Comparative effectiveness of less commonly used systemic monotherapies and common combination therapies for moderate to severe psoriasis in the clinical setting

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Background: The effectiveness of psoriasis therapies in real-world settings remains relatively unknown.

Objective: We sought to compare the effectiveness of less commonly used systemic therapies and commonly used combination therapies for psoriasis.

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Methods: This was a multicenter cross-sectional study of 203 patients with plaque psoriasis receiving less common systemic monotherapy (acitretin, cyclosporine, or infliximab) or common combination therapies (adalimumab, etanercept, or infliximab and methotrexate) compared with 168 patients receiving methotrexate evaluated at 1 of 10 US outpatient dermatology sites participating in the Dermatology Clinical Effectiveness Research Network.

Results: In adjusted analyses, patients on acitretin (relative response rate 2.01; 95% confidence interval [CI] 1.18-3.41), infliximab (relative response rate 1.93; 95% CI 1.26-2.98), adalimumab and methotrexate (relative response rate 3.04; 95% CI 2.12-4.36), etanercept and methotrexate (relative response rate 2.22; 95% CI 1.25-3.94), and infliximab and methotrexate (relative response rate 1.72; 95% CI 1.10-2.70) were more likely to have clear or almost clear skin compared with patients on methotrexate. There were no differences among treatments when response rate was defined by health-related quality of life.

Limitations: Single time point assessment may result in overestimation of effectiveness.

Conclusions: The efficacy of therapies in clinical trials may overestimate their effectiveness as used in clinical practice. Although physician-reported relative response rates were different among therapies, absolute differences were small and did not correspond to differences in patient-reported outcomes. (J Am Acad Dermatol 2014;71:1167-75.)

Key words: biologics; combination therapy; comparative effectiveness; Dermatology Life Quality Index; Physician Global Assessment; psoriasis; quality of life; systemic treatments.

CAPSULE SUMMARY

- Little is known about the effectiveness of therapies for psoriasis in the real-world setting.
- Clinical trials may overestimate the effectiveness of therapies in the clinical setting. Objective response rates vary by treatment but patient-reported outcomes are similar in clinical practice.
- Longitudinal comparative effectiveness studies of psoriasis therapies are needed.

Psoriasis is a common chronic inflammatory disease that affects approximately 125 million people worldwide.[1] Nearly 25% with psoriasis have moderate to severe disease,[1] which is an indication for treatment with systemic therapy or phototherapy. Despite the major advances in psoriasis treatments that have accompanied the development of several targeted biologic medications over the past decade, there are few head-to-head comparisons of the currently available psoriasis therapies. As a result, no clear first-line therapy for moderate to severe psoriasis exists.[2] In addition, although clinical trials generally report high efficacy, especially for biologic therapies, clinical experience and long-term follow-up of patients receiving biologics suggest loss of efficacy over time.[3,4] Furthermore, we have observed that the efficacy of treatments as reported in clinical trials may overestimate their effectiveness as used in the clinical setting.[5] Additional comparative effectiveness studies of moderate to severe psoriasis therapies are, therefore, greatly needed to help guide physicians' and patients' treatment choices in the real-world setting. The purpose of this multicenter cross-sectional study was to expand our previous comparative effectiveness study findings by determining the effectiveness of less commonly used systemic monotherapies and commonly used combination therapies for treatment of moderate to severe psoriasis.

METHODS

Study design and participant protection

We conducted a multicenter cross-sectional study to determine the effectiveness of less commonly used systemic monotherapy and commonly used combination therapies for moderate to severe psoriasis. The study was approved by the University of Pennsylvania and University of Utah institutional review boards, and informed consent was obtained from all patients. The study was conducted in accordance with the Declaration of Helsinki and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[6]

Setting

Data were collected by 12 clinicians (10 dermatologists and 2 physician assistants) who are members of the Dermatology Clinical Effectiveness Research Network (DCERN), which includes 2 academic medical centers (University of Pennsylvania and University of Utah, each with a hospital-based

Abbreviations used:

BSA: body surface area
DLQI: Dermatology Life Quality Index
FDA: Food and Drug Administration
IQR: interquartile range
PASI: Psoriasis Area and Severity Index
PGA: Physician Global Assessment
RCT: randomized controlled trial

site and a separate community-based site) and 6 private practices in Georgia, Pennsylvania, New York, and Colorado (see www.dermcern.org for details). Patient data were collected prospectively at a single, regularly scheduled clinic appointment from February 2010 through June 2011.

