

# Patient-reported reasons for the discontinuation of commonly used treatments for moderate to severe psoriasis

Howa Yeung, BS,<sup>a</sup> Joy Wan, BA,<sup>a</sup> Abby S. Van Voorhees, MD,<sup>a</sup> Kristina Callis Duffin, MD,<sup>c</sup> Gerald G. Krueger, MD,<sup>c</sup> Robert E. Kalb, MD,<sup>d</sup> Jamie D. Weisman, MD,<sup>c</sup> Brian R. Sperber, MD, PhD,<sup>f</sup> Bruce A. Brod, MD,<sup>a</sup> Stephen M. Schleicher, MD,<sup>g</sup> Bruce F. Bebo, Jr, PhD,<sup>h</sup> Daniel B. Shin, MS,<sup>a,b</sup> Andrea B. Troxel, ScD,<sup>b</sup> and Joel M. Gelfand, MD, MSCE<sup>a,b</sup>  
*Philadelphia and Hazelton, Pennsylvania; Salt Lake City, Utah; Buffalo, New York; Atlanta, Georgia; Colorado Springs, Colorado; and Portland, Oregon*

**Background:** Despite widespread dissatisfaction and low treatment persistence in moderate to severe psoriasis, patients' reasons behind treatment discontinuation remain poorly understood.

**Objectives:** We sought to characterize patient-reported reasons for discontinuing commonly used treatments for moderate to severe psoriasis in real-world clinical practice.

**Methods:** A total of 1095 patients with moderate to severe plaque psoriasis from 10 dermatology practices who received systemic treatments completed a structured interview. Eleven reasons for treatment discontinuation were assessed for all past treatments.

**Results:** A total of 2231 past treatments were reported. Median treatment duration varied by treatment, ranging from 6.0 to 20.5 months ( $P < .001$ ). The frequency of each cited discontinuation reasons differed by

From the Department of Dermatology<sup>a</sup> and Department of Epidemiology and Biostatistics, Center for Clinical Epidemiology and Biostatistics,<sup>b</sup> University of Pennsylvania Perelman School of Medicine, Philadelphia; Department of Dermatology, University of Utah School of Medicine<sup>c</sup>; Department of Dermatology, State University of New York at Buffalo School of Medicine and Biomedical Sciences<sup>d</sup>; Peachtree Dermatology Associates, Atlanta<sup>e</sup>; Colorado Springs Dermatology Clinic<sup>f</sup>; DermDox Centers for Dermatology, Hazelton<sup>g</sup>; and National Psoriasis Foundation, Portland.<sup>h</sup>

Supported by the T32-AR07465 (Mr Yeung, Ms Wan, Mr Shin) and 1KM1CA156723 (Dr Callis Duffin) training grants from the National Institutes of Health, and the RC1-AR058204 grant from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (Dr Gelfand). The sponsors had no role in the design and conduct of the study; in the collection, analysis, and interpretation of data; or in the preparation, review, or approval of the manuscript.

Disclosure: Dr Van Voorhees has served on advisory boards for Amgen, Abbott, Genentech, Warner Chilcott, and Centocor; as an investigator for Amgen and Genentech; as a consultant for Amgen and Leo Pharma; as a speaker for Amgen, Abbott, and Centocor; and received honoraria from Synta. Dr Callis Duffin has served on advisory boards for Amgen; as a consultant for Amgen and Centocor; as an investigator for Abbott, Amgen, Centocor, and Pfizer; and received payments for lectures from Abbott, Amgen, and Centocor. Dr Krueger has served as a consultant for Abbott, Amgen, and Centocor; had grants from Abbott and Amgen; and received payment for lectures and travel-related expenses from Abbott, Amgen, and Centocor. Dr Kalb has served as a consultant for Abbott, Amgen, Centocor, LEO Pharma, and Stiefel; an investigator for Abbott, Amgen, Astellas, and Centocor; and a speaker for Abbott,

Amgen, Centocor, Galderma, LEO Pharma, and Stiefel. Dr Weisman has served as an investigator for Abbott, Braintree Laboratories, Celgene, Cipher Pharmaceuticals, LEO Pharma, Pfizer, Novartis, and Eli Lilly; and received payments for lectures from Abbott and Amgen. Dr Sperber is the medical director of Stephens & Associates, has served as a consultant for Amgen, and had grants or has pending grants from Abbott and Centocor. Dr Bebo is employed by the National Psoriasis Foundation, which receives unrestricted financial support from Amgen, Abbott, Janssen, Stiefel Laboratories, Wyeth, Pfizer, Eli Lilly, Galderma, and PhotoMedex. Dr Gelfand has served as a consultant for Abbott, Amgen, Celgene, Centocor, Novartis, and Pfizer; had grants from Abbott, Amgen, Genentech, Novartis, and Pfizer; and received payment for continuing medical education work related to psoriasis. He received a donation from Amgen to the University of Pennsylvania to further develop Dermatology Clinical Effectiveness Research Network, which was not used for the current study. Mr Yeung, Ms Wan, Dr Brod, Dr Schleicher, Mr Shin, and Dr Troxel have no conflicts of interest to declare.

Part of this study will be presented as an oral presentation to the International Conference on Pharmacoepidemiology and Therapeutic Risk Management in Barcelona, Spain on August 23-26, 2012.

Accepted for publication June 26, 2012.

Reprints not available from the authors.

