Treatment-to-Target With Apremilast in Psoriatic Arthritis: The Probability of Achieving Targets and Comprehensive Control of Disease Manifestations

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Objective. The present study was undertaken to evaluate the probability of achieving the Clinical Disease Activity Index for Psoriatic Arthritis (cDAPSA) treatment targets of remission or low disease activity (LDA) with apremilast based on disease activity categories and corresponding responses in arthritis and other domains of psoriatic arthritis (PsA) not included in the cDAPSA.

Methods. Pooled analyses from the Psoriatic Arthritis Long-term Assessment of Clinical Efficacy studies 1, 2, and 3 were performed. Probability analyses assessing the likelihood of achieving cDAPSA treatment targets by week 52 were performed using multiple imputation for discontinuations and missing values. Longitudinal analyses were performed in patients grouped by cDAPSA category at week 52.

Results. Among 494 patients in the probability analyses, 46.9% with moderate disease activity and 24.9% with high disease activity at baseline achieved treatment targets (remission or LDA) by week 52. For patients with moderate disease activity at baseline, small improvements (cDAPSA reductions ≥30%) by week 16 were associated with achieving targets. Patients achieving remission or LDA by week 16 had high probabilities of remaining at treatment targets at week 52. Of 375 patients with cDAPSA components available at week 52, achieving targets with apremilast was associated with continuous disease activity improvements and no or mild arthritis and other PsA manifestations.

Conclusion. The probability of achieving treatment targets (remission or LDA) at week 52 was greater for patients with moderate versus high disease activity at baseline. At a mean level, partial improvements by week 16 were associated with achieving treatment targets. Patients receiving apremilast who achieved cDAPSA targets by week 52 also had no or mild arthritis or other PsA manifestations.

INTRODUCTION

Apremilast, an oral phosphodiesterase 4 inhibitor, has demonstrated clinical improvements in patients with active psoriatic arthritis (PsA), including signs, symptoms, and quality of life, and was generally well tolerated in the phase 3, randomized Psoriatic Arthritis Long-term Assessment of Clinical Efficacy (PALACE) 1, 2, and 3 studies (1–3). Because apremilast is 1 of many therapies available for the treatment of PsA, a need exists to identify subgroups of patients who are most likely to achieve optimal outcomes with apremilast treatment to help guide clinical practice. To address this, it is important to determine which patients are more...
likely to achieve treatment targets of remission or low disease activity (LDA) with apremilast.

Treatment-to-target recommendations stipulate that the treatment target should be clinical remission or inactive disease of musculoskeletal (arthritis, dactylitis, enthesitis, axial disease) and nonmusculoskeletal domains of PsA (4). An alternative treatment target may be LDA or minimal disease activity. It is recommended that patients be offered regular evaluations and treatment adjustments if they are not achieving treatment targets associated with desirable long-term outcomes (4,5). In addition, therapeutic decisions should be individualized and should account for complications from untreated active disease and from therapy (5).

A fundamental question that remains is how to identify the most appropriate instruments to monitor disease activity in patients with PsA who may have multiple manifestations in clinical practice. In this regard, treatment-to-target and American College of Rheumatology recommendations for PsA support the use of the Disease Activity Index for Psoriatic Arthritis (DAPSA) as a valid instrument to monitor the achievement of treatment targets among other treatment targets (4,6–8). A potential, inherent limitation associated with the DAPSA relates to its focus on articular features. The DAPSA uses a composite score based on swollen joint count (SJC), tender joint count (TJC), patient assessment of pain (PAP), patient global assessment of disease activity (PtGA), and C-reactive protein (CRP) levels. A related measure, the Clinical DAPSA (cDAPSA), which excludes the CRP measurement, has been used in clinical practice (7,9). Because the cDAPSA mainly focuses on articular manifestations, it remains to be determined whether patients who achieve these disease targets with apremilast could achieve comprehensive disease control across a wider range of disease manifestations that are not included in this measure, such as skin involvement, enthesitis, or dactylitis.