Participants

As previously described in detail, broad inclusion criteria were used to enroll consecutive patients seen by their dermatology provider in DCERN practices for a routine follow-up appointment to minimize selection bias.[5] Eligible participants included patients who met at least one of the following criteria: were currently receiving or had previously received systemic therapy or phototherapy prescribed by a dermatology provider for treatment of psoriasis; or were candidates for systemic therapy with a documented history of at least 5% body surface area (BSA) involvement. In the analyses presented, we included patients who were currently receiving a single less commonly used oral systemic or biologic therapy (acitretin, cyclosporine, or infliximab) or a commonly used combination of therapies (methotrexate and adalimumab, etanercept, or infliximab) for a primary indication of plaque psoriasis.

Variables

As previously described, detailed patient and provider level data were collected by trained study coordinators using standardized case report forms and via patient self-report with confirmation by the patient's dermatology clinic record and assessments by the clinician investigators.[5] The main exposures were current less common monotherapy or common combination therapy, and the other variables served as potential confounders or effect modifiers. The primary outcome was a widely used 6-point Physician Global Assessment (PGA) scale of psoriasis lesions (0, clear; 1, minimal; 2, mild; 3, moderate; 4, marked; and 5, severe; scored separately for erythema, induration, and scaling and then averaged), dichotomized as clear or almost clear disease (0-1) versus mild to severe disease (2-5).[7,8] Secondary outcomes were also evaluated including the Psoriasis Area and Severity Index (PASI) score and affected BSA as objective outcomes, and the Dermatology Life Quality Index (DLQI) score and patient report of prescription topical medication use within the past week as patient-reported outcomes. The PASI was dichotomized such that a score of 2 or less was considered to indicate no or minimal disease (based on a receiver operating characteristic analysis comparing PASI scores with PGA scores). Presence of psoriasis involving less than 3% BSA was considered to be mild disease based on National Psoriasis Foundation definitions, which have been extensively used in research.[9] Previously published banding of DLQI scores was used to determine cutoff points upon which to dichotomize DLQI score as an outcome.[10]

Study size

Target enrollment was established for the primary comparative effectiveness study,[5] within which the current study was nested. This study was descriptive in nature, thus the sample size was not determined a priori. The maximum number of eligible subjects was included, and all effect measures are reported with 95% confidence intervals (CIs).

Statistical analysis

First, the patient population was characterized using descriptive statistics. Univariate analyses were conducted using the one-way analysis of variance or Kruskal-Wallis tests for grouped continuous data, and χ^2 or Fisher exact test for dichotomous or categorical data. Multivariable analyses were performed using modified Poisson regression with robust error variance to determine which factors independently predicted optimal patient outcomes as defined in the "Variables" section.[11] Methotrexate was chosen as the reference treatment because it is often considered the standard against which novel therapies are compared. To build our multivariable model, we used a purposeful selection approach in which all covariates thought to be clinically relevant a priori and any covariates with a significance at $P < .10$ in univariate analyses were included in the initial model.[12] Nonsignificant covariates were eliminated from the model if their removal did not change the risk ratio estimates of other covariates by more than 10%. Variables were considered for removal first if they were included in the model base on P value and subsequently based on their perceived clinical importance. Model fit was assessed using goodness-of-fit tests based on deviance and Pearson statistics. The modified Poisson modeling approach was used

to yield the clinically relevant statistic of relative response rate (ie, relative risk), which was then used to calculate the relative response difference and the number needed to treat. As a sensitivity analysis, we performed logistic regression and converted odds ratios to relative risks using published formulas.[13] We also performed additional sensitivity analyses including varying the outcome definition by using PASI, BSA, and DLQI and restricting the analysis to patients on at least 3 months of therapy. Missing data did not exceed 2.7% for any of the variables analyzed, and patients with missing data were excluded from analyses.