Correspondence to: Joel M. Gelfand, MD, MSCE, Department of Dermatology, University of Pennsylvania Perelman School of Medicine, 1471 Penn Tower, One Convention Ave, Philadelphia, PA 19104. E-mail: [joel.gelfand@uphs.upenn.edu](mailto:joel.gelfand@uphs.upenn.edu).

Published online July 28, 2012.

0190-9622/\$36.00

© 2012 by the American Academy of Dermatology, Inc.

<http://dx.doi.org/10.1016/j.jaad.2012.06.035>

treatment (all  $P < .01$ ). Patients who received etanercept (odds ratio [OR] 5.19; 95% confidence interval [CI] 3.23-8.33) and adalimumab (OR 2.10; 95% CI 1.20-3.67) were more likely to cite a loss of efficacy than those who received methotrexate. Patients who received etanercept (OR 0.34; 95% CI 0.23-0.49), adalimumab (OR 0.48; 95% CI 0.30-0.75), and ultraviolet B phototherapy (OR 0.21; 95% CI 0.14-0.31) were less likely to cite side effects than those who received methotrexate, whereas those who received acitretin (OR 1.56; 95% CI 1.08-2.25) were more likely to do so. Patients who underwent ultraviolet B phototherapy were more likely to cite an inability to afford treatment (OR 7.03; 95% CI 3.14-15.72).

**Limitations:** The study is limited by its reliance on patient recall.

**Conclusions:** Different patterns of treatment discontinuation reasons are important to consider when developing public policy and evidence-based treatment approaches to improve successful long-term psoriasis control. (J Am Acad Dermatol 10.1016/j.jaad.2012.06.035.)

**Key words:** biologics; cost; effectiveness; inconvenience; phototherapy; psoriasis; safety; systemic treatments; treatment discontinuation.

Psoriasis is a chronic inflammatory disorder of the skin and joints associated with significant impairments in physical health and psychosocial well-being.<sup>1</sup> Patients with moderate to severe psoriasis have excess mortality risk, largely attributable to cardiovascular disease, independent of traditional risk factors.<sup>2-11</sup> Despite the availability of treatment options with established safety and efficacy profiles for moderate to severe psoriasis, studies have reported widespread treatment dissatisfaction, underutilization of systemic treatments, and poor adherence to treatment recommendations.<sup>12-18</sup>

Because psoriasis is a lifelong disease for which most patients do not achieve prolonged clinical remission and require maintenance therapies, it is crucial for patients to continue with their prescribed treatments to achieve long-term treatment success.<sup>19-21</sup> Nevertheless, studies have demonstrated annual treatment discontinuation rates of 15% to 25% among traditional systemic therapies and phototherapy.<sup>18</sup> Studies on biologics also showed a progressive loss of treatment persistence, with first-year attrition rate of 10% to 15%.<sup>19,20</sup> As a composite surrogate marker of treatment efficacy, safety, tolerability, and overall satisfaction, treatment persistence in moderate to severe psoriasis is low and may contribute to suboptimal treatment response and increased health care use.<sup>17-20</sup>

### CAPSULE SUMMARY

- Patients with moderate to severe psoriasis have low long-term treatment persistence, but little is known about why they stop treatments.
- Discontinuation reasons for various treatments highlight the importance of treatment effectiveness, safety, convenience, cost, and other patient-oriented factors in long-term treatment use.
- These results may inform the development of public policy and evidence-based strategies to improve successful long-term psoriasis control.

Although treatment persistence has just started to be quantified, there is a paucity of research identifying why patients stop their psoriasis treatments.<sup>22</sup> Available data on treatment discontinuation are mostly derived from short-term clinical trials or chart reviews that emphasize efficacy and safety parameters.<sup>20</sup> Other patient-oriented factors that may affect long-term treatment persistence in clinical practice (eg, treatment satisfaction, treatment process burden, cost, and other systemic barriers) remain poorly understood. Cons-

equently, efforts to promote treatment persistence lack an adequate evidence base for targeting specific patient needs and providing patients with better accepted treatment regimens.<sup>23</sup> The importance of incorporating patient perspectives in balancing clinical outcomes against treatment process burdens is now increasingly recognized.<sup>24,25</sup> Therefore, improving our understanding of the patients' views on treatment discontinuation is essential to integrate patient needs more fully in shared decision-making and to optimize effective, patient-centered care with the goal of successful long-term psoriasis control.

The purpose of this study was to assess and compare patient-reported reasons behind discontinuing systemic treatments, biologics, and phototherapy for moderate to severe psoriasis in routine clinical practice.

*Abbreviations used:*

DCERN:	Dermatology Clinical Effectiveness Research Network
PUVA:	psoralen plus ultraviolet A
UV:	ultraviolet

**METHODS****Study design**

As part of a multicenter comparative effectiveness study,<sup>26</sup> we conducted a cross-sectional study to determine the reasons for the discontinuation of systemic treatments, biologics, and phototherapy for moderate to severe psoriasis. The study was approved by the University of Pennsylvania and University of Utah Institutional Review Boards and conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all patients.

**Setting**

Data were collected by 10 dermatologists and 2 physician assistants who are members of the Dermatology Clinical Effectiveness Research Network (DCERN) from February 2010 through June 2011. DCERN includes 2 academic medical centers (University of Pennsylvania and University of Utah, each with a hospital-based site and a separate community-based site) and 6 private practices in Georgia, Pennsylvania, New York, and Colorado (see [www.dermcern.org](http://www.dermcern.org) for details). Patient data were collected prospectively at a single, regularly scheduled clinic appointment.

