Real-world effectiveness and safety of apremilast in psoriasis at 52 weeks: a retrospective, observational, multicenter study by the Spanish Psoriasis Group

Authors: Elena del Alcázar[1],Jorge A. Suárez-Pérez[2] , Susana Armesto[3], Raquel Rivera[4], Enrique Herrera-Acosta[2] , Pedro Herranz[5], Isabel Martín[6], Encarnación Montesinos[7], Mercedes Hospital[8], Eva Vilarrasa[9], Marta Ferran[10], Ricardo Ruiz-Villaverde[11], Antonio Sahuquillo-Torralba [12], Diana P Ruiz-Genao[13], Silvia Pérez-Barrio [14], Carlos Muñoz[15], Mar Llamas[16], Francesc Valentí [17], Miren Josune Mitxelena[18], Anna López-Ferrer[9], Gregorio Carretero [19], David Vidal [20], Jordi Mollet [21], Isabel Belinchón [22], José Manuel Carrascosa[1]

Affiliations:

1. Department of Dermatology. Hospital Universitari Germans Trias i Pujol. Universitat Autònoma de Barcelona (UAB. Badalona, Spain

2. Department of Dermatology. Hospital Universitario Virgen de la Victoria. Málaga, Spain.

3. Department of Dermatology. Hospital Universitario de Valdecilla. Santander,Spain

4. Department of Dermatology. Hospital Universitario 12 de Octubre. Madrid, Spain.

5. Department of Dermatology. Hospital Universitario La Paz. Madrid, Spain

6. Department of Dermatology. Hospital Universitario Getafe. Madrid, Spain

7. Department of Dermatology. Hospital Clínico Universitario de Valencia. Valencia, Spain

8. Department of Dermatology. Hospital Universitario Puerta de Hierro Majadahonda Madrid. Spain

9. Department of Dermatology. Hospital Hospital de la Santa Creu I Sant Pau. Barcelona, Spain

10. Department of Dermatology. Hospital del Mar- Institut Mar d'Investigacions Mèdiques. Barcelona, Spain

11. Department of Dermatology.Hospital Universitario San Cecilio. Granada, Spain

12. Department of Dermatology. Hospital Universitario y Politécnico La Fe, Valencia. Instituto de Investigación Sanitaria La Fe. Valencia, Spain.

13. Department of Dermatology. Hospital Universitario Fundación Alcorcón. Madrid, Spain

14. Department of Dermatology. Hospital Universitario Basurto. Bilbao,Spain

15. Department of Dermatology. Hospital de Granollers. Granollers, Spain

16. Department of Dermatology. Hospital Universitario La Princesa. Madrid, Spain

17. Department of Dermatology. Hospital Universitari de Bellvitge. Hospitalet de Llobregat, Spain

18. Department of Dermatology. Hospital Universitario de Navarra. Pamplona,Spain

19. Department of Dermatology. Hospital Universitario Gran Canaria Doctor Negrín. Las Palmas de Gran Canaria. Spain

20. Department of Dermatology. Hospital MoisèsBroggi. Sant Joan Despí, Spain

21. Department of Dermatology. Hospital Universitari Vall d'Hebrón.Barcelona, Spain

22. Department of Dermatology. Derpartment of Dermatology. Hospital Universitario de Alicante -ISABIAL, UMH Alicante, Spain.

Corresponding author:

Elena del Alcázar, MD. E-mail: elenadelalcázarviadomiu@gmail.com

Conflicts of interest:

Elena del Alcázar has received speakers honoraria and/or participated in clinical trials sponsored by from Abbvie, Leo Pharma, Almirall, Jansen-Cilag, Lilly, Novartis, and UCB.

Jorge A. Suárez-Pérez received grants, and research support or received honoraria from Lilly, Pfizer, Janssen, Leo Pharma, Celgene, Abbvie y Novartis.

