

Real-World Clinical Experience With Apremilast in a Large US Retrospective Cohort Study of Patients With Moderate to Severe Plaque Psoriasis

April Armstrong MD MPH,[a] and Eugenia Levi PharmD[b]
[a]University of Southern California, Keck School of Medicine, Los Angeles, CA
[b]Celgene Corporation, Summit, NJ

ABSTRACT

Objective: To examine real-world use and patient outcomes with apremilast, an oral PDE4 inhibitor, in the dermatology practice setting for treatment of patients with moderate to severe plaque psoriasis.

Methods: This retrospective, multicenter, longitudinal, observational cohort study used Modernizing Medicine's electronic medical record (EMR) database of >5000 US dermatology providers. There were 7517 adults aged ≥18 years with a psoriasis diagnosis (ICD-9, ICD-10) who received apremilast therapy from October 1, 2015, to January 31, 2016, and were included in efficacy and safety analyses. Among patients who switched from non-apremilast to apremilast monotherapy, the majority (74.2%) switched from prior topical treatment.

Results: At apremilast initiation, in systemic-naive and systemic-experienced patients, mean (SD) Physician Global Assessment (PGA) was 2.79 (0.13) and 2.48 (0.15); mean (SD) psoriasis-affected body surface area (BSA) was 17.85% (2.27) and 12.93% (2.59); and mean itch numeric rating scale (NRS; 0=no itch, 10=worst itch possible) score was 4.14 and 3.82, respectively. Within 6 months of apremilast initiation, PGA decreased (mean [SD]) in systemic-naive patients (−1.71 [0.19], $P<0.001$) and systemic-experienced patients (−1.02 [0.18], $P<0.001$); 26.8% (systemic-naive) and 25.5% (systemic-experienced) of patients achieved a PGA score of 0 or 1. Likewise, statistically significant reductions in BSA were noted in systemic-naive patients (~62% reduction from baseline; $P<0.01$) and systemic-experienced patients (~60% reduction from baseline; $P=0.002$). Mean itch NRS decreased to 2.38 in systemic-naive patients ($P=0.139$) and 0.0 in systemic-experienced patients ($P=0.034$). Of 160 patients with ≥1 assessment of patient-perceived overall treatment effectiveness, 138 (86.2%) strongly/somewhat agreed apremilast was effective in clearing their skin of psoriasis. For safety analyses, body weight was available in the EMR database and decreased in systemic-naive patients (−1.75 kg) and systemic-experienced patients (−1.09 kg).

Conclusions: Findings support the effectiveness of apremilast in patients with moderate to severe psoriasis in dermatology clinical practices. Patients perceived apremilast to be effective.

J Drugs Dermatol. 2017;16(12):1240-1245.

INTRODUCTION

Psoriasis is a chronic, systemic inflammatory disease affecting 1% to 4% of the world's population.[1-3] Although treatment options for moderate to severe psoriasis have expanded in recent years, many patients with all levels of psoriasis severity continue to experience undertreatment or receive no treatment.[4-7] Systemic treatments are recommended for the management of moderate to severe psoriasis[8]; however, evidence suggests that treatment patterns for patients with psoriasis across all levels of disease severity (ie, mild and moderate to severe) are dominated by topical therapy alone.[5,6,8] Some key drivers of undertreatment include patient and physician concerns about long-term safety, poor tolerability, lack or loss of efficacy, and treatment costs associated with both conventional oral systemic agents (ie, methotrexate) and biologics.[6,7] Furthermore, approximately one-half of patients have reported that they are dissatisfied with their current therapy.[5]

Apremilast, an oral, small-molecule phosphodiesterase 4 inhibitor indicated for the treatment of psoriatic arthritis and psoriasis in patients who are candidates for phototherapy or systemic therapy, has been studied in phase 2 and phase 3 clinical trials in >2000 adult patients with moderate to severe plaque psoriasis.[9-11] It is the first new oral systemic, nonbiologic medication approved by the US Food and Drug Administration for treatment of psoriasis in the past 20 years. Clinical trial data provide invaluable insight into the efficacy of apremilast versus placebo; however, these data do not fully provide insight into the effectiveness of apremilast at the patient level from populations that are reflective of the demographically and clinically diverse patients treated at dermatology practices. Real-world outcomes research in psoriasis is scarce in the United States because of the complexity required to collect valid, clinically relevant, granular data from a large number of dermatologists'

offices at the point of care. To address this knowledge gap, this study examined prescribing patterns, clinical effectiveness, and patient-perceived overall treatment effectiveness (POTE) of apremilast in the US dermatology practice setting using Modernizing Medicine's electronic medical record (EMR) database of >5000 US dermatology providers and >550,000 psoriasis patients.