In this study, we aimed to identify patients who are more likely to achieve the cDAPSA treatment targets of remission or LDA with apremilast using a pooled analysis of the PALACE 1, 2, and 3 studies. We also assessed the performance of the cDAPSA as an instrument to monitor the achievement of treatment goals by evaluating the extent of musculoskeletal and nonmusculoskeletal disease control among patients achieving cDAPSA treatment targets with apremilast.

**PATIENTS AND METHODS**

**Study population.** Detailed inclusion and exclusion criteria for the PALACE studies have been previously published (1–3). Briefly, the studies enrolled adult patients (≥18 years of age at the time of consent) with active PsA of ≥6 months duration who met the Classification of Psoriatic Arthritis Study Group criteria and had ≥3 swollen and ≥3 tender joints despite treatment with prior conventional disease-modifying antirheumatic drugs (DMARDs) and/or biologics (prior therapeutic failure with tumor necrosis factor blockers was limited to ≤10% of enrolled patients). In PALACE 3, patients were also required to have active skin disease with ≥1 plaque psoriasis skin lesion that was ≥2 cm in size. Patients were excluded from the studies if they had experienced therapeutic failure of >3 conventional DMARDs or biologic agents or >1 tumor necrosis factor blocker therapy. The PALACE 1, 2, and 3 studies were approved by the institutional review boards at each investigational site and conducted in accordance with good clinical practice, as described in International Conference on Harmonisation guideline E6, and in accordance with the general ethical principles outlined in the Declaration of Helsinki. All patients provided written informed consent.

Amgen, Astra-Zeneca, Astro, Celgene, Celtrion, Eli Lilly and Company, GlaxoSmithKline, ILTOO Pharma, Janssen, MedImmune, Merck Sharp & Dohme, Novartis, Pfizer, Roche, SanoFil, Sanofi, and UCB (less than $10,000 each) and research support from AbbVie, Eli Lilly and Company, Janssen, Merck Sharp & Dohme, Pfizer, and Roche. No other disclosures relevant to this article were reported.

Qualified researchers may request data from Amgen clinical studies. Complete details are available at http://www.amgen.com/datasharing.

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Study design. PALACE 1, 2, and 3 (NCT01172938, NCT01212757, and NCT01212770) were phase 3, multicenter, randomized, double-blind, placebo-controlled clinical trials with similar study designs, which have been previously described in detail (1–3). Briefly, patients were randomized (1:1:1) to receive apremilast 30 mg twice a day, apremilast 20 mg twice a day, or placebo. Randomization was stratified according to current DMARD use (yes/no) in all 3 studies and by psoriasis-involved body surface area (<3%/≥3%) in PALACE 3. Patients whose SJC and TJC had not improved by at least 20% at week 16 were considered nonresponders and either continued on the original apremilast dose or were re-randomized from placebo to receive apremilast 30 mg twice a day or apremilast 20 mg twice a day. At week 24, all remaining placebo patients were re-randomized to receive apremilast 30 mg twice a day or 20 mg twice a day, and double-blind treatment continued to week 52. Upon completion of the 52-week double-blind treatment phase, patients were eligible to participate in a long-term treatment extension phase (for up to 5 years of total follow-up). Herein, we report the results from analyses of pooled data from PALACE studies 1, 2, and 3 that included patients who were randomized to receive apremilast 30 mg twice a day at baseline and who had available cDAPSA components to calculate responses.

End points. The probability of achieving cDAPSA categories at week 52 was evaluated on the basis of baseline and week 16 cDAPSA categories. The cDAPSA was calculated as a composite score including SJC, TJC, PAP, and PtGA, with possible scores ranging from 0 to 154 (4). The cDAPSA disease activity categories were defined as follows: remission ≤4; LDA >4 to ≤13; moderate disease activity >13 to ≤27; and high disease activity (HDA) >27 (9). To determine the extent of changes from baseline to week 16 in cDAPSA values associated with achieving the cDAPSA categories at week 52, mean changes in the cDAPSA values over time were assessed, and individual probabilities of treatment success were calculated.