Susana Armesto has received grants, and research support or received honoraria from Abbive, Leo Pharma, Celgene, Almirall, Jansen-Cilag and Lilly

Raquel Rivera acted as a consultant and/or speaker for and/or participated in clinical trials sponsored by companies that manufacture drugs used for the treatment of psoriasis, including Abbvie/Abbott, Almirall, Amgen, Celgene, Janssen-Cilag, Leo Pharma, Lilly, MSD-Schering-Plough, Novartis, Pfizer and UCB .

Enrique Herrera-Acosta has received grants, and research support or received honoraria from Lilly, Pfizer, Janssen, Leo Pharma, Celgene, Abbvie y Novartis.

Pedro Herranz Pinto has received grants, and research support, served as a consultant or received honoraria from Abbvie, Almirall, Janssen, Leo-pharma, Lilly, Novartis, Pfizer, Regeneron, Sandoz, Sanofi-Aventis,

Isabel Martín has participated as a consultant for Abbvie, Celgene, Janssen, Ucbfharma.

Encarnación Montesinos Villaescusa has received grants, and research support, served as a consultant or received honoraria from Novartis, Galderma, Almirall, Janssen, Celgene and Gebro.

Mercedes Hospital has participated as a consultant for Abbvie, Almirall, Celgene, Janssen, Leo pharma, Lilly, Novartis, UCB pharma

Eva Vilarrasa has received grants and research support, and/or served as a consultant or received honoraria from AbbVie, Almirall, Amgen, Boheringer, Celgene, Janssen, Leo Pharma, Lilly, MSD, Novartis, Pfizer and UCB.

Marta Ferran has received grants, and research support, served as a consultant or received honoraria from Abbvie, Pfizer, Janssen, Novartis, Lilly, Almirall, Leo and Celgene

Ricardo Ruiz-Villaverde has received grants, and research support, served as a consultant or received honoraria from Pfizer, Novartis, Lilly, Cellgene, Almirall and Abbvie

Antonio Sahuquillo-Torralba has served a consultant or paid speaker or participated in clinical trials sponsored by companies that manufactured drugs used for the treatment of psoriasis, inlcudind Abbvie, Celgene, Janssen-Cilag, Leo Pharma, Lilly, Novartis and Pfizer.

Diana Patricia Ruiz Genao has received fees as a consultant and speaker form Celgene, Abbvie, Lilly, Novartis, Leo Pharma, Janssen, Pfizer.

Silvia Pérez-Barrio has received grants and research support, served as a consultant or received honoraria from Pfizer, Abbvie, Celgene, Jannssen, Leo-Pharma, Novartis, Lilly, UCB, MSD and Almirall

Carlos Muñoz has received grants, and research support, served as a consultant or received honoraria from Celgene corporation and Novartis

M. Llamas-Velasco has potential conflict of interests (advisory board member, consultant, research support, participation in clinical trials and honorary for speaking) with the following pharmaceutical companies: Abbvie, Amgen, Janssen-Cilag, Leo Pharma, Novartis, Lilly and Celgene.

Fransec Valentí-Medina has received consultancy/speakers honoraria and/or participated in clinical trials sponsored by Abbvie, Janssen-Cilag, Celgene, Novartis and Leo Pharma

Josune Mitxelena Ezeiza has received grants, and research support, served as a consultant or received honoraria from Novartis, Abbvie, Celgene, Lilly, Leo Pharma, Almirall and Janssen.

Anna López- Ferrer has perceived consultancy/educational support/speakers honoraria and/or participated in clinical trials sponsored by AbbVie, Almirall, Amgen, Boehringer Ingelheim, Celgene, Janssen, Leo Pharma, Lilly, MSD, Novartis, Pfizer and UCB.

Gregorio Carretero has received grants, and research support, served as a consultant or received honoraria from Abbvie, Janssen, Novartis, Lilly, Celgene, Pfizer, Leo-Pharma, UCB, Almirall, Galderma.

David Vidal has received grants, and research support, served as a consultant or received honoraria from Lilly, Janssen, Abbvie, Novartis, UCB, Celgene, Gebro and Leo.

Jordi Mollet has served as a consultant or received honoraria from Abbvie, Celgene, Janssen, Lilly, Novartis and Pfizer.