**Participants**

Broad inclusion criteria were used in enrolling consecutive patients seen by their dermatology provider in DCERN practices for a routine follow-up appointment to minimize selection bias. Eligible participants included patients established in the practice who were currently receiving or had previously received a systemic treatment, biologic agent, or phototherapy for treating psoriasis, or were candidates for systemic therapy with a documented history of 5% or more body surface area involvement.<sup>27</sup> Patients new to the practice became eligible only at their subsequent regularly scheduled visit; in other words, all enrolled patients had at least 1 prior visit at that practice to qualify for study entry. Patients were excluded if they did not meet these criteria or were unable or unwilling to provide consent. Enrolled patients were compensated \$10 upon study completion. In the analysis presented herein, we included patients who had previously used and

discontinued at least 1 treatment of interest for a primary indication of plaque psoriasis, which encompassed commonly used systemic treatments (methotrexate, acitretin, and cyclosporine), biologics (etanercept, adalimumab, and infliximab), and phototherapy (ultraviolet [UV] B and oral psoralen plus UVA [PUVA]). To be considered as a past treatment, the duration since last treatment use had to be 9 weeks or longer for infliximab and 3 weeks or longer for all other treatments. We did not analyze data on treatments for which few patients had reported discontinuation (eg, only 12 patients discontinued ustekinumab within our study). Patients who did not report any past use of a treatment of interest for psoriasis or whose primary indication was a variant of psoriasis other than plaque psoriasis were excluded.

The study was descriptive in nature; therefore, the sample size for specific analyses was not determined a priori. We aimed to collect data for about 2000 patients in the main comparative effectiveness study to yield precise estimates, with the half-width of the 95% confidence interval around rates for dichotomous variables being approximately 0.02.

**Questionnaire and variables**

Trained study coordinators gathered data through structured patient interviews with confirmation by the patient's dermatology clinic record and assessments by the clinicians. Detailed data were collected on sociodemographic factors, medical history, body mass index, alcohol and tobacco use history, and psoriasis characteristics. All current and past use of systemic treatments, biologics, and phototherapy were specifically assessed. Eleven treatment discontinuation reasons were devised a priori by the principal investigator, with review by DCERN coinvestigators and steering committee and the Outcomes Measurements Methods Core at University of Pennsylvania to ensure face and content validity. For each treatment, patients could select 1 or more of these 11 reasons for discontinuation and/or provide other reasons. Elaborations of the a priori reasons and other elicited reasons were recorded as free text.

**Data analysis**

Descriptive statistics were used to summarize patient demographics and clinical characteristics. Reasons for treatment discontinuation were analyzed by treatment using  $\chi^2$  and Fisher exact tests, as appropriate. Statistical significance was defined as *P* less than .05 in 2-tailed tests. Open-ended responses for other treatment discontinuation reasons were independently categorized by 2 authors (H. Y. and

J. W.) into a priori codes from the 11 predetermined reasons and other reasons. Substantial interrater agreement was observed ( $\kappa = 0.79$ )<sup>28</sup> and discordances were resolved through independent coding by a third rater (J. M. G.). All a priori reasons for treatment discontinuation were pooled for analysis, whereas other elicited reasons were presented separately.

Mixed-effects logistic regression models were fitted to compare specific discontinuation reasons (lack of efficacy, loss of efficacy, any side effect, and cannot afford treatment) among treatments.<sup>29</sup> Because each patient may contribute data on multiple past treatments, the models adjusted for response clustering at the patient level as random effects along with socio-demographic and disease-related confounders as fixed effects. Methotrexate was chosen as reference as it is often considered the standard to which other therapies are compared. Covariates were selected using a backward elimination approach and significance was assessed with likelihood ratio tests. Sensitivity analyses were conducted by further adjusting for all other discontinuation reasons because of potential competing risks among reasons and by excluding treatments with duration less than 6 months. All statistical analyses were performed using Stata IC 12.1 (Stata Corp, College Station, TX).

## RESULTS

### Sample characteristics

Data were collected on 1755 eligible patients (5% of patients declined to participate). Among the 1158 patients who reported any previous treatment for chronic plaque psoriasis, 1095 patients reporting at least 1 previous biologic, systemic, or phototherapy were included in the analysis. Patient demographics and clinical characteristics are shown in Table I. Based on self-reported categories on the extent of psoriasis involvement at its worst, 29.5% of patients reported 3% to 10% body surface area involvement, whereas 60.5% of the patients reported greater than 10% body surface area involvement.

### Patterns of past treatments

A total of 2231 past treatments of interest were reported (Table II). Patients reported a median of 2 past treatments (interquartile range, 1-3). Treatment duration varied widely by treatment ( $P < .001$ ), ranging from 20.5 months with etanercept to 6 months with acitretin, cyclosporine, UVB, and oral PUVA. Time of last treatment use also differed significantly by treatment, with median ranging from 1 to 2 years ago for biologics, 3 to 4 years ago for systemic treatments and UVB, to greater than 4 years ago for oral PUVA ( $P < .001$ ).