To assess the value of the cDAPSA as an indicator of comprehensive clinical responses with apremilast, patients were grouped according to the cDAPSA categories achieved at week 52. Musculoskeletal and nonmusculoskeletal domains of PsA were longitudinally assessed at baseline and at weeks 16, 24, 40, and 52 according to cDAPSA categories achieved at week 52. These domains included the cDAPSA and its core components (SJC [0–66], TJC [0–68], the PAP visual analog scale (VAS) [0–100 mm] and PtGA VAS [0–100 mm], other musculoskeletal domains (enthesitis assessment, Maastricht Ankylosing Spondylitis Enthesitis Score [MASES; range 0–13], and dactylitis count [0–20]) and nonmusculoskeletal domains (Psoriasis Area and Severity Index score [range 0–72]), as well as the physician global assessment of disease activity (PhGA) VAS (0–100 mm) and the Health Assessment Questionnaire disability index (range 0–3) assessments.

Statistical analysis. For the probability analyses, the cDAPSA shift categories and longitudinal data were analyzed in patients who had cDAPSA components available at baseline, following multiple imputations to account for those who discontinued or had missing values. Multiple imputations were repeated 30 times, each time with continuous cDAPSA missing data imputed and categorized, and shifts of cDAPSA categories from baseline to week 52 were averaged more than 30 times of multiple imputation. The multiple imputation and categorization procedures were repeated for shifts of cDAPSA categories from week 16 to week 52, separately for patients with moderate disease activity and with HDA at baseline. As a subset analysis to see the probability of achieving treatment target at week 52 for patients who showed partial response at an early time point, the procedure was repeated for patients who had ≥30% improvement in cDAPSA at week 16.

Longitudinal analysis assessing the control of musculoskeletal and nonmusculoskeletal domains associated with the achievement of cDAPSA response categories were performed for patients who had cDAPSA components available at week 52. Results are presented for patients who achieved cDAPSA categorical responses (remission, LDA, moderate disease activity, and HDA) at week 52 using data as observed.

RESULTS

Baseline characteristics of study population. A total of 1,493 patients were randomized and received ≥1 dose of study medication in the PALACE 1, 2, and 3 studies (placebo [n = 496], apremilast 30 mg twice a day [n = 497], apremilast 20 mg twice a day [n = 500]). Of these, 494 patients randomized to receive apremilast 30 mg twice a day at baseline who had cDAPSA scores available at baseline were included in the probability analysis assessing the likelihood of achieving cDAPSA remission or LDA. At baseline, 6 patients (1.2%) had LDA, 121 patients (24.5%) had moderate disease activity, and 367 patients (74.3%) had HDA.

A total of 375 patients who received apremilast 30 mg twice a day at baseline and had cDAPSA components available at week 52 were included in the longitudinal analyses of cDAPSA and musculoskeletal and nonmusculoskeletal domains of PsA. Baseline characteristics of the patients categorized by cDAPSA outcomes at week 52 are presented in Table 1. Mean age, body mass index, and concomitant treatment with conventional DMARDs were generally similar for patients in all cDAPSA categories at week 52, and the percentage of female patients was lowest among those in remission at week 52 and highest among patients with HDA at week 52. Overall, patients across all cDAPSA categories at week 52 had moderate-to-severe disease at baseline, as defined by mean cDAPSA values. Patients who achieved cDAPSA treatment targets (remission or LDA) at week 52 generally exhibited numerically lower levels of disease activity at baseline compared with those who did not achieve targets.
Among patients with moderate disease activity at baseline, the mean ± SD baseline SJC and TJC were comparable between patients who achieved treatment targets (remission or LDA) at week 52 versus those who did not (SJC 5.7 ± 2.2 versus 5.4 ± 2.1 and TJC 8.9 ± 3.1 versus 8.0 ± 3.0), whereas the mean ± SD PAP, PtGA, and PhGA scores at baseline were lower for patients who achieved treatment targets at week 52 versus those who did not (PAP 41.0 ± 20.7 versus 50.6 ± 17.2; PtGA 39.9 ± 22.0 versus 51.5 ± 15.7; and PhGA 43.8 ± 16.6 versus 50.7 ± 14.6). Among patients with HDA at baseline, mean ± SD disease activity domains at baseline were lower for patients who achieved treatment targets at week 52 versus those who did not (SJC 11.7 ± 6.2 versus 14.0 ± 9.3; TJC 19.4 ± 8.1 versus 29.5 ± 15.7; PAP 59.0 ± 17.8 versus 63.8 ± 18.7; PtGA 58.6 ± 18.5 versus 63.0 ± 19.5; and PhGA 55.4 ± 17.3 versus 62.8 ± 17.7).