Isabel Belinchón acted as a consultant and/or speaker for and/or participated in clinical trials sponsored by companies that manufacture drugs used for the treatment of psoriasis, including Janssen Pharmaceuticals Inc, Almirall SA, Lilly, AbbVie, Novartis, Celgene, Biogen Amgen, Leo-Pharma, Pfizer-Wyeth, UCB, and MSD

José Manuel Carrascosa has participated as PI/SI,and/or member of steering comitee, and/or advisor and/or invited speaker for Celgene, Amgen, Abbvie, Almirall, Novartis, Leo-Pharma, Lilly, Sandoz, Mylan, Janssen

Funding Sources: None

Manuscript word count: 2728

References: 22

Tables:3

Figures: 3 (1a, 1b,1c), 2 (2a, 2b), 3

Keywords: psoriasis, apremilast, clinical practice

Short title: Apremilast in plaque and palmoplantar psoriasis

ABSTRACT

Background: Little has been published on the real-world effectiveness and safety of apremilast in psoriasis.

Objectives: To evaluate the effectiveness, safety, and drug survival of apremilast at 52 weeks in patients with moderate to severe plaque psoriasis or palmoplantar psoriasis in routine clinical practice.

Methods: Retrospective, multicenter study of adult patients with moderate to severe plaque psoriasis or palmoplantar psoriasis treated with apremilast from March 2016 to March 2018.

Results: We studied 292 patients with plaque psoriasis and 85 patients with palmoplantar psoriasis. The mean (SD) Psoriasis Area and Severity Index (PASI) score was 10.7 (7.0) at baseline and 3.0 (4.2) at 52 weeks. After 12 months of treatment, 73.6% of patients had a PASI score of 3 or less. In terms of relative improvement by week 52, 49.7% of patients achieved PASI-75 (≥ 75% reduction in PASI score) and 26.5% achieved PASI-90. The mean physician global assessment score for palmoplantar psoriasis fell from 4.2 (5.2) at baseline to 1.3 (1.3) at week 52. Overall drug survival after 1 year of treatment with apremilast was 54.9 %. The main reasons

for treatment discontinuation were loss of efficacy (23.9%) and adverse events (15.9%). Almost half of the patients in our series (47%) experienced at least one adverse event. The most common events were gastrointestinal problems.

Conclusions: Apremilast may be a suitable alternative for the treatment of moderate to severe psoriasis and palmoplantar psoriasis. Although the drug has a good safety profile, adverse gastrointestinal effects are common.

Introduction

Apremilast is an oral phosphodiesterase-4 (PDE4) inhibitor approved by the US Food and Drug Administration in 2014 and the European Medicines Agency (EMA) in 2015. According to the EMA, apremilast is indicated for the treatment of *1*) moderate to severe psoriasis in adults unresponsive to, intolerant of, or with a contraindication to other systemic therapies and *2*) psoriatic arthritis (1).

The clinical manifestations of psoriasis are caused by a dysregulated immune response. Compared with the skin of healthy controls, psoriatic skin contains elevated levels of the four isoforms (A-D) of PDE4, a member of the PDE enzyme family that regulates cyclic adenosine monophosphate levels and immune homeostasis (2). Apremilast interrupts the inflammatory cascade via selective inhibition of PDE4, which is the predominant PDE in most inflammatory cells, including eosinophils, macrophages, dendritic cells, T cells, and monocytes.

Phase III clinical trials (ESTEEM 1 and 2) have shown apremilast to be both efficacious and safe in the treatment of moderate to severe plaque psoriasis (3,4). ESTEEM 1 and 2 showed that apremilast achieved a 75% or greater reduction in Psoriasis Area and Severity Index (PASI-75) scores after 16 weeks of treatment in 33.1% and 28.8% of patients respectively compared with 5.3% and 5.8% for placebo ($P < 0.0001$). This response was maintained by 50% of patients at week 52, and over

75% achieved PASI-70. The most common adverse events (AEs) were diarrhea (17.3%), nausea (15.7%), upper respiratory tract infections (15.5%), nasopharyngitis (14.4%), tension headache (9.0%), and headache (6.3%) Most of the AEs were mild to moderate and did not result in treatment discontinuation. Little, however, has been published on the effectiveness and safety of apremilast in real-life settings and the few studies that exist are characterized by small samples and short follow-up periods.

