis skin test, 1	$116
UV-B + acetretin[20,36]	Complete physical, 1; Liver function, 15; Lipid panel, 15	$618
Psoralen with UV-A + acitretin[20,36]	Complete physical, 1; Liver function, 15; Lipid panel, 15	$618

*Costs were based on 2004 Medicare rates[13] and were calculated as follows: Complete physical, $105.66; Brief examination, $8.96; Liver function, $15.43; Lipid panel, $18.72; Serum creatinine, $10; CD4 T-lymphocyte, $88.71; Electrolytes, $13.24; Magnesium, $12.65; Blood urea nitrogen, $7.45; Uric acid, $8.53; Complete blood cell (CBC) count, $14.68; Red blood cell count, automated, $8.12; Tuberculosis skin test, $10; Renal function, $16.39; Chest x-ray, $35.84; Liver biopsy, $884 (includes $200 reimbursement for biopsy procedure and assumed additional facility costs for ambulatory services of $684).

Table 4. Biologics Administration Costs

Drug	Mode of Delivery	No. of Clinician Administrations/y	2004 Medicare Reimbursement Rate[13]	Total Annual Costs
Alefacept	IM bolus	24	$33.60	$806
Efalizumab	SC	0 (patient-administered)	—	$0
Etanercept	SC	0 (patient-administered)	—	$0
Infliximab	2-h IV infusion	9	$157.99	$1422

been available long enough to determine whether they contribute to development of malignancies, we did not incorporate biologic-related adverse events into our assumptions of risk-adjusted adverse event costs. Table 5 summarizes our assumptions of risk-adjusted costs of adverse events by treatment. Table 6 presents annualized costs of treatment, PASI% efficacy, and costs to achieve PASI1, PASI50, and PASI75.

Discussion

Oral systemic medications, UV therapy, and UV therapy in combination with acitretin appear to be the most cost-effective treatments of moderate to severe psoriasis. The cost to achieve PASI1 ranged from $31 (methotrexate) to $602 (alefacept), and annualized costs to achieve PASI75, a clinically meaningful threshold of efficacy, ranged from approximately $2300 to $45,000. Key drivers of cost-effectiveness were medication or phototherapy costs and PASI efficacy rates. Treatment administration, monitoring, and risk-adjusted costs for adverse events contributed little to total costs of care.

Cost is an important factor in both formulary determination and clinical decision making. Other factors include the safety of treatments. The most cost-effective treatment was methotrexate, which has serious potential long-term risks not calculated in our analysis. These risks will need to be weighed when comparing use of methotrexate with other options.

Phototherapy, as monotherapy and in combination with acitretin, appears to hold an intermediate position in terms of cost-effectiveness and has an excellent short- and long-term safety profile. Health care systems should reconsider any current disincentives in plan design for access to these treatments.

Wide variation in PASI score improvement (47% to 80.1%) and associated cost-effectiveness ($56 to $100) was found for broadband UV-B. We included 2 randomized, placebo-controlled trials that reported PASI improvement of approximately 80%.[41,42] A small (n = 11), open-label study reported PASI improvement of 47%.[43] Although this study meets all inclusion criteria, results may not be as robust as those of the larger, double-blind, placebo-controlled trials. Consequently, the cost-effectiveness of broadband UV-B may be underestimated when this smaller study's PASI improvement of 47% is applied.

Our estimate of combination broadband UV-B and acitretin therapy is based on efficacy of treatment from commercial tanning beds; therefore, no health care systems–related costs for UV-B were included. If UV-B were administered in a clinic (5 exposures per week and 25 mg acitretin for 12 weeks, followed by twice weekly exposures and 25 mg acitretin every other day for the remainder of the year), total annual costs are estimated to be $7108; at a PASI% efficacy of 80.7%, costs to achieve PASI1, PASI50, and PASI75 would be $88, $4400, and $6600, respectively.