**Table I.** Baseline patient and psoriasis characteristics (N = 1095)

Characteristic	
Median age (IQR), y	49 (37-60)
Female sex, N (%)	532 (48.6)
Practice setting of dermatologist, N (%)	
Academic	714 (65.2)
Private	381 (34.8)
Race, N (%)	
Caucasian	935 (85.4)
African American	43 (3.9)
Other*	117 (10.7)
Hispanic ethnicity, N (%)	50 (4.6)
Median BMI (IQR), kg/m <sup>2</sup>	28.7 (25.0-33.3)
Median total No. of comorbidities <sup>†</sup> (IQR)	2 (1-4)
Median age of psoriasis onset (IQR), y	23 (15-36)
Median duration of psoriasis (IQR), y	20 (10-31)
Psoriatic arthritis diagnosed by a physician, N (%)	308 (28.1)
Self-reported worst severity of psoriasis, body surface area affected, N (%)	
1-2 Palms	109 (10.0)
3-10 Palms	323 (29.5)
11-20 Palms	330 (30.1)
>20 Palms	333 (30.4)

Percentages may not total 100% because of rounding errors or missing data, which did not exceed 0.5% for any particular characteristic.

BMI, Body mass index; IQR, interquartile range.

\*Includes responses of American Indian/Alaskan, Hawaiian/Pacific Islander, Asian, multiracial, other, or prefer not to answer.

<sup>†</sup>Includes cardiovascular, lung, infection, gastrointestinal, renal, endocrine, musculoskeletal, psychiatric, neurologic, malignant, or autoimmune diseases.

### Reasons for treatment discontinuation

Although most past treatments (70.8%) had only 1 discontinuation reason indicated, 22.6% had 2 reasons and 6.5% had 3 or more reasons. The frequency of citing each of 11 discontinuation reasons differed significantly by treatment (Table III). The most common reason for stopping etanercept was that it “worked well at first but stopped working well”; for adalimumab was that it “did not work well enough”; for infliximab, methotrexate, acitretin, and cyclosporine was non-life-threatening side effects; for UVB was treatment inconvenience and “psoriasis improved and prefer not to be on continuous treatment”; and for oral PUVA was treatment inconvenience.

Of note, non-life-threatening side effects were often reported in patients stopping systemic therapies, infliximab and oral PUVA (21.0%-36.3%). This contrasts with life-threatening side effects, seen predominantly with infliximab (9.1%). Treatment inconvenience was noted by 22.3% to 31.5% of patients

**Table II.** Past treatment use pattern (N = 1095)

Type	Treatment	Patients		Median duration (IQR), mo	Time of last treatment use, %*				
		N	%		<6 mo	6-12 mo	1-2 y	3-4 y	>4 y
Systemic	Methotrexate	446	40.7	12 (5-39.6)	15.7	10.3	22.0	12.8	37.0
	Acitretin	204	18.6	6 (2-12)	12.3	5.9	26.0	14.2	39.7
	Cyclosporine	151	13.8	6 (2-12)	11.9	12.6	22.5	14.6	37.7
Biologic	Etanercept	393	35.9	20.5 (7-36)	15.8	8.7	36.1	18.8	19.3
	Adalimumab	200	18.3	11 (5-16.8)	25.5	18.0	38.5	12.5	4.5
	Infliximab	99	9.0	12 (4-24)	15.2	10.1	35.4	9.1	28.3
Phototherapy	UVB	590	53.9	6 (2-12)	15.3	7.8	20.7	11.0	44.4
	Oral PUVA	148	13.5	6 (3-24)	2.7	2.0	9.5	6.8	79.1

Number of treatments totaled 2231 because the 1095 patients may each have received more than 1 past treatment.

IQR, Interquartile range; PUVA, psoralen plus ultraviolet A; UV, ultraviolet.

\*Percentages may not total 100% because of unknown/missing data, which did not exceed 2.3%.

treated with UVB and oral PUVA phototherapy, as opposed to no more than 4% among those treated with systemic therapies and biologics. Denied insurance coverage was cited most often in stopping biologics and oral PUVA (4.7%-7.5%); post hoc analyses did not reveal significant difference in the proportions citing insurance denial among the 3 biologics ( $P = .55$ ).

Four specific reasons were analyzed in fully adjusted regression models (Table IV). Despite indications that the random effects may not be normally distributed, the models have high discriminative abilities with area under the receiver operating characteristic curve ranging from 0.80 to 0.98. Compared with patients who received methotrexate, those who received adalimumab were more likely to cite that the treatment “did not work well enough,” whereas those who received etanercept, adalimumab, and infliximab were more likely to cite that the treatment “work welled at first but stopped working well.” Patients who received etanercept, adalimumab, and UVB phototherapy were less likely to stop treatment because of side effects than those who received methotrexate; in contrast, patients who received acitretin were more likely to stop treatment because of side effects. Patients who underwent UVB phototherapy were more likely to report an inability to afford treatment in its discontinuation than those who received methotrexate.

These results were largely robust to sensitivity analyses. After adjusting the models for all other reasons, point estimates of the associations between treatments and specific discontinuation reasons remained largely similar, except the odds ratios between acitretin and treatment “did not work well enough” and inability to afford treatment reached significance (data not shown). After excluding treatments that were received for less than 6 months, point estimates of the associations also remained similar.