The main aim of this study was to evaluate the effectiveness and drug survival of apremilast at 1 year (52 weeks) in the treatment of moderate to severe plaque and palmoplantar psoriasis. The secondary aims were to evaluate short- and medium-term effectiveness (at 12, 24, and 36 weeks), treatment-associated AEs, and clinical characteristics of the patients, and to investigate which variables might influence treatment response.

Materials and methods

Study design, patients, and data collection

Twenty hospitals agreed to participate in this retrospective, observational, multicenter study designed by the Spanish Psoriasis Group. The study participants were adults (≥ 18 years) with a diagnosis of moderate to severe plaque psoriasis or non-pustular palmoplantar psoriasis treated with apremilast between March 2016 and March 2018. To qualify for inclusion, patients had to have a follow-up time of at least 52 weeks; censoring, therefore, was not needed for the Kaplan-Meier survival analysis.

The following patient data were extracted from anonymized electronic medical records: age, sex, weight, height, body mass index (BMI) (calculated as kg/m^2 and categorized as normal [18.5 to < 25], overweight [25 to < 30], or obesity [≥ 30]), comorbidities, a personal history of cancer, and previous treatment for psoriasis, including systemic and biologic therapies. Patients were included according to their

predominant form of psoriasis (plaque or palmoplantar). They were prescribed apremilast 30 mg every 12 hours as per the summary of product characteristics and advised to take the tablets with food. Where necessary, dose reductions and adjustments were made in accordance with adverse effects and clinical response.

The study was conducted in accordance with the Declaration of Helsinki on ethical principles for medical research involving human subjects and was approved by the local clinical research ethics committees at Hospital Clínico Universitario de la Princesa (EDT-SIA-2017-01) and Hospital Universitari Germans Trias i Pujol (EDA-APR-2019-01).

Effectiveness

Data on the following variables were obtained from the patients' medical records to assess treatment response among patients with plaque psoriasis: PASI, body surface area (BSA) involvement, physician global assessment (PGA) scores, and Dermatology Life Quality Index (DLQI) scores at baseline (initiation of treatment) and at 12, 24, 36, and 52 weeks for patients with plaque psoriasis. Palmoplantar psoriasis PGA (PPPGA) and DLQI scores were assessed for patients with palmoplantar psoriasis at the same time points. PGA and PPPGA scores were evaluated on a 6-point scale (0=clear, 1=almost clear, 2=mild, 3=moderate, 4=severe and 5= very severe). The primary endpoint for patients with plaque psoriasis was improvement in mean PASI score and percentage of patients who achieved a PASI score of 3 or less (PASI ≤3) at week 52. For patients with palmoplantar psoriasis, the primary endpoint was improvement in mean PPPGA score and percentage of patients who achieved a PPPGA score of 0 or 1 (PPPGA 0/1) at week 52. Secondary outcomes were PASI-50, PASI-75, and PASI-90, and improvements in BSA, PGA, and DLQI scores.

Safety

Data were collected on all serious AEs that might require dose adjustments or lead to treatment discontinuation or interruption and other relevant AEs, such as gastrointestinal problems (nausea, diarrhea, abdominal pain), upper respiratory tract infections, and headache. Reasons for treatment discontinuation were also noted and classified as follows: lack or loss of effectiveness, serious AEs, and other (transfer to another reference hospital, loss to follow-up, skin clearance, etc.).