Baseline probability analysis assessing the likelihood of achieving cDAPSA remission or LDA. Probabilities of achieving cDAPSA categories at week 52 based on cDAPSA categories at baseline are presented in Figure 1. Approximately one-half (46.9%) of patients with moderate disease activity at baseline and approximately one-quarter (24.9%) of patients with HDA at baseline achieved treatment targets by week 52.

Week 16 probability analysis assessing the likelihood of achieving cDAPSA remission or LDA. Among the 494 patients who started with apremilast treatment at baseline, the week 16 remission, LDA, moderate disease activity (Mod) and HDA response rates, respectively, were as follows: 40.0%, 40.0%, 20%, and 0% for patients with LDA at baseline; 7.0%, 29.8%, 44.7%, and 18.4% for patients with moderate disease activity at baseline; and 2.1%, 11.5%, 38.1%, and 48.3% for patients with HDA at baseline (data as observed).

Patients who had moderate disease activity at baseline and achieved remission or LDA by week 16 had high probabilities (58.9–88.5%) of remaining at treatment targets at week 52 (Figure 2A). Among patients with moderate disease activity at baseline, a mean improvement in cDAPSA score of ≥30% by week 16 was associated with achievement of treatment targets at week 52 (see Supplementary Figure 1A, available on the Arthritis Care & Research web site at http://onlinelibrary.wiley.com/doi/10.1002acr.24134/abstract). At a patient level, achieving early and partial responses (defined as cDAPSA improvement of ≥30% by week 16) was associated with a 63% probability of achieving treatment targets by week 52.

### Table 1. Baseline patient demographics and clinical characteristics (n = 375) according to Clinical Disease Activity Index for Psoriatic Arthritis (cDAPSA) category at week 52*

|                  | REM (n = 25) | LDA (n = 106) | Mod (n = 152) | HDA (n = 92) |
|------------------|--------------|---------------|---------------|--------------|
| Age, mean years  | 49.3         | 49.9          | 51.1          | 52.2         |
| Female sex, no. (%) | 9 (36.0)     | 59 (55.7)     | 80 (52.6)     | 59 (64.1)    |
| Body mass index, kg/m² | 28.5         | 28.9          | 30.2          | 30.9         |
| Duration of PsA, years | 8.6          | 6.4           | 7.9           | 7.2          |
| Duration of psoriasis, years | 13.7         | 16.8          | 17.2          | 18.5         |
| cDAPSA score (0–154) | 30.7         | 33.9          | 41.0          | 57.2         |
| SJC (0–66)       | 9.1          | 8.8           | 10.1          | 13.7         |
| TJC (0–68)       | 12.2         | 14.8          | 18.9          | 30.7         |
| PAP (VAS 0–100 mm) | 50.6         | 51.2          | 59.9          | 63.4         |
| PtGA (VAS 0–100 mm) | 44.5         | 51.5          | 60.1          | 61.3         |
| PhGA (VAS 0–100 mm) | 48.8         | 50.7          | 57.0          | 65.9         |
| PASI score (0–72)† | 9.5          | 8.2           | 9.2           | 7.8          |
| MASES (0–13)‡    | 1.9          | 3.3           | 4.4           | 5.2          |
| Dactylitis count (0–20)§ | 2.3          | 2.8           | 2.7           | 4.7          |
| HAQ DI score (0–3) | 0.9          | 1.0           | 1.3           | 1.5          |
| Baseline concomitant conventional DMARD use, no. (%) | 22 (88.0) | 84 (79.2) | 124 (81.6) | 70 (76.1) |
| Baseline corticosteroid use, no. (%) | 5 (20.0) | 9 (8.5) | 14 (9.2) | 12 (13.0) |
| Baseline NSAID use, no. (%) | 16 (64.0) | 70 (66.0) | 116 (76.3) | 68 (73.9) |