### Other reasons

Various other discontinuation reasons were reported (data not shown). The most commonly reported other reason was switching treatments with no particular reported reason for the switch. Personal issues (eg, job, moving, or travel-related issues) and patient preference (eg, desire to try new treatment or to substitute with natural sunlight in summer months) were noted frequently in stopping UVB and oral PUVA phototherapy. Pregnancy and desires to become pregnant were implicated in discontinuing methotrexate, cyclosporine, etanercept, and oral PUVA. The need for vaccination and surgical procedures was cited with stopping biologics, although we could not discern if the discontinuation was temporary or permanent. Issues with treatment monitoring, particularly regarding liver biopsy, were cited with methotrexate.

### DISCUSSION

This study comprehensively characterized patient-reported reasons for discontinuing commonly used treatments for moderate to severe psoriasis in clinical practice. We demonstrated different patterns of reasons among systemic, biologic, and phototherapy treatments. Perceived treatment inefficacy and side effects were the predominant issues leading to treatment withdrawal; however, treatment inconvenience and economic barriers were also commonly cited, emphasizing the value of patient-oriented factors in long-term psoriasis treatment.

The paradigm for psoriasis treatment has evolved with the introduction of biologic agents, inspiring prospects of controlling acute flares and maintaining disease remission using an appropriate long-term treatment.<sup>20,21</sup> In our study, patients stopped systemic treatments and phototherapy after medians of 6 to 12 months and biologic agents after medians of 12 to 20.5 months. One previous study also showed

**Table III.** Reasons for discontinuing past treatments

	Systemic treatment			Biologic			Phototherapy		P value*
	Methotrexate (N = 446)	Acitretin (N = 204)	Cyclosporine (N = 151)	Etanercept (N = 393)	Adalimumab (N = 200)	Infliximab (N = 99)	UVB (N = 590)	Oral PUVA (N = 148)	
Discontinuation reasons, n (%)									
Did not work well enough	94 (21.1)	65 (31.9)	37 (24.5)	102 (26.0)	68 (34.0)	20 (20.2)	136 (23.1)	32 (21.6)	.004
Worked well at first but stopped working well	56 (12.6)	25 (12.3)	24 (15.9)	126 (32.1)	44 (22.0)	21 (21.2)	58 (9.8)	20 (13.5)	<.001
Non-life-threatening side effects	126 (28.3)	74 (36.3)	43 (28.5)	48 (12.2)	29 (14.5)	24 (24.2)	49 (8.3)	31 (21.0)	<.001
Life-threatening side effects <sup>†</sup>	3 (0.7)	2 (1.0)	1 (0.7)	2 (0.5)	3 (1.5)	9 (9.1)	2 (0.3)	2 (1.4)	<.001 <sup>‡</sup>
Developed illness unrelated to treatment	19 (4.3)	3 (1.5)	8 (5.3)	33 (8.4)	15 (7.5)	7 (7.1)	9 (1.5)	0 (0.0)	<.001
Concern about safety of continuous treatment	54 (12.1)	9 (4.4)	14 (9.3)	18 (4.6)	6 (3.0)	2 (2.0)	31 (5.3)	17 (11.5)	<.001
Psoriasis improved and prefer not to be on continuous treatment	78 (17.5)	26 (12.8)	18 (11.9)	16 (4.1)	12 (6.0)	5 (5.1)	180 (30.5)	33 (22.3)	<.001
Too inconvenient	10 (2.2)	2 (1.0)	0 (0.0)	8 (2.0)	1 (0.5)	4 (4.0)	180 (30.5)	35 (23.7)	<.001
Cannot afford treatment <sup>§</sup>	19 (4.3)	11 (5.4)	9 (6.0)	22 (5.6)	9 (4.5)	4 (4.0)	68 (11.5)	7 (4.7)	<.001
Insurance denied <sup>§</sup>	8 (1.8)	3 (1.5)	3 (2.0)	21 (5.3)	15 (7.5)	7 (7.1)	11 (1.9)	7 (4.7)	<.001 <sup>‡</sup>
Delay in obtaining refills from doctor, pharmacy, or insurance company <sup>§</sup>	43 (9.6)	5 (2.5)	6 (4.0)	22 (5.6)	20 (10.0)	4 (4.0)	7 (1.2)	2 (1.4)	<.001

Number of treatments totaled 2231 because the 1095 patients may each have received more than 1 past treatment. Percentages do not total 100% because patients may have more than 1 reason for discontinuing any particular treatment.

PUVA, Psoralen plus ultraviolet A; UV, ultraviolet.

\* $\chi^2$  Test.

<sup>†</sup>Includes side effects that were life threatening or required hospitalization.

<sup>‡</sup>Fisher exact test.

<sup>§</sup>Correlations among these treatment discontinuation reasons are low (Pearson  $r = 0.25$  between "cannot afford treatment" and "insurance denial";  $r = 0.14$  between "cannot afford treatment" and "delays in obtaining refills"), thus role of "cannot afford treatment" on treatment discontinuation may not be entirely attributed to other 2 reasons.