Statistical analysis

Descriptive statistics were calculated as frequencies and percentages for categorical variables and mean and standard deviation (SD) for quantitative variables. Between-group comparisons for categorical variables were analyzed using the Pearson χ^2 test applied to contingency tables. Mean PASI, BSA, PGA, and DLQI scores at the different sampling points were analyzed by analysis of variance with subsequent Bonferroni correction for pairwise comparison. No substitution methods were used for missing data (as observed). Drug survival was analyzed using Kaplan-Meier survival curves. Drug survival categorized by BMI was analyzed by means of a log-rank test. The statistical analysis was performed using the SPSS software package (version 22.0 for Windows). In all cases a *P* value of less than 0.05 was considered statistically significant.

Results

Demographic and clinical characteristics

Apremilast was used to treat 377 patients (292 patients with plaque psoriasis and 85 with palmoplantar psoriasis) at the 20 participating hospitals. Their clinical and demographic characteristics are summarized in Table 1. The patients (176 men and 201

women) had a mean (SD) age of 57.0 (13.8) years, a mean weight of 78.7 (16.6) kg, a mean BMI of 28.6 (5.6), a mean baseline PASI score of 10.7 (7.0), and a mean PPPGA score of 4.2 (5.2). Previous treatments included conventional systemic therapy (ciclosporin, methotrexate, acitretin, or phototherapy) (75.3%) and biologic agents (21.7%). Seventeen patients received concomitant treatment with phototherapy (n=10), methotrexate (n=6), and acitretin (n=1). None of the patients were treated with apremilast in combination with biology therapy. Thirty percent of patients had one concomitant condition and 17% had two. Thirty-three patients had a past history of hepatitis (hepatitis C in 17 patients, hepatitis B in 13, hepatitis B and C in two, and hepatitis A in one) and almost 25% (93 patients) had a past history of cancer. The two most common cancers were breast cancer (16) and lung cancer (13). Eight patients had a past history of depression.

Effectiveness and safety

Mean PASI score at baseline was 10.7 (7.0) in the plaque psoriasis group. This decreased to 5.4 (5.8) at week 12, 3.6 (3.3) at week 24, and 3.0 (4.2) at week 52. Significant differences were noted at week 12 ($P < 0.05$) (Figure 1a). The relative reductions in mean PASI scores were 49.6%, 66.3%, and 72.0%, respectively. Of the 155 patients still on apremilast after 12 months, 73.6% achieved PASI ≤3 and 41.3 % achieved PASI ≤1 (Figure 1b). In terms of relative PASI improvement by week 52, 77.4% of patients achieved PASI-50, 49.7% PASI -75, and 26.5% PASI-90 (Figure 1c) — data as observed. Improvements in the other variables were also observed at week 52, with significant differences ($P < 0.05$) noted at week 12. Mean affected BSA decreased from 9.6 (7.6) at baseline to 3.1 (4.9) at week 12 and 2.5 (5.3) at week 52. Mean PGA, in turn, decreased from 4.5 (4.0) at baseline to 2.8 (2.9) at month 3 and 1.4 (1.6) at week 52.

In the palmoplantar psoriasis group, mean PPPGA score decreased from 4.2 (5.2) at baseline to 1.3 (1.3) at week 52 (Figure 2a). Again, significant differences were observed at week 12 ($P < 0.05$). All patients had a PPPGA score higher than 1 at baseline, but 36%, 57%, and 83% of patients achieved PPPGA 0/1 by week 12, 24, and 52, respectively (Figure 2b)

Finally, the mean DLQI score of 11.4 (6.0) at baseline fell to 5.2 (5.2) at week 12 ($P<0.05$) and 2.3 (4.0) at week 52.

The overall drug survival rate after 1 year of treatment (without censoring of data in the Kaplan-Meier analysis) was 54.9 % (Figure 3a). Categorized BMI (<25, ≥25-<30, and ≥ 30) was the only variable associated with an increased risk of treatment discontinuation, with drug survival rates of 62.5% for normal-weight patients, 48.5% for overweight patients, and 45% for obese patients (Figure 3b). The hazard ratio after Cox regression model analysis for BMI was 1.2 ($P < 0.05$) after 1 year of follow-up. Non-significant differences were observed for sex, psoriatic arthritis, number of previous biologic drugs, baseline psoriasis severity (PASI score > 10 vs. ≤10), and PASI-75 after 6 months of treatment.