* Values are the mean unless indicated otherwise. Includes patients randomized at baseline who had cDAPSA components available at week 52. Remission (REM) score ≤4; low disease activity (LDA) score >4 to ≤13; moderate disease activity (Mod) score >13 to ≤27; high disease activity (HDA) score >27. The number of patients by cDAPSA category may vary for each parameter due to missing data at baseline. PsA = psoriatic arthritis; SJC = swollen joint count; TJC = tender joint count; PAP = patient assessment of pain; VAS = visual analog scale; PtGA = patient global assessment of disease activity; PhGA = physician global assessment of disease activity; PASI = Psoriasis Area and Severity Index; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; HAQ DI = Health Assessment Questionnaire disability index; DMARD = disease-modifying antirheumatic drug; NSAID = nonsteroidal antiinflammatory drug.
† Patients with baseline psoriasis body surface area involvement ≥3%.
‡ Patients with preexisting enthesitis.
§ Patients with preexisting dactylitis.
Patients whose cDAPSA scores at baseline placed them within the lower range of HDA were more likely to be associated with achieving treatment targets by week 52 than were HDA patients with higher baseline cDAPSA scores (see Supplementary Figure 1B, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24134/abstract).

Longitudinal analysis assessing the control of musculoskeletal and nonmusculoskeletal manifestations associated with the achievement of cDAPSA remission or LDA. Longitudinal assessment of disease activity through week 52, as measured by cDAPSA and categorized by achievement of cDAPSA categories at week 52, is presented in Figure 3 and Supplementary Table 1, available on the Arthritis Care & Research web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.24134/abstract. Patients who achieved treatment targets at week 52 had lower mean and median cDAPSA scores at baseline compared with patients who did not. Patients treated with apremilast 30 mg twice a day who achieved remission or LDA at week 52 experienced continuous improvements in disease activity over 52 weeks.

Achievement of cDAPSA treatment targets by week 52 following treatment with apremilast 30 mg twice a day was associated with early and sustained improvements across all manifestations.
of PsA, including SJC and TJC (Figure 4 and Supplementary Table 1, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24134/abstract), enthesitis, dactylitis, and skin involvement (Figure 5 and Supplementary Table 1). In addition, it was associated with normal or near normal physical function (Figure 5 and Supplementary Table 1). Patients reported mean and median levels of pain, PtGA, and PhGA outcomes consistent with cDAPSA categories at week 52 (Supplementary Table 1). Taken together, the results suggest that, at a population level, achieving cDAPSA targets with apremilast was associated with control of musculoskeletal and nonmusculoskeletal domains of PsA not included in the cDAPSA formula.