METHODS

Study Design

This was a retrospective, multicenter, longitudinal, observational cohort study that examined outcomes from adults with psoriasis in real-world dermatology practices in 49 states and 2 territories across the United States. The study period was from October 1, 2014, through January 31, 2016. Structured data were collected from Modernizing Medicine's EMR database Electronic Medical Assistant® (EMA™), which is a dermatology-specific, Health Insurance Portability and Accountability Act–compliant EMR platform, from >5000 dermatology practices. During clinic visits, data were entered directly into the EMR system by dermatology providers and their staff at the point of care.

Patient Inclusion Criteria

Patients eligible for study inclusion were adults ≥18 years of age with a dermatologist-given, psoriasis-specific diagnosis (ICD-9, ICD-10) who at study initiation or at any time during the study period received apremilast either alone or in combination with other psoriasis treatments. Psoriasis was defined as any of the following psoriasis-specific diagnoses, which were selected by a dermatologist in the EMR database during routine clinical encounters: "psoriasis," "psoriasis vulgaris," "generalized plaque psoriasis," "localized plaque psoriasis," "localized scalp psoriasis," "palmoplantar psoriasis," "nail psoriasis," "guttate psoriasis," "inverse psoriasis," and "ostraceous psoriasis."

Assessments and Analysis

Patient demographic and disease characteristics were recorded at the most recent clinic visit. Frequencies of psoriasis-related comorbidities were determined. Efficacy and weight outcomes were evaluated for patients who received apremilast monotherapy and who had ≥2 efficacy assessments of the same outcome during the study period, the first at the time of initial apremilast prescription and ≥1 thereafter within 6 months. For analyses of apremilast monotherapy, patients were stratified according to whether they had received any conventional or biologic systemic treatment prior to initiation of apremilast (naive/experienced).

Outcomes at Month 6 that were compared with apremilast baseline included Physician Global Assessment of Disease Severity (PGA; 0=clear, 1=minimal, 2=mild, 3=moderate, 4=marked, and 5=severe); achievement of low disease severity (PGA score of 0 or 1) in patients with ≥1 PGA score ≥2; percentage of psoriasis-involved body surface area (BSA; 0% to 100%); itch numeric rating scale (NRS; 0 to 10; 0=no itch, 10=worst itch possible); and changes in body weight.

Longitudinal changes in PGA, BSA, itch NRS, and body weight were examined using a linear mixed-effect model, adjusted for demographic characteristics and psoriasis-related comorbidities. POTE was examined among patients receiving apremilast monotherapy for ≥90 days using a 5-point Likert scale (1=strongly agree, 5=strongly disagree) in response to the following statement: "I believe this treatment is effective in clearing my skin of psoriasis." The POTE assessment from the most recent clinic visit was included in the analysis. Frequency of each response category was determined.

RESULTS

Patients

A total of 7517 patients received apremilast during the study period and were included in the analysis of apremilast prescribing patterns. Demographic characteristics are summarized in the Table. More than one-half of the patients (52.4%) had a psoriasis-related comorbidity. The most common comorbidity was cardiovascular disease (33.1% of patients).