The main reasons for treatment discontinuation were loss of effectiveness (90 patients, 23.9%) and AEs (60 patients, 15.9%) (Table 2). AEs were reported for 177 (47%) of the 377 patients. The most common events were gastrointestinal problems (diarrhea in 44 patients, gastrointestinal intolerance in 21, and nausea in 20), followed by headache (21) and asthenia (12). Diarrhea was the main cause of treatment discontinuation due to AEs (5.6%). Treatment was withdrawn in one patient because of an infection (pneumonia) and four patients stopped treatment because of depression. None of them had a past history of a psychiatric disorder. There were no cases of hepatitis reactivation or cancer recurrence.

Discussion

We have presented the largest series to date (377 patients) of the use of apremilast in a real-life clinical setting.

We observed a drug survival rate of 54.9% at 12 months and a mean survival time of 52 weeks (range, 2–147 weeks). Loss of effectiveness, followed by AEs, was the main reason for treatment discontinuation. Drug survival is the time during which a specific drug remains an adequate option for a given patient (5), and while there is some controversy, it is generally considered to be an indirect marker of a drug's effectiveness and safety. Little has been published on drug survival for apremilast. Papadavid *et al* (6) (50 patients) and Kishimoto *et al* (7) (138 patients) both reported a survival rate of 53.4% at 12 months, which is similar to the rate observed in our series. Lee *et al* (22) (84 patients), in turn, reported that 50.6% of patients were still on apremilast after 3 years, and in this case, mean drug survival was 341 days.

Only obesity (compared with overweight and normal weight) was associated with a lower drug survival rate at 52 weeks. Obesity is known to have a limiting effect on treatment response (8), and Naldi *et al* (9) found BMI to be a predictor of response to systemic therapy. On analyzing the effectiveness of apremilast according to BMI in 37 patients, Vujic *et al* (10) found that none of the patients with a BMI of 30 or higher achieved PASI-75 by week 16, but the differences between obese (n = 6) and non-obese patients (n = 31) were non-significant ($P = 0.1$) . Their sample, however, was small.

The profile of our patients differs to that of patients from the ESTEEM 1 and 2 trials. Apart from the difference in age (57.0 vs. 45–46 years) and previous treatments (75.3% of patients in our series had received conventional systemic therapy vs. 38%–39% in ESTEEM 1 and 2), there was a substantial difference in baseline PASI scores

due mainly to the lack of a washout period in routine clinical practice. Baseline PASI was lower in our study than in ESTEEM 1 and 2 (10.7 [7.0] vs 19–20), explaining why fewer patients in our series achieved PASI-75 in the short term, although they did reach this goal in the later months. This observation suggests that the indication for apremilast is different in everyday practice to in clinical trials, as the patients in the pivotal ESTEEM trials had a very similar profile to that of candidates for biologic therapy. It would therefore seem reasonable to establish treatment goals based on absolute rather than relative PASI scores. In our series, the overall mean PASI score at week 52 was 3, but almost 75% of the patients had PASI ≤ 3 and approximately 40% had PASI ≤ 1. Almost 45% and approximately 50% of patients achieved PASI ≤ 3 in the short and medium term (12 and 24 weeks respectively). These rates are slightly higher than those observed in a post-hoc pooled analysis of data from the ESTEEM trials (31.3%) (11) and APPRECIATE (Apremilast Clinical Treatment Experience in Psoriasis study) (41.8%) (12).

Results in clinical practice also vary widely (6,10,15–19) (Table 3). Outcomes at week 16, for example, range from a 49.5% reduction in mean PASI in our series to a 70.2% reduction in the series by Ighani *et al* (17) and from a PASI-75 response rate of 18.8% described by Viujic *et al* (10) to a rate of 59.3% described by Papapvid *et al* (6).