Study Limitations

Our study has several limitations. First, only peer-reviewed, published studies were included. As a result of potential publication bias, treatment effects (ie, PASI outcomes) may be overestimated.[44] As previously noted, our approach is consistent with the formulary review process typically conducted by US health care systems. Second, we excluded studies in languages other than English. However, our review of hand-searched bibliographies does not suggest that this restriction caused any important studies to be missed.

Third, we evaluated treatment effectiveness solely in terms of PASI. Other indices, such as global assessments of improvement, willingness-to-pay, quality of life, and duration of remission, may be used in clinic settings or be more sensitive to patient preferences, response to therapy, level of suffering, or treatment ef-

fects.[45-49] However, the PASI was selected because of its acceptance by the FDA as an index of treatment efficacy, its use in clinical trials across targeted treatments, and its correspondence to clinically meaningful outcomes.

Physicians widely vary in their clinical and billing practices; therefore, the monitoring regimen included in our cost calculations reflects product labeling recommendations rather than actual practice. Furthermore, we included a conservative estimate of charges for administration of biologics and phototherapy. To the extent that actual practice varies from our assumptions, costs of treatment should be adjusted accordingly. To facilitate such adjustment, we have made our cost assumptions as transparent as possible.

Another limitation was that this analysis was developed for patients with moderate to severe "skin" psoriasis. Consequently, findings may not extend to patients with psoriatic arthritis. In addition, this study was limited by the short-term nature of extant study results (1 year) and, thus, we did not feel confident in extending reported efficacy and safety findings beyond this 1-year period. Because psoriasis is a lifelong disease, many patients go in and out of treatment; a Markov analysis might be more appropriate to study such treatment, but we know of no studies that examined actual utilization across a range of psoriasis treatments. Therefore, we calculated the comparative cost-effectiveness required to achieve 1 year of successful treatment. Furthermore, our dosing assumptions ignore potential

Table 5. Adverse Event Risk Costs and Annual Risk-Adjusted Costs by Treatment

Therapy	Risk of Adverse Event	Costs of Adverse Events	Annualized Risk-Adjusted Costs of Adverse Events
UV-B	NMSC: 2% annual incidence[25]	$875*/y[26]	$18
PUV-A	NMSC: 5-year risk, 1.2%[19,27]	$875*/y[26]	$11
Acitretin	Hyperlipidemia: 8.25% of patients will require lipid-lowering agents[28,61,62]	20 mg atorvastatin: $2.76/d (AWP)[12]	$83
Cyclosporine	Hypertension: 18% of patients will require calcium channel antagonists[31]	300 mg long-acting diltiazem: $2.10/d (AWP)[12]	$138
Methotrexate	Unknown at dosages < 20 mg/wk	—	—
Alefacept	Unknown	—	—
Efalizumab	Unknown	—	—
Etanercept	Unknown	—	—
Infliximab	Unknown	—	—
UV-B + acitretin	Hyperlipidemia: 4.13% of patients will require lipid-lowering agents[28,61,62] NMSC: 5-year risk, 1%[25] (acitretin reduced risk 70%[39])	20 mg atorvastatin: $2.76/d (AWP)[12] + $875*/y[26]	$54
PUV-A + acitretin	Hyperlipidemia: 4.13% of patients will require lipid-lowering agents[28,61,62] NMSC: 5-year risk, 2%[19,27] (acitretin reduced risk 70%[39])	20 mg atorvastatin: $2.76/d (AWP)[12] + $875*/y[26]	$49

NMSC, nonmelanoma skin cancer; PUV-A, psoralen with UV-A.
*Adjusted to 2004 dollars.

"dosage creep," which would have increased cost estimates and decreased cost-effectiveness results.

The systematic review selection criteria used in this analysis may have been too stringent—we were surprised to find so few studies meeting our criteria for inclusion. In a review of the quality of psoriasis-related studies published from 1977 through 2000, consistently poor quality in study design and reporting of results was found.[50] Given that such a small number of studies met our criteria for inclusion, we had very few data points to consider. Consequently, our findings are limited to the data available.