Treatment Patterns With Apremilast

Among the patients who changed from non-apremilast treatments to apremilast monotherapy during the study period,

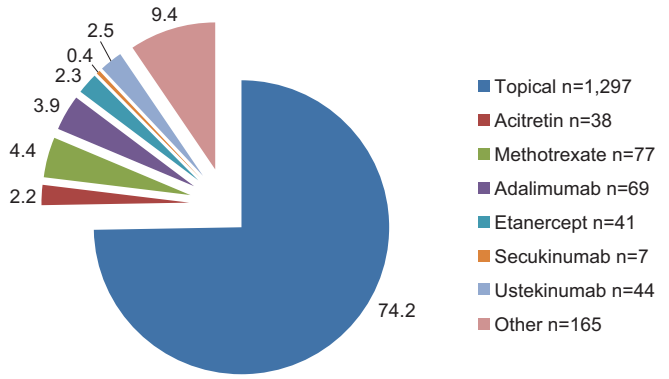
TABLE 1.

Characteristics of Patients Prescribed Apremilast

Characteristic	Patients N=7517
Age, mean (SD), years	52.3 (14.8)
Male, n (%)	3611 (48.0)
Race/ethnicity, n (%)	
White	4795 (63.8)
African American	191 (2.5)
Asian	155 (2.1)
Hispanic	439 (5.8)
Other	422 (5.6)
Unknown	1515 (20.2)
Comorbidity, n (%)	
Arthritis	1781 (23.7)
Cardiovascular disease	2487 (33.1)
Depression	762 (10.1)
Diabetes	991 (13.2)
Hepatitis	152 (2.0)
Lymphoma	23 (0.3)

Note: Some patients were recorded as having multiple comorbidities and, therefore, are counted more than once.

FIGURE 1. Prior treatments in patients who switched to apremilast monotherapy.
Data are based on the subset of patients who switched from non-apremilast treatment to apremilast monotherapy during the study period. The numbers in the pie chart do not add up to 100% because treatment groups with <5 patients were concealed to comply with Health Insurance Portability and Accountability Act privacy regulations.



almost three-quarters (74.2%) changed from topical treatment alone to apremilast monotherapy (Figure 1). Most patients who started on phototherapy, methotrexate, adalimumab, or ustekinumab received apremilast as add-on therapy to their ongoing treatment (range, 78.1% to 88.1%).

Effect of Apremilast Monotherapy on PGA

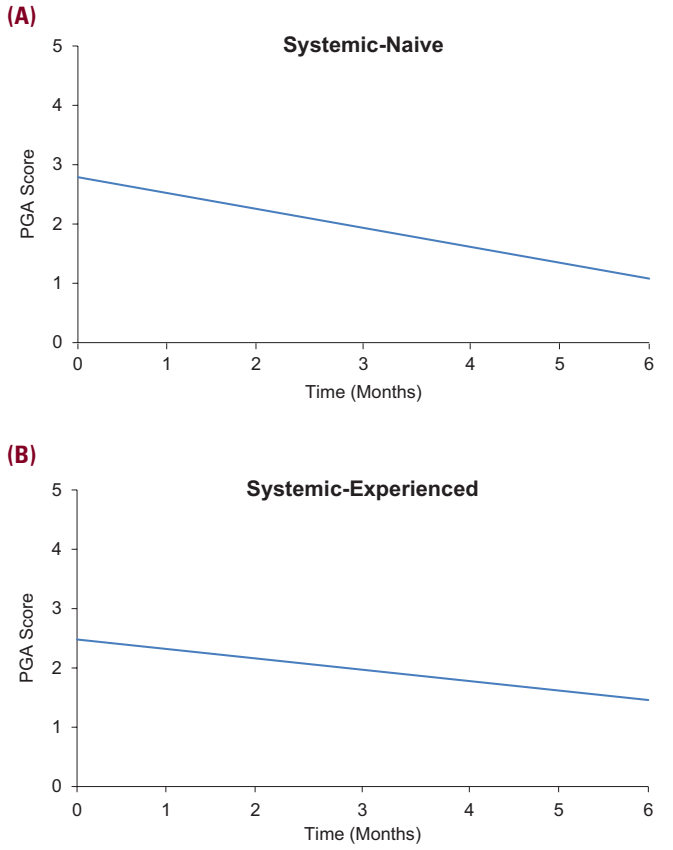
A total of 381 patients (n=173 systemic-naive; n=208 systemic-experienced) on apremilast monotherapy met inclusion criteria for analysis of PGA scores (ie, they had PGA values recorded at ≥2 visits during the study period). In this patient subgroup, mean adjusted PGA scores at the time of apremilast initiation were 2.79 and 2.48 for systemic-naive and systemic-experienced patients, respectively. PGA scores decreased significantly in both the systemic-naive patients (–1.71; $P<0.001$; approximately –61%) and the systemic-experienced patients (–1.02; $P<0.001$; approximately –41%) within 6 months of initiating apremilast monotherapy (Figure 2).