**DISCUSSION**

The current analysis suggests that patients with moderate disease activity at baseline were more likely to achieve cDAPSA treatment targets of remission or LDA with apremilast 30 mg twice a day than patients with HDA scores at baseline. Approximately twice as many patients (46.9% versus 24.9%) who started with moderate disease activity at baseline achieved treatment targets compared with patients who started with HDA. Baseline characteristics provided limited discriminative ability to differentiate patients who were more likely to achieve treatment targets from those who were not. Importantly, an early and partial response by week 16 (cDAPSA improvement of ≥30%) was asso-

![Figure 3](image1.png)

**Figure 3.** Disease activity through week 52 (n = 375) by Clinical Disease Activity Index for Psoriatic Arthritis (cDAPSA) (score range 0–154) category in patients receiving apremilast 30 mg twice a day from baseline, including patients randomized at baseline who had cDAPSA components available at week 52. Data are as observed. Remission (REM) score ≤4; low disease activity (LDA) score >4 to ≤13; moderate disease activity (Mod) score >13 to ≤27; and high disease activity (HDA) score >27. Error bars indicate the SEM.

![Figure 4](image2.png)

**Figure 4.** Musculoskeletal disease activity by Clinical Disease Activity Index for Psoriatic Arthritis (cDAPSA) category at week 52 for swollen joint count (SJC) (A) and tender joint count (TJC) (B), including patients randomized at baseline who had cDAPSA components available at week 52. Data are as observed. Remission (REM) score ≤4; low disease activity (LDA) score >4 to ≤13; moderate disease activity (Mod) score >13 to ≤27; and high disease activity (HDA) score >27. Error bars indicate the SEM.
associated with a greater likelihood of achieving treatment targets by week 52. As a result, the absence of treatment response by week 16 would reinforce the need for a treatment adjustment. Taken together, these findings provide a framework of reference for the selection and monitoring of patients with the highest likelihood of achieving optimal treatment responses with apremilast in clinical practice.

Another important objective of this analysis was to assess the relevance of the cDAPSA as an indicator of comprehensive treatment responses to apremilast. Because the cDAPSA includes SJC, TJC, PAP, and PtGA, whether achievement of cDAPSA treatment targets also represents achievement of control in other manifestations of PsA has not previously been fully examined. In this study, patients receiving apremilast who achieved cDAPSA treatment targets by week 52 also experienced improvements in musculoskeletal and nonmusculoskeletal domains that are not directly captured by the cDAPSA. In fact, patients who achieved remission or LDA with apremilast had absent or mild musculoskeletal and nonmusculoskeletal manifestations of PsA by week 52. This finding has important implications in validating the cDAPSA as a tool to monitor patients treated with apremilast in routine practice. Indeed, this suggests that for patients receiving apremilast, domains not measured by the cDAPSA follow a more comparable course of improvements than that included in the cDAPSA formula.

This study is limited by the use of MASES to assess enthesis because, unlike other enthesis assessments (i.e., Leeds Enthesitis Index, Spondyloarthritis Research Consortium of Canada Index), MASES only measures 1 peripheral enthesis site, the Achilles tendon (10). In our study, it is possible that peripheral enthesis may have been indirectly accounted for through the cDAPSA, which, by including the PAP and PtGA, constitutes an overall assessment of the disease presentation.

In conclusion, our findings indicate that patients with moderate disease activity at baseline have a higher likelihood of achieving optimal outcomes with apremilast compared with those with HDA at baseline. Early and partial responses by week 16 were associated with achieving long-term treatment targets. Finally, the results support the use of the cDAPSA to monitor patients treated with apremilast given that domains not captured by the cDAPSA traveled in the same direction as the cDAPSA. At a population level, patients who achieved cDAPSA remission or LDA also had no or mild musculoskeletal and nonmusculoskeletal disease manifestations.

**AUTHOR CONTRIBUTIONS**

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Mease had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
**Study conception and design.** Mease, Gladman, O gidie, Coates, Behrens, Kavanaugh, McInnes, Queiro, Guerette, Brunori, Teng, Smolen.

**Acquisition of data.** Mease, Gladman, Behrens, Kavanaugh, Queiro, Guerette, Brunori, Teng.

**Analysis and interpretation of data.** Mease, Gladman, O gidie, Coates, Behrens, Kavanaugh, McInnes, Queiro, Guerette, Brunori, Teng, Smolen.

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