PPPGA 0/1 was achieved by almost 40% of patients in the palmoplantar psoriasis group at week 12 and by over 80% of patients at week 52. According to a post-hoc analysis of the ESTEEM 1 and 2 trials (427 patients), 46% of patients with PPPGA ≥1 achieved a score of 0 by week 16 versus 25% of those in the placebo group ($P < 0.001$) (13). In the only randomized controlled trial to specifically analyze the effect of apremilast on palmoplantar psoriasis (100 patients), Bissonnette *et al* (14) found no significant differences in PPPGA after 16 weeks' treatment between patients in the

treatment and placebo arms (14% vs. 4%, *P* = 0.1595). Nonetheless, 24% of patients treated with apremilast achieved PPGGA 0/1 by week 32. Apremilast also resulted in an improvement in PASI-75 response rates (22% vs. 8% for placebo, *P* = 0.0499) and DLQI scores (-4.3 [5.1] vs. -0.8 [4.5], *P* = 0.0004).

Although the AE rate was lower in our series (47%) than in the ESTEEM 1 (68%) and 2 (69.3%) trials, a higher proportion of patients discontinued treatment because of AEs in our study (16% vs. 7.3%). It should be noted, however, that the systematic reporting of all AEs within the setting of a clinical trial probably results in higher rates of non-serious events compared with real-world studies. The findings of the LAPIS-PSO study (20), which analyzed 500 patients from real-life clinical scenarios, also suggest that apremilast is associated with a lower overall rate of AEs in routine practice than in clinical trials. The higher discontinuation rates observed in our study may also be explained by the availability of alternative treatments in real-world situations. Similarly to us, Ighani *et al* (21) (208 patients) and Lee *et al* (22) (77 patients) found higher rates of apremilast discontinuation due to AEs (18.8% and 23.4% respectively versus 5.3% in the ESTEEM trials). The main reasons for discontinuation were diarrhea (21) and headache (22).

Finally, it should be noted that some of the patients in our cohort would not have qualified for inclusion in the ESTEEM trials because of their past medical history: hepatitis in 33 cases and cancer in 93. There were no cases of hepatitis reactivation or cancer recurrence following treatment with apremilast. However, given the scarcity of specific studies in these populations, no absolute conclusions can be drawn on the safety of this drug in patients with a history of hepatitis or recurrence.

Our study has some limitations. As in any retrospective study, there are missing or unrecorded data and the evaluation “as observed” may have resulted in an

overestimation of effectiveness. A small number of patients were treated concomitantly with conventional systemic therapy, including phototherapy. We did not include topical treatments in our evaluation of concomitant treatments and cannot therefore rule out that they may have contributed to the results described. Our study, however, also has strengths. It is the largest study to date (377 patients) of the use of apremilast to treat psoriasis in real-world settings and the first to evaluate this drug in the routine treatment of palmoplantar psoriasis. We also analyzed outcomes over a follow-up period of 52 weeks. We believe that apremilast may be an alternative for treating moderate psoriasis with a PASI score of around 10 and palmoplantar psoriasis. Although the drug has a good safety profile, a substantial percentage of patients in our series stopped treatment due to AEs.

Acknowledgements

We would like to thank José Aguilera for his assistance with the statistical analysis.

LEGENDS

Figure 1a. Mean PASI after 12, 24, 36, and 52 weeks of treatment (a). Asterisk shows significant differences between mean baseline values and values for the other sampling points after one-way analysis of variance.

Figure 1b.Number of patients with a PASI score of ≤ 1, > 1 to ≤3, and ≥ 3 after 12, 24, 36, and 52 weeks of treatment (b). The number and percentage of patients at each sampling point is shown above each column.

Figure 1c. Number of patients (cumulative data) who achieved PASI < 50, 50, 75 and 90, after 12, 24, 36, and 52 weeks of treatment (c). The number and percentage of patients at each sampling point is shown above each column.

Figure 2a. Mean physician global assessment (PGA) score for patients with palmoplantar psoriasis after 12, 24, 36, and 52 weeks of treatment (a). Asterisk shows significant differences between mean baseline values and values for the other sampling points after one-way analysis of variance.

Figure 2b. Number of patients who achieved a PPPGA score of 0 or 1 after 12, 24, 36, and 52 weeks of treatment (b). The number and percentage of patients at each sampling point are shown above each column.