A total of 360 patients met inclusion criteria for analysis of PGA score achievement of 0 or 1 (ie, patients with PGA values recorded at ≥2 visits during the study period, and with ≥1 PGA score ≥2; n=168 systemic-naive; n=192 systemic-experienced). Among these, 45 (26.8%) systemic-naive and 49 (25.5%) systemic-experienced patients had a PGA score of 0 or 1 at follow-up within 6 months of treatment initiation. The median time to achievement of low disease severity was 62 and 63 days for systemic-naive and systemic-experienced patients, respectively.

Effect of Apremilast Monotherapy on BSA

A total of 373 patients (n=196 systemic-naive; n=177 systemic-experienced) on apremilast monotherapy met

FIGURE 2. Adjusted PGA scores during apremilast monotherapy in systemic-naive (A) and systemic-experienced (B) patients.
Adjusted PGA scores for systemic-naive and systemic-experienced patients at Month 6, both $P<0.001$ vs. apremilast baseline (Month 0). PGA scores adjusted for demographic characteristics and psoriasis-related comorbidities. PGA=Physician Global Assessment.

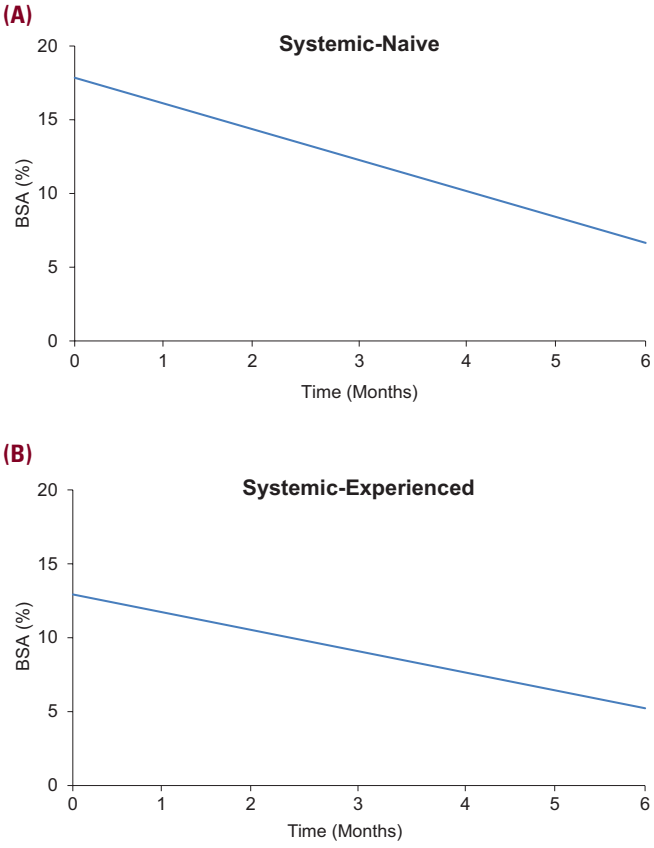


inclusion criteria for analysis of BSA scores (ie, BSA values recorded at ≥2 visits during the study period). In this patient subgroup, at apremilast initiation, mean adjusted BSA was 17.85% and 12.93% for systemic-naive and systemic-experienced patients, respectively, and significantly decreased by 11.12 and 7.70 percentage points ($P<0.001$) within 6 months of initiating apremilast monotherapy (Figure 3). These BSA reductions represent a decrease from baseline of approximately 62% in systemic-naive patients and a decrease from baseline of approximately 60% in systemic-experienced patients.