RESULTS

The baseline characteristics of 371 patients receiving methotrexate (reference therapy), less common systemic monotherapies, or common combination therapies for the primary indication of plaque psoriasis are summarized in Table I. In addition to having plaque psoriasis, 75 (20.2%) patients also had other types of psoriasis as follows: 38 (10.2%) with scalp, 20 (5.4%) with guttate, 22 (5.9%) with nail, 16 (4.3%) with inverse or genital, 11 (3.0%) with palmar plantar, and 2 (0.5%) with pustular psoriasis. Mean age, practice setting of the patient's dermatologist, median body mass index, median psoriasis duration, psoriasis extent at its worst, and prevalence of physician-diagnosed psoriatic arthritis were each found to be significantly different among the therapies examined. Treatment characteristics are summarized in Table II. Patients receiving infliximab monotherapy (24 months; interquartile range [IQR] 7-60) and infliximab and methotrexate combination therapy (18 months; IQR 6-44) exhibited the longest median uninterrupted treatment duration compared with the other examined therapies ($P = .003$). Notably, a high proportion of patients on infliximab alone (70.7%) or in combination with methotrexate (79.4%) were receiving doses greater than 5 mg/kg every 8 weeks. A comparison of the median methotrexate doses for patients on methotrexate alone (15 mg/wk; IQR 15-20) and in combination with adalimumab (10 mg/wk; IQR 7.5-15), etanercept (11.3 mg/wk; IQR 7.5-17.5), or infliximab (15 mg/wk; IQR 10-22.5) demonstrated methotrexate doses to be lower among patients receiving adalimumab or etanercept and methotrexate combination therapies ($P < .001$). The median number of prior therapies used was also significantly different among the treatment groups ($P < .001$) with patients on infliximab and methotrexate combination therapy (3; IQR 1-4) and infliximab monotherapy (2.5; IQR 1-5) reporting the greatest number of previous treatments.

Across all examined treatment groups, there were significant differences in median PGA ($P = .001$), PASI ($P < .001$), and BSA ($P < .001$) scores, although absolute differences were small (Table III). There was no significant difference in median DLQI score ($P = .08$). Frequency of prescription topical medication use during the preceding week was significantly different among treatment groups with patients on acitretin reporting the most frequent use ($P < .001$) (Table II). Crude response rate defined by PGA score of 1 or less, which corresponds to being clear or almost clear of psoriasis, was highest for adalimumab and methotrexate combination therapy (59.2%; 95% CI 44.2%-73.0%) and lowest for methotrexate monotherapy (22.3%; 95% CI 16.2%-29.3%) (Table III). In contrast, when the outcome was defined by DLQI score 5 or less, which corresponds to no or small effect on the patient's quality of life, crude response rates were generally higher but not significantly different among therapies ($P = .43$).

Patients who were clear or almost clear of psoriasis (PGA score ≤ 1) were more likely to be underweight or normal weight and treated in a private practice setting, and they were less likely to have used prescription topical medications in the preceding week (data not shown). Compared with methotrexate, adjusted relative rates of PGA response were significantly higher for all treatment groups except cyclosporine, which was associated with a higher but not statistically significant relative response rate (Table IV). For the therapies with statistically significant response rate differences, the number needed to treat ranged from 2.2 for adalimumab and methotrexate combination therapy to 6.2 for infliximab and methotrexate combination therapy. The significance of the number needed to treat is that, for example, 3 patients (rounded up from 2.2 per convention) would need to be treated with adalimumab and methotrexate combination therapy for 1 additional patient to reach treatment response over what would be expected from methotrexate monotherapy of the same 3 patients.