**Table IV.** Adjusted odds ratios of citing specific discontinuation reasons

	Systemic treatment				Biologics			Phototherapy	
	Methotrexate	Acitretin	Cyclosporine	Etanercept	Adalimumab	Infliximab	UVB	Oral PUVA	
Discontinuation reasons, OR (95% CI)									
Did not work well enough*	1.00 [ref.]	1.56 (0.97-2.46)	0.75 (0.46-1.23)	1.28 (0.89-1.83)	1.74 (1.11-2.74)	0.59 (0.30-1.15)	0.90 (0.63-1.30)	0.67 (0.39-1.17)	
Worked well at first but stopped working well†	1.00 [ref.]	0.86 (0.46-1.62)	1.43 (0.77-2.68)	5.19 (3.23-8.33)	2.10 (1.20-3.67)	2.07 (0.95-4.51)	0.88 (0.55-1.40)	1.09 (0.56-2.12)	
Any side effect‡,§	1.00 [ref.]	1.56 (1.08-2.25)	1.08 (0.70-1.67)	0.34 (0.23-0.49)	0.48 (0.30-0.75)	1.30 (0.78-2.17)	0.21 (0.14-0.31)	0.66 (0.41-1.06)	
Cannot afford treatment¶	1.00 [ref.]	2.06 (0.76-5.61)	1.47 (0.51-4.20)	1.45 (0.68-3.10)	0.83 (0.29-2.32)	0.89 (0.21-3.82)	7.03 (3.14-15.72)	2.40 (0.75-7.61)	

CI, Confidence interval; OR, odds ratio; PUVA, psoralen plus ultraviolet A; UV, ultraviolet.

\*Adjusted for duration of psoriasis diagnosis, heavy drinking, time of last treatment use, treatment duration, and number of past treatments.

†Adjusted for treatment duration and number of past treatments.

‡Includes non-life-threatening and/or life-threatening side effects.

§Adjusted for age, sex, marital status, household income level, and health insurance status.

¶Adjusted for age, health insurance status, heavy drinking, psoriatic arthritis, and time of last treatment.

median treatment durations for psoriasis monotherapies were at most 12 months.<sup>26</sup> These treatment persistence figures are modest for a lifelong disease and highlight an unmet need for effective, well-tolerated, accessible, and acceptable treatments for long-term use.

The substantial proportion of patients citing treatment inefficacy and side effects in discontinuation underscored the importance of achieving good clinical outcomes. More patients treated with etanercept and adalimumab reported discontinuation because of a loss of treatment efficacy than those treated with methotrexate. There is evidence for the loss of efficacy in some patients receiving etanercept, adalimumab, and infliximab.<sup>30-32</sup> Our findings are consistent with a registry study noting loss of efficacy as the predominant reason for discontinuing these 3 tumor necrosis factor inhibitors.<sup>20</sup> Our results are robust to the sensitivity analysis excluding treatments received for less than 6 months, suggesting that the loss of treatment efficacy was independent from short-term dosing changes; however, we did not obtain treatment dosing data to exclude the possibility of premature discontinuation as a result of suboptimal regimens.

More patients treated with adalimumab reported discontinuation because the treatment “did not work well enough” than those treated with methotrexate. This result sharply conflicts with the established superior efficacy of adalimumab over methotrexate.<sup>26,33</sup> Channeling bias, which occurs when different drugs are prescribed according to different baseline prognoses, may explain part of this difference. For instance, because adalimumab was the newest therapy for moderate to severe plaque psoriasis among those studied (approved by the Food and Drug Administration in 2008), it might have been prescribed preferentially to patients failing older treatments, including previous biologics, thus allowing for a greater degree of lack of efficacy. Competing risks (eg, patients are more likely to stop methotrexate from side effects) may also introduce error in comparing drug discontinuation reasons. Given these limitations and the poor correlation between objective disease improvement and patients’ perception of treatment effectiveness, this finding should be cautiously interpreted.<sup>34</sup>

Side effects are important limiting factors for treatment persistence, particularly for conventional systemic therapies with long-term cumulative toxicity. Fewer patients treated with adalimumab and etanercept cited side effects as the reason for discontinuation compared with those treated with methotrexate. These results are consistent with a meta-analysis showing higher rates of treatment withdrawal from adverse events caused by

methotrexate than adalimumab, etanercept, and infliximab.<sup>35</sup> The high percentage of infliximab discontinuation because of serious side effects also reflected the results from a cohort study, whereby infliximab showed a 5.9 times higher incidence of treatment withdrawal because of serious adverse effects than etanercept.<sup>36</sup>

Treatment logistics outweighed efficacy and safety concerns as the main reasons for stopping UVB phototherapy. UVB phototherapy has been shown to be safe, effective, and one of the preferred, first-line treatments for moderate to severe psoriasis.<sup>37</sup> Our data similarly showed that side effects were the least likely to be reported by patients treated with UVB phototherapy. Given the frequent office visits required, inconvenience was understandably one of the most cited barriers for continuing phototherapy. Inability to afford UVB phototherapy was also frequently cited. In commercial health insurance plans, patients face higher out-of-pocket costs for multiple phototherapy sessions than for the more costly biologic agents (\$3040 vs \$920 for the first year of treatment, respectively).<sup>38,39</sup> Indirect costs to the patient from loss of work earnings and travel also contribute to its financial burden. Given the favorable cost-effectiveness of UVB phototherapy, increasing access to phototherapy centers, reducing out-of-pocket costs, expanding home phototherapy, and eliminating other systemic barriers may promote patient use of UVB phototherapy, reduce health care expenditure, and improve long-term outcomes.<sup>39,40</sup>

Our study should be reviewed in the context of its limitations. Its reliance on patient recall could be subject to bias: for instance, median time elapsed since last treatment use was the longest for oral PUVA and shortest for biologics, which might introduce differential recall among treatments. We adjusted for the time of last treatment use and numerous other confounders in multivariate analyses; nevertheless, residual confounding from unmeasured factors, eg, the effects of other financial resources (philanthropic organizations) and constraints (Medicare “doughnut hole”), on treatment discontinuation cannot be excluded as potential sources of error. Medical records at the time of discontinuation were not acquired to corroborate with patient reports of treatment inefficacy or side effects or to analyze the effects of drug dosing. Psychometric properties of the survey instrument should be further determined. Despite the multicentered setting, broad eligibility criteria, and high response rate, external validity of the study could be extended by including more patients from various regions across the United States. Given the paucity of patient-oriented comparative effectiveness research, future prospective studies will be

necessary to confirm our results and to elaborate on the patients' views on psoriasis treatments.