Effect of Apremilast Monotherapy on Itch NRS

A total of 51 patients (n=28 systemic-naive; n=23 systemic-experienced) had itch NRS values recorded at ≥2 visits during the study period. At apremilast initiation, mean adjusted itch NRS scores were 4.14 and 3.82 for systemic-naive and systemic-experienced patients, respectively. Within 6 months of apremilast initiation, adjusted itch NRS scores decreased by 1.76 points in systemic-naive patients, although the decrease

FIGURE 3. Adjusted psoriasis-affected BSA (%) during apremilast monotherapy in systemic-naive (A) and systemic-experienced (B) patients.
Adjusted psoriasis-affected BSA (%) for systemic-naive and systemic-experienced patients at Month 6, *P*<0.001 and *P*=0.002, respectively, vs apremilast baseline (Month 0). BSA scores adjusted for demographic characteristics and psoriasis-related comorbidities. BSA=psoriasis-affected body surface area.



did not reach statistical significance. In systemic-experienced patients, adjusted itch NRS scores decreased by 3.82 points (*P*=0.034), approaching a score of 0 approximately 5 months after apremilast initiation (Figure 4).

Changes in Body Weight

A total of 352 patients (n=179 systemic-naive; n=173 systemic-experienced) had body weight recorded at ≥2 visits during the study period. At apremilast initiation, the mean adjusted body weight was 76.45 kg in systemic-naive patients and 75.66 kg in systemic-experienced patients. Mean decrease from baseline in body weight was –1.75 kg in systemic-naive patients and –1.09 kg in systemic-experienced patients.

POTE of Apremilast Monotherapy

Among patients who received apremilast monotherapy for ≥90 days and had ≥1 POTE assessment (n=160), the majority (n=138; 86.2%) agreed or strongly agreed that apremilast treatment was effective in clearing their skin of psoriasis (Figure 5).

DISCUSSION

Apremilast has demonstrated efficacy in the treatment of adult patients with moderate to severe plaque psoriasis in phase 2 and 3 clinical trials.[9-11] Clinical trial data, however, do not fully reflect the demographically and clinically diverse population of patients treated at dermatology practices. Determining treatment patterns and clinical effectiveness of therapies at the point of care is critical for ascertaining real-world patient outcomes, devising treatment strategies, and improving patient outcomes. EMR databases can serve as an important source of real-world data for outcomes research.

Based on data captured from >5000 US dermatology providers, apremilast-treated patients appeared to have chronic plaque psoriasis that was at least moderate in severity. Specifically, at the time of apremilast initiation, systemic-naive and

FIGURE 4. Adjusted itch NRS during apremilast monotherapy in systemic-naive (A) and systemic-experienced (B) patients.
Adjusted itch NRS for systemic-naive and systemic-experienced patients at Month 6, *P*=NS and *P*=0.034, respectively, vs apremilast baseline (Month 0). Itch NRS scores adjusted for demographic characteristics and psoriasis-related comorbidities. NRS=numeric rating scale.

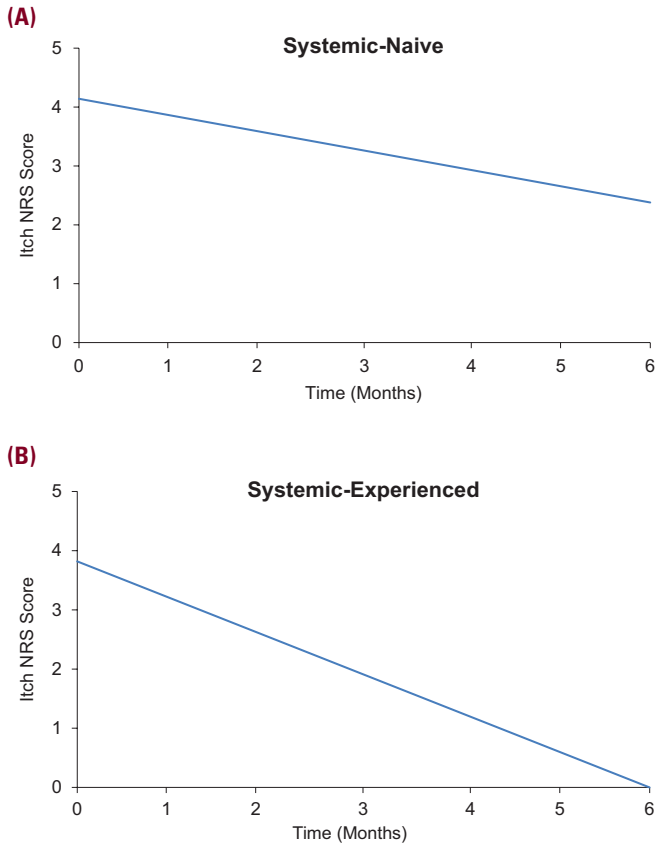
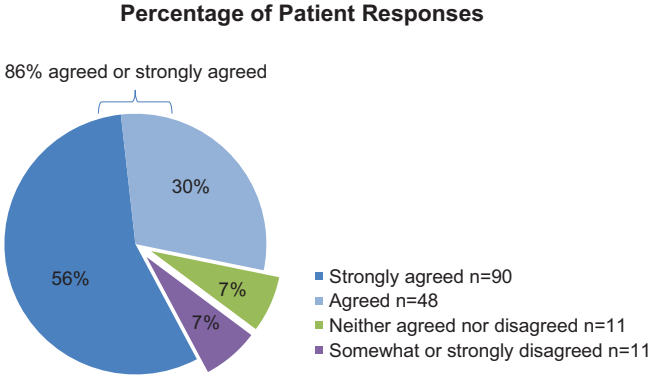