In sensitivity analyses (data not shown), we found no differences in response rates when DLQI score was defined as the outcome. When the outcome was defined by BSA or PASI, the differences in response rates were attenuated for all therapies, and statistical significance was lost in the cases of infliximab and acitretin monotherapy, respectively. To ensure capture of maximal effect on current therapy, we restricted our analyses to those patients on at least 3 months of therapy and

Table I. Baseline demographics and psoriasis characteristics among patients with plaque psoriasis

Characteristic	Methotrexate (N = 168)	Acitretin (N = 37)	Cyclosporine (N = 19)	Infliximab (N = 42)	Adalimumab + methotrexate (N = 49)	Etanercept + methotrexate (N = 22)	Infliximab + methotrexate (N = 34)	*P* value*
Age, y								
Mean (SD)	53.5 (15.9)	53.7 (14.7)	42.8 (18.5)	48.5 (14.5)	49.4 (14.0)	55.9 (15.3)	51.2 (11.4)	.03†
Median (IQR)	53 (42-66)	54 (49-63)	48 (26-58)	47 (38-56)	49 (39-61)	57 (49-68)	52 (44-59)	.06‡
Female sex, N (%)	101 (60.1)	16 (43.2)	9 (47.4)	15 (35.7)	27 (54.2)	12 (54.6)	21 (61.8)	.08
White race, N (%)	148 (88.1)	32 (86.5)	19 (100)	39 (92.9)	45 (91.8)	21 (95.5)	32 (94.1)	.62
Practice setting of dermatologist, N (%)								<.01
Academic	101 (60.1)	15 (40.5)	12 (63.2)	7 (16.7)	29 (59.2)	15 (68.2)	19 (55.9)	
Private	67 (39.9)	22 (59.5)	7 (36.8)	35 (83.3)	20 (40.8)	7 (31.8)	15 (44.1)	
BMI, median (IQR)§	29.4 (25.7-33.1)	30.4 (24.7-37.5)	25.8 (22.3-29.5)	31.9 (26.2-35.7)	31.6 (26.8-35.2)	27.8 (25.9-36.9)	31.4 (30.0-36.9)	.03‡
Total no. of comorbidities, median (IQR)	3 (1-4)	2 (1-5)	1 (1-2)	3 (1-4)	3 (1-5)	3 (2-5)	4 (3-5)	.11‡
Age of psoriasis onset, median (IQR), y‖	30 (17-45)	33 (22-46)	31 (11-48)	26 (15-38)	23 (18-34)	31 (22-50)	21 (16-31)	.05‡
Psoriasis duration, median (IQR), y‖	19 (8-33)	18 (10-29)	8 (2-13)	21 (12-30)	22 (16-30)	19 (8-33)	27 (19-38)	<.01‡
Psoriasis extent at its worst, N (%)								<.01
Mild	21 (12.5)	9 (24.3)	0 (0)	2 (4.8)	5 (10.2)	1 (4.5)	0 (0)	
Moderate	70 (41.7)	11 (29.7)	6 (31.6)	8 (19.0)	12 (24.5)	6 (27.3)	5 (14.7)	
Severe	77 (45.8)	17 (46.0)	13 (68.4)	32 (76.2)	32 (65.3)	15 (68.2)	29 (85.3)	
Psoriatic arthritis diagnosed by a physician, N (%)	35 (20.8)	5 (13.5)	2 (10.5)	17 (40.5)	23 (46.9)	6 (27.3)	26 (76.5)	<.01

BMI, Body mass index; *IQR*, interquartile range.
*Fisher exact test or χ^2 test.
†One-way analysis of variance test.
‡Kruskal-Wallis test.
§BMI was missing for 2 (0.5%) patients.
‖Age of psoriasis onset and psoriasis duration were missing for 3 (0.8%) patients.