A broad range of clinically relevant, patient-oriented reasons may explain why patients discontinue treatments. Our data highlighted key areas to target to improve long-term treatment use, including: (1) maintenance of long-term effectiveness for biologic agents; (2) improvement in treatment tolerability and safety for systemic treatments; and (3) elimination of logistical and financial barriers for phototherapy. These results may inform the development of public policy and evidence-based strategies to improve treatment satisfaction and to maintain successful long-term psoriasis control.

We would like to thank Dr Michael B. Stierstorfer for contributing data to this study.

#### REFERENCES

- Kimball AB, Gladman D, Gelfand JM, Gordon K, Horn EJ, Korman NJ, et al. National Psoriasis Foundation clinical consensus on psoriasis comorbidities and recommendations for screening. *J Am Acad Dermatol* 2008;58:1031-42.
- Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. *JAMA* 2006;296:1735-41.
- Abuabara K, Azfar RS, Shin DB, Neimann AL, Troxel AB, Gelfand JM. Cause-specific mortality in patients with severe psoriasis: a population-based cohort study in the UK. *Br J Dermatol* 2010;163:586-92.
- Brauchli YB, Jick SS, Miret M, Meier CR. Psoriasis and risk of incident myocardial infarction, stroke or transient ischemic attack: an inception cohort study with a nested case-control analysis. *Br J Dermatol* 2009;160:1048-56.
- Chen YJ, Chang YT, Shen JL, Chen TT, Wang CB, Chen CM, et al. Association between systemic anti-psoriatic drugs and cardiovascular risk in patients with psoriasis and psoriatic arthritis: a nationwide cohort study. *Arthritis Rheum* 2012;64:1879-87.
- Gladman DD, Ang M, Su L, Tom BD, Schentag CT, Farewell VT. Cardiovascular morbidity in psoriatic arthritis. *Ann Rheum Dis* 2009;68:1131-5.
- Prodanovich S, Ma F, Taylor JR, Pezon C, Fasihi T, Kirsner RS. Methotrexate reduces incidence of vascular diseases in veterans with psoriasis or rheumatoid arthritis. *J Am Acad Dermatol* 2005;52:262-7.
- Ahlehoff O, Gislason GH, Charlott M, Jorgensen CH, Lindhardsen J, Olesen JB, et al. Psoriasis is associated with clinically significant cardiovascular risk: a Danish nationwide cohort study. *J Intern Med* 2011;270:147-57.
- Ahlehoff O, Gislason GH, Lindhardsen J, Olesen JB, Charlott M, Skov L, et al. Prognosis following first-time myocardial infarction in patients with psoriasis: a Danish nationwide cohort study. *J Intern Med* 2011;270:237-44.
- Li WQ, Han JL, Manson JE, Rimm EB, Rexrode KM, Curhan GC, et al. Psoriasis and risk of nonfatal cardiovascular disease in US women: a cohort study. *Br J Dermatol* 2012;166:811-8.
- Maradit-Kremers H, Icen M, Ernste FC, Dierkhising RA, McEvoy MT. Disease severity and therapy as predictors of cardiovascular risk in psoriasis: a population-based cohort study. *J Eur Acad Dermatol Venereol* 2012;26:336-43.