FIGURE 5. Patient-perceived effectiveness of apremilast monotherapy.
Responses were captured by providers asking patients to indicate level of agreement with the statement, "I believe this treatment is effective in clearing my skin of psoriasis."



systemic-experienced patients had mean PGA scores of 2.79 and 2.48 and mean psoriasis-affected BSA of 17.85% and 12.93%, respectively. Their baseline demographic characteristics and pattern of comorbidities were also reflective of the broader population of US patients with moderate to severe psoriasis, with >50% having psoriasis-related comorbidities.[1,12-14] Most patients who switched to apremilast monotherapy were previously receiving only topical therapy, indicating inadequate treatment and a possible place for apremilast in the treatment of patients with psoriasis immediately after topical therapy is no longer adequately managing symptoms.

The current findings from dermatology clinical practices confirm those from the phase 3 ESTEEM 1 and 2 clinical trials, which demonstrated efficacy of apremilast in patients with moderate to severe plaque psoriasis.[9,10] Approximately one-quarter of patients achieved low disease severity as measured by PGA of 0 or 1 after approximately 2 months of apremilast therapy, which is consistent with reductions in PGA observed in apremilast clinical trials.[9,10]

In our study, PGA and BSA scores were each significantly reduced by approximately 60% with apremilast monotherapy within 6 months of treatment initiation, regardless of whether patients were systemic-naive or systemic-experienced. Patients who were systemic-naive had slightly better efficacy responses, indicating that these patients might be a more appropriate population for apremilast than systemic-experienced patients.

Clinically significant reductions in itch were seen in both systemic-naive and systemic-experienced patients.[15] Although the decrease in itch NRS did not reach statistical significance in systemic-naive patients, systemic-experienced patients reported a significant reduction within 6 months after apremilast initiation, approaching a score of 0 approximately 5 months after apremilast initiation and complete resolution in some patients. The majority of patients (86.2%) considered apremilast to be effective in clearing their skin of psoriasis, suggesting a high level of patient satisfaction with treatment.

Both treatment experience groups had reductions in body weight that were comparable to those observed in clinical trials of apremilast.[9,10]

Limitations

Data represent dermatology providers' EMR entries, and reporting may not be uniform across providers. Medication data reflect what dermatology providers prescribed; medication adherence was not evaluated. The statistical power of efficacy subanalyses may be limited by small numbers of patients with evaluable data.

CONCLUSION

Based on this retrospective, multicenter, longitudinal, observational cohort study using an EMR database, apremilast was prescribed to patients with features typical of a population with moderate to severe psoriasis, including a high prevalence of comorbid conditions. With up to 6 months of apremilast monotherapy, psoriasis severity was reduced as measured by PGA and BSA, regardless of whether patients were systemic-naive or systemic-experienced, with slightly better responses seen in the systemic-naive patient population. Most patients considered apremilast to be effective in reducing their psoriasis symptoms.