Table II. Treatment characteristics: dosage, duration, and concomitant use of prescription topical medications

Current psoriasis treatment	No. (%)	Dosage (%)*	Methotrexate dose, median (IQR), mg/wk ($P < .001$)†	Duration without interruption,‡ median (IQR), mo ($P = .003$)†	Prescription topical medication use in past week, median (IQR), d ($P < .001$)†	No. of prior therapies, median (IQR) ($P < .001$)†
Methotrexate	168 (45.3)	<7.5 mg/wk (1.8) 7.5-15 mg/wk (62.9) 17.5-27.5 mg/wk (29.3) ≥30 mg/wk (6.0)	15 (15-20)	10 (4-24)	2 (0-7)	1 (0-2)
Acitretin	37 (10.0)	10 mg up to once/d (8.1) 25 mg up to once/d (83.8) 30-50 mg once/d (8.1)	NA	15 (4-33)	5 (3-7)	1 (1-2)
Cyclosporine	19 (5.1)	<2.5 mg/kg/d (47.4) 2.5-5 mg/kg/d (36.8) >5 mg/kg/d (15.8)	NA	4 (1-12)	0 (0-7)	1 (0-2)
Infliximab	42 (11.3)	5 mg/kg every 8 wks (29.3) >5 mg/kg every 8 wks (70.7)	NA	24 (7-60)	0 (0-4)	2.5 (1-5)
Adalimumab + methotrexate	49 (13.2)	40 mg every wk (18.4) 40 mg every 2 wks (79.6) 40 mg every >2 wks (2.0)	10 (7.5-15)	8 (4-16)	1 (0-6)	2 (1-4)
Etanercept + methotrexate	22 (5.9)	25 mg every wk (4.6) 50 mg every wk (72.7) 75 mg every wk (4.6) 100 mg every wk (18.2)	11.3 (7.5-17.5)	11.5 (3-24)	4 (2-7)	2 (1-3)
Infliximab + methotrexate	34 (9.2)	5 mg/kg every 8 wks (20.6) >5 mg/kg every 8 wks (79.4)	15 (10-22.5)	18 (6-44)	0 (0-4)	3 (1-4)

IQR, Interquartile range; *NA*, not applicable.
*Dose information was missing for 1 (0.6%) patient receiving methotrexate and 1 (2.4%) patient receiving infliximab. For combination therapies, dose information provided is for the biologic therapy.
†Kruskal-Wallis test.
‡Treatment duration was missing for 1 (2.7%) patient receiving acitretin.

found crude response rates to be similar to those of the primary analysis.

DISCUSSION

In this comparative effectiveness study of less commonly used systemic monotherapies and common combination therapies for moderate to severe psoriasis in the real-world clinical setting, we report similar findings to those of our previous study of the effectiveness of common systemic monotherapies and phototherapy.[5] Using a single PGA assessment, the proportions of patients achieving clear or almost clear response to treatment were 50% or less for all examined therapies except for adalimumab and methotrexate combination therapy (59.2%). Importantly, the effectiveness of therapies was lower than their efficacy as reported in randomized controlled trials (RCTs). For example, the proportion of patients with clear or almost clear skin on infliximab in our study compared with the European Infliximab for Psoriasis (Remicade) Efficacy and Safety Study I[14] (an RCT of infliximab vs placebo) was 46.3% versus 74% (Table III). Similarly, the PGA response rate for patients on etanercept and methotrexate combination therapy in our study compared with an RCT of etanercept and methotrexate versus etanercept only[15] was 50.0% versus 71.8%.