12. Nijsten T, Margolis DJ, Feldman SR, Rolstad T, Stern RS. Traditional systemic treatments have not fully met the needs of psoriasis patients: results from a national survey. *J Am Acad Dermatol* 2005;52:434-44.
13. Stern RS, Nijsten T, Feldman SR, Margolis DJ, Rolstad T. Psoriasis is common, carries a substantial burden even when not extensive, and is associated with widespread treatment dissatisfaction. *J Invest Dermatol Symp Proc* 2004;9:136-9.
14. Krueger G, Koo J, Lebwohl M, Menter A, Stern RS, Rolstad T. The impact of psoriasis on quality of life: results of a 1998 National Psoriasis Foundation patient-membership survey. *Arch Dermatol* 2001;137:280-4.
15. Richards HL, Fortune DG, O'Sullivan TM, Main CJ, Griffiths CE. Patients with psoriasis and their compliance with medication. *J Am Acad Dermatol* 1999;41:581-3.
16. Horn EJ, Fox KM, Patel V, Chiou CF, Dann F, Lebwohl M. Are patients with psoriasis undertreated? Results of National Psoriasis Foundation survey. *J Am Acad Dermatol* 2007;57:957-62.
17. Augustin M, Holland B, Dartsch D, Langenbruch A, Radtke MA. Adherence in the treatment of psoriasis: a systematic review. *Dermatology* 2011;222:363-74.
18. Feldman SR, Evans C, Russell MW. Systemic treatment for moderate to severe psoriasis: estimates of failure rates and direct medical costs in a north-eastern US managed care plan. *J Dermatolog Treat* 2005;16:37-42.
19. Brunasso AM, Puntoni M, Salvini C, Delfino C, Curcic P, Gulia A, et al. Tolerability and safety of biological therapies for psoriasis in daily clinical practice: a study of 103 Italian patients. *Acta Derm Venereol* 2011;91:44-9.
20. Gniadecki R, Kragballe K, Dam TN, Skov L. Comparison of drug survival rates for adalimumab, etanercept and infliximab in patients with psoriasis vulgaris. *Br J Dermatol* 2011;164:1091-6.
21. Lebwohl M. A Clinician's paradigm in the treatment of psoriasis. *J Am Acad Dermatol* 2005;53(Suppl):S59-69.
22. Brown KK, Rehmus WE, Kimball AB. Determining the relative importance of patient motivations for nonadherence to topical corticosteroid therapy in psoriasis. *J Am Acad Dermatol* 2006;55:607-13.
23. Elliott RA, Barber N, Horne R. Cost-effectiveness of adherence-enhancing interventions: a quality assessment of the evidence. *Ann Pharmacother* 2005;39:508-15.
24. Fouere S, Adjadj L, Pawin H. How patients experience psoriasis: results from a European survey. *J Eur Acad Dermatol Venereol* 2005;19(Suppl):2-6.
25. Schaarschmidt ML, Schmieder A, Umar N, Terris D, Goebeler M, Goerdts S, et al. Patient preferences for psoriasis treatments: process characteristics can outweigh outcome attributes. *Arch Dermatol* 2011;147:1285-94.
26. Gelfand JM, Wan J, Callis Duffin K, Krueger GG, Kalb RE, Weisman JD, et al. Comparative effectiveness of commonly used systemic treatments or phototherapy for moderate to severe plaque psoriasis in the clinical practice setting. *Arch Dermatol* 2012;148:487-94.
27. Pariser DM, Bagel J, Gelfand JM, Korman NJ, Ritchlin CT, Strober BE, et al. National Psoriasis Foundation clinical consensus on disease severity. *Arch Dermatol* 2007;143:239-42.
28. Mezzich JE, Kraemer HC, Worthington DR, Coffman GA. Assessment of agreement among several raters formulating multiple diagnoses. *J Psychiatr Res* 1981;16:29-39.
29. Rabe-Hesketh S, Skrondal A, Pickles A. GLLAMM manual; working paper 160. Berkeley (CA): UC Berkeley Division of Biostatistics Working Paper Series; 2004.
30. Tyring S, Gordon KB, Poulin Y, Langley RG, Gottlieb AB, Dunn M, et al. Long-term safety and efficacy of 50 mg of etanercept twice weekly in patients with psoriasis. *Arch Dermatol* 2007;143:719-26.
31. Lecluse LL, Driessen RJ, Spuls PI, de Jong EM, Stapel SO, van Doorn MB, et al. Extent and clinical consequences of antibody formation against adalimumab in patients with plaque psoriasis. *Arch Dermatol* 2010;146:127-32.
32. Menter A, Feldman SR, Weinstein GD, Papp K, Evans R, Guzzo C, et al. A randomized comparison of continuous vs intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. *J Am Acad Dermatol* 2007;56:31.e1-15.
33. Saurat JH, Stingl G, Dubertret L, Papp K, Langley RG, Ortonne JP, et al. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs methotrexate vs placebo in patients with psoriasis (CHAMPION). *Br J Dermatol* 2008;158:558-66.
34. Schafer I, Hacker J, Rustenbach SJ, Radtke M, Franzke N, Augustin M. Concordance of the Psoriasis Area and Severity Index (PASI) and patient-reported outcomes in psoriasis treatment. *Eur J Dermatol* 2010;20:62-7.
35. Schmitt J, Zhang Z, Wozel G, Meurer M, Kirch W. Efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate-to-severe psoriasis: meta-analysis of randomized controlled trials. *Br J Dermatol* 2008;159:513-26.
36. Brunasso AM, Puntoni M, Massone C. Drug survival rates of biologic treatments in patients with psoriasis vulgaris. *Br J Dermatol* 2012;166:447-9.
37. Wan J, Abuabara K, Troxel AB, Shin DB, Van Voorhees AS, Bebo BF Jr, et al. Dermatologist preferences for first-line therapy of moderate to severe psoriasis in healthy adult patients. *J Am Acad Dermatol* 2012;66:376-86.
38. Staidle JP, Dabade TS, Feldman SR. A pharmacoeconomic analysis of severe psoriasis therapy: a review of treatment choices and cost efficiency. *Expert Opin Pharmacother* 2011;12:2041-54.
39. Yentzer BA, Yelverton CB, Simpson GL, Simpson JF, Hwang W, Balkrishnan R, et al. Paradoxical effects of cost reduction measures in managed care systems for treatment of severe psoriasis. *Dermatol Online J* 2009;15:1.
40. Evers AW, Kleinpenning MM, Smits T, Boezeman J, van de Kerkhof PC, Kraaimaat FW, et al. Treatment nonadherence and long-term effects of narrowband UV-B therapy in patients with psoriasis. *Arch Dermatol* 2010;146:198-9.