DISCLOSURES

April Armstrong: AbbVie, Janssen, Lilly, Modernizing Medicine, Novartis, Pfizer, Regeneron, and Sanofi – grants, consulting fees, and/or honorarium. Eugenia Levi: Celgene Corporation – employment.

ACKNOWLEDGMENTS

The authors received editorial support in the preparation of this report from Amy Shaberman, PhD, of Peloton Advantage, LLC, Parsippany, NJ, USA, funded by Celgene Corporation, Summit, NJ, USA. The authors, however, directed and are fully responsible for all content and editorial decisions for this manuscript.

REFERENCES

1. Helmick CG, Lee-Han H, Hirsch SC, et al. Prevalence of psoriasis among adults in the U.S.: 2003-2006 and 2009-2010 National Health and Nutrition Examination Surveys. *Am J Prev Med.* 2014;47(1):37-45.
2. Rachakonda TD, Schupp CW, Armstrong AW. Psoriasis prevalence among adults in the United States. *J Am Acad Dermatol.* 2014;70(3):512-516.
3. Parisi R, Symmons DP, Griffiths CE, Ashcroft DM. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. *J Invest Dermatol.* 2013;133(2):377-385.
4. Dubertret L, Mrowietz U, Ranki A, et al. European patient perspectives on the impact of psoriasis: the EUROPSO patient membership survey. *Br J Dermatol.* 2006;155(4):729-736.

5. Armstrong AW, Robertson AD, Wu J, et al. Undertreatment, treatment trends, and treatment dissatisfaction among patients with psoriasis and psoriatic arthritis in the United States: findings from the National Psoriasis Foundation surveys, 2003-2011. *JAMA Dermatol.* 2013;149(10):1180-1185.
6. Lebwohl MG, Bachelez H, Barker J, et al. Patient perspectives in the management of psoriasis: results from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis Survey. *J Am Acad Dermatol.* 2014;70(5):871-881.
7. van de Kerkhof PCM, Reich K, Kavanaugh A, et al. Physician perspectives in the managment of psoriasis and psoriatic arthritis: results from the population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis survey. *J Eur Acad Dermatol Venereol.* 2015;29(10):2002-2010.
8. Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 6. Guidelines of care for the treatment of psoriasis and psoriatic arthritis: case-based presentations and evidence-based conclusions. *J Am Acad Dermatol.* 2011;65(1):137-174.
9. Papp K, Reich K, Leonardi CL, et al. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: results of a phase III, randomized, controlled trial (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM 1]). *J Am Acad Dermatol.* 2015;73(1):37-49.
10. Paul C, Cather J, Gooderham M, et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate to severe plaque psoriasis over 52 weeks: a phase III, randomized, controlled trial (ESTEEM 2). *Br J Dermatol.* 2015;173(6):1387-1399.
11. Ohtsuki M, Okubo Y, Komine M, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in the treatment of Japanese patients with moderate to severe plaque psoriasis: Efficacy, safety and tolerability results from a phase 2b randomized controlled trial. *J Dermatol.* 2017;44(8):873-884.
12. Yeung H, Wan J, Van Voorhees AS, et al. Patient-reported reasons for the discontinuation of commonly used treatments for moderate to severe psoriasis. *J Am Acad Dermatol.* 2013;68(1):64-72.
13. Davidovici BB, Sattar N, Prinz J, et al. Psoriasis and systemic inflammatory diseases: potential mechanistic links between skin disease and co-morbid conditions. *J Invest Dermatol.* 2010;130(7):1785-1796.
14. Armstrong AW, Schupp C, Bebo B. Psoriasis comorbidities: results from the National Psoriasis Foundation surveys 2003 to 2011. *Dermatology.* 2012;225(2):121-126.
15. Sobell JM, Foley P, Toth D, et al. Effects of apremilast on pruritus and skin discomfort/pain correlate with improvements in quality of life in patients with moderate to severe plaque psoriasis. *Acta Derm Venereol.* 2016;96(4):514-520.

AUTHOR CORRESPONDENCE

April Armstrong MD MPH

E-mail:.....april.armstrong@med.usc.edu