More than 70% of patients on either infliximab monotherapy or infliximab and methotrexate combination therapy were receiving higher doses than what is approved by the Food and Drug Administration (FDA) (ie, >5 mg/kg every 8 weeks). The proportions of patients receiving escalated doses of infliximab were higher than what we observed with adalimumab or etanercept alone (11.8% and 36.1%, respectively)[5] or in combination with methotrexate (18.4% and 22.8%, respectively). In addition, median duration of uninterrupted therapy was longest for infliximab monotherapy compared with all other available monotherapies[5] and common combination therapies, suggesting greater treatment persistence with infliximab. This finding is consistent with a Danish study that similarly reported infliximab to have the highest drug survival rate compared with adalimumab and etanercept.[3] In contrast, RCT data suggest infliximab to have lower patient retention rates compared with

Table III. Physician- and patient-reported outcomes and crude response rates of Physician Global Assessment clearance* and minimal Dermatology Life Quality Index effect† by current monotherapy and combination therapy

Current treatment	PGA median (IQR) (P = .001)‡	PASI median (IQR) (P < .001)‡	BSA, % median (IQR) (P < .001)‡	DLQI median (IQR) (P = .08)‡	Crude response rate PGA ≤ 1, % (95% CI) (P < .001)§	Crude response rate DLQI ≤ 5, % (95% CI) (P = .43)§
Methotrexate sodium (N = 168)	1.7 (1.3-2)	4 (1.8-6.6)	3 (1-6)	3 (1-5)	22.3 (16.2-29.3)	76.8 (69.7-82.9)
Acitretin (N = 37)	1.3 (1-1.7)	3 (1.8-5)	2 (1.2-6)	2 (1-6)	35.1 (20.2-52.5)	73.0 (55.9-86.2)
Cyclosporine (N = 19)	1.3 (0.7-2)	4.8 (1.2-8.8)	7 (1-11)	5 (2-15)	36.8 (16.3-61.6)	52.9 (27.8-77.0)
Infliximab (N = 42)	1.3 (1-2)	2.1 (0.9-4.2)	2.0 (0.5-3.2)	1 (0-4)	46.3 (30.7-62.6)	81.0 (65.9-91.4)
Adalimumab + methotrexate (N = 49)	1 (0.3-2)	1.4 (0.2-3.1)	1 (0.2-2.3)	1 (0-5)	59.2 (44.2-73.0)	77.6 (63.4-88.2)
Etanercept + methotrexate (N = 22)	1.2 (1-2)	1.7 (0.8-4.2)	1.1 (0.8-3)	4 (1-7)	50.0 (28.2-71.8)	72.7 (49.8-89.3)
Infliximab + methotrexate (N = 34)	1.3 (0-2)	1.6 (0-5.4)	1.8 (0-3)	1 (0-6)	44.1 (27.2-62.1)	72.7 (54.5-86.7)

BSA, Body surface area; *CI*, confidence interval; *DLQI*, Dermatology Life Quality Index score; *IQR*, interquartile range; *PASI*, Psoriasis Area and Severity Index score; *PGA*, Physician Global Assessment score.
*PGA clearance defined as clear or almost clear disease (PGA score ≤ 1).
†Minimal Dermatology Life Quality Index effect defined as no or small effect on patient's life (DLQI score ≤ 5).
‡Kruskal-Wallis test.
§χ^2 test.

Table IV. Relative response rate of Physician Global Assessment clearance* and response rate differences by current monotherapy and combination therapy

Current treatment	Unadjusted RR (95% CI)	Adjusted RR (95% CI)†	Risk difference (95% CI)‡	NNT§
Methotrexate sodium (n = 168)	1 [Reference]	1 [Reference]		
Acitretin (n = 37)	1.58 (0.93-2.66)	2.01 (1.18-3.41)	0.22 (0.04-0.54)	4.4
Cyclosporine (n = 19)	1.65 (0.86-3.18)	1.44 (0.75-2.74)	0.10 (−0.05-0.39)	NA
Infliximab (n = 42)	2.08 (1.35-3.21)	1.93 (1.26-2.98)	0.21 (0.06-0.44)	4.8
Adalimumab + methotrexate (n = 49)	2.66 (1.84-3.83)	3.04 (2.12-4.36)	0.45 (0.25-0.75)	2.2
Etanercept + methotrexate (n = 22)	2.24 (1.35-3.72)	2.22 (1.25-3.94)	0.27 (0.05-0.66)	3.7
Infliximab + methotrexate (n = 34)	1.98 (1.23-3.18)	1.72 (1.10-2.70)	0.16 (0.02-0.38)	6.2