Despite its limitations, our study had several strengths. First, we conducted a systematic, evidence-based approach to the identification of effectiveness across treatments and applied these results to our cost-effectiveness calculations. Second, we included risk-adjusted costs of adverse events in calculations of total costs. Third, we considered the clinical relevance of our findings in terms of PASI50 and PASI75.

Conclusion

Few systematic reviews of the effectiveness of treatments of psoriasis have been conducted. None of them were completed before biologics entered the market, and all of them included studies in which doses administered exceeded current recommendations.[48,51,52] There have also been few studies of psoriasis that compared the cost-effectiveness of phototherapies, oral systemic medications, and biologics. Rapp and associates[53] estimated the cost of psoriasis treatment in terms of PASI75.

Table 6. Annualized Costs of Care, Efficacy, and Cost-Effectiveness

	Annualized Costs of Care, $						Cost-Effectiveness, $		
Treatment	Rx	Del	Mon	AE	Total	PASI%	PASI1	Cost/y, PASI50	Cost/y, PASI75
Methotrexate 7.5 mg	595	—	1188	—	1783	58.4	31	1526	2290
Methotrexate 15 mg	1190	—	1188	—	2378	71.6	33	1660	2491
PUV-A	3737	—	106	11	3854	92.9	41	2074	3111
	3737	—	106	11	3854	61.1	63	3154	4731
Broadband UV-B + acitretin 25 mg	3792	—	618	54	4464	80.7	55	2766	4149
Broadband UV-B	4600	—	106	18	4724	83.7	56	2822	4233
	4807	—	106	18	4931	80.1	62	3078	4617
	4558	—	106	18	4682	47.0	100	4981	7472
Narrowband UV-B	4558	—	106	18	4682	73.0	64	3207	4811
PUV-A + acitretin 20 mg	6773	—	618	49	7440	97.3	76	3823	5735
Cyclosporine 3 mg/kg	5019	—	1794	138	6951	52.0	134	6683	10,025
Cyclosporine 1.5 mg/kg	2789	—	1794	138	4721	33.4	141	7067	10,600
Acitretin 50 mg	12,359	—	618	83	13,060	60.4	216	10,811	16,217
Infliximab 5 mg/kg	24,898	1422	116	—	26,436	82.8	319	15,964	23,946
Etanercept 50 mg	21,052	0	106	—	21,158	64.2	330	16,478	24,717
Efalizumab 1 mg/kg	17,836	0	163	—	17,999	52.0	346	17,307	25,960
Alefacept 15 mg IM	23,880	806	2412	—	27,098	45.0	602	30,109	45,163

Rx, therapy; Del, delivery; Mon, monitoring; AE, adverse events; PASI%, average percentage change in Psoriasis Area and Severity Index score from baseline to end point; PUV-A, psoralen with UV-A.

These findings, which were based on expert opinion of PASI efficacy, mirror ours in that methotrexate, PUV-A, and UV-B were the least costly treatments, followed by cyclosporine and acitretin monotherapy; combined UV treatment with acitretin was not included in their analysis. Rapp and colleagues[53] also found that biologic agents were the most costly therapies, and among these, infliximab was relatively less costly than etanercept or alefacept.

There is no doubt that the suffering of patients with moderate to severe psoriasis can be extensive. Patients may endure pain, disfigurement, and decrements in quality of life.[53] Although treatment with toxic or expensive medications may be well justified, decisions about which treatments to apply, and the order in which they are initiated, should take into account safety, efficacy, and costs.[54]

The most costly medications were not necessarily the most effective. Biologic treatments do not appear to be as cost-effective as oral systemic agents, phototherapy, or phototherapy used in combination with acitretin. Although biologics may present as an important option in the psoriasis treatment armamentarium, our results do not justify positioning biologics as first-line therapy for moderate to severe psoriasis. ■

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