CI, Confidence interval; *NA*, not applicable; *NNT*, number needed to treat; *RR*, relative risk.
*Physician Global Assessment clearance defined as clear or almost clear disease (Physician Global Assessment ≤ 1).
†Adjusted for age, sex, marital status, practice setting of dermatologist, body mass index, psoriasis response to natural light, prescription topical medication frequency.
‡Difference between adjusted and baseline risk.
§No. of patients needed to treat with the particular treatment to gain 1 additional patient with Physician Global Assessment clearance relative to the response achieved with methotrexate.

other biologic therapies.[16] The greater treatment persistence that we and Gniadecki et al[3] observed may be explained by infliximab being the only FDA-approved tumor necrosis factor-α inhibitor to have weight-based dosing, and by use of off-label dosing schedules in the clinical setting, as noted in our study. In contrast, median duration of uninterrupted therapy was shortest for cyclosporine, which is expected considering the known renal and other potential toxicities associated with long-term use.

In multivariable analyses, we found all examined therapies except for cyclosporine to be significantly more effective than methotrexate based on PGA response, even after adjustment for multiple potential confounding variables. The relatively low and statistically nonsignificant relative response rate associated with cyclosporine is consistent with RCTs that have shown mixed results of both equal and greater efficacy compared with methotrexate.[17,18] Furthermore, almost half of the patients on cyclosporine were receiving low doses (<2.5 mg/kg/d), which may, in part, account for its low effectiveness observed in our study. Although the relative response rates of most of the therapies examined were significantly higher than that of methotrexate,

the absolute differences in PGA response among therapies were small. In addition, our sensitivity analyses revealed relative response rates to be dependent on the outcome definition. When DLQI score was used as a patient-reported outcome, we generally observed greater crude response to therapy compared with physician-reported outcomes. However, in adjusted analyses, the relative response rates were essentially equal across all evaluated therapies. Furthermore, differences in PGA response rates were not reflected in patient-reported use of prescription topical medication use. Thus, these patient-reported data suggest that observed differences in physician-reported response rates among therapies may not be clinically significant.

Our findings should be interpreted in light of the study's strengths and limitations. Strengths include its broad inclusion criteria, high (95%) participation rate, patient population drawn from multiple clinical practices across the United States, and use of multivariable statistical models to account for potential confounding factors. Limitations include the cross-sectional design with assessment at a single time point, which renders the study susceptible to the phenomenon of clinical drift and resulting possible overestimation of the effectiveness of therapies because only those patients with good response to treatment continue on therapy. In addition, the cross-sectional nature of our study prevents adequate assessments of time to treatment response, response duration, therapy compliance, and other factors that are important in determining treatment effectiveness. Treatment was also assigned in a nonrandom manner that may result in residual confounding and channeling bias, which are methodologically challenging to adjust for in the setting of our small study of less commonly used therapies for moderate to severe psoriasis. Finally, although the use of DLQI in clinical trials of biologic therapy for psoriasis suggests that it is highly correlated with physician-reported outcomes such as PASI score,[19] it is possible that DLQI is not sensitive enough to detect differences in response to therapies used in the clinical setting.

In summary, our comparative effectiveness study of less commonly used systemic therapies and common combination therapies for treatment of moderate to severe psoriasis provides additional evidence to suggest that the performance of therapies for psoriasis in the real-world clinical setting is lower than what is reported by RCTs for reasons that remain incompletely understood. We also confirmed our previous findings that absolute differences in objective response among therapies are small and may not translate to clinically significant differences. Importantly, we found infliximab to be associated with the longest duration of uninterrupted therapy among all therapies and that treatment persistence may be improved by biologic dose escalation. Together, our results further highlight the need for future longitudinal comparative effectiveness studies to better understand the performance of psoriasis therapies in the real-world clinical setting.

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