Figure 3. Overall drug survival (a) and drug survival according to body mass index (BMI) (b).

References

1. Apremilast SPC. Database of medicines of the European Medicines Agency. European Medicines Agency. URL www.aemps.es/cima

2. Pincelli C, Schafer PH, French LE, Augustin M, Krueger JG. Mechanisms Underlying the Clinical Effects of Apremilast for Psoriasis. J Drugs Dermatol. 2018 Aug 1;17(8):835–40.

3. Papp K, Reich K, Leonardi CL, Kircik L, Chimenti S, Langley RGB, 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 Jul;73(1):37–49.

4. Paul C, Cather J, Gooderham M, Poulin Y, Mrowietz U, Ferrandiz C, 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):1387–99.

5. Carrascosa JM, Notario J. Supervivencia en terapia biológica. ¿Sabemos a qué nos referimos? ¿ Podemos usarla? Actas Dermosifiliogr. 2014 Oct;105(8):729–33.

6. Papadavid E, Rompoti N, Theodoropoulos K, Kokkalis G, Rigopoulos D. Real-world data on the efficacy and safety of apremilast in patients with moderate-to-severe plaque psoriasis. J Eur Acad Dermatology Venereol. 2018;32(7):1173–9.

7. Kishimoto M, Komine M, Kamiya K, Sugai J, Ohtsuki M. Drug survival of apremilast in a real-world setting. J Dermatol. 2019 Jul 10;46(7):615–7.

8. Carrascosa JM, Rocamora V, Fernandez-Torres RM, Jimenez-Puya R, Moreno JC, Coll-Puigserver N, et al. Obesidad y psoriasis: naturaleza inflamatoria de la obesidad, relación entre psoriasis y obesidad e implicaciones terapéuticas. Actas Dermosifiliogr. 2014 Jan;105(1):31–44.

9. Naldi L, Addis A, Chimenti S, Giannetti A, Picardo M, Tomino C, et al. Impact of body mass index and obesity on clinical response to systemic treatment for psoriasis: Evidence from the psocare project. Dermatology. 2008;217(4):365–73.

10. Vujic I, Herman R, Sanlorenzo M, Posch C, Monshi B, Rappersberger K, et al. Apremilast in psoriasis – a prospective real-world study. J Eur Acad Dermatology Venereol. 2018;32(2):254–9.

11. Iversen L, Paul C, Cirulli J, Chen R, Andersson C YP. Efficacy of apremilast versus placebo in patients with lower plaque psoriasis disease activity: Results of a pooled post hoc analysis of the esteem 1 and 2 trials.Proceedings of the 26th Congress of the EADV; 2017 Sep 13-17; Geneva, Switzerland.

12. M A. Real World Experience with Apremilast: Analysis of 250 patients from the APPRECIATE study with Psoriasis in Difficult-to-treat Areas. Presented at: the 2019 AAD Annual Meeting; March 1–5, 2019; Washington, DC. Poster [9776].

13. Bissonnette R, Pariser DM, Wasel NR, Goncalves J, Day RM, Chen R, et al. Apremilast, an oral phosphodiesterase-4 inhibitor, in the treatment of palmoplantar psoriasis: Results of a pooled analysis from phase II PSOR-005 and phase III Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis (ESTEEM) clinical trials in patients with moderate to severe psoriasis. J Am Acad Dermatol. 2016 Jul 1;75(1):99–105.

14. Bissonnette R, Haydey R, Rosoph LA, Lynde CW, Bukhalo M, Fowler JF, et al.

Apremilast for the treatment of moderate-to-severe palmoplantar psoriasis: results from a double-blind, placebo-controlled, randomized study. J Eur Acad Dermatology Venereol. 2018;32(3):403–10.

15. Mayba JN, Gooderham MJ. Real-world experience with apremilast in treating psoriasis. J Cutan Med Surg. 2017;21(2):145–51.

16. Wong TH, Sinclair S, Smith B, Fraser C, Morton CA. Real-world, single-centre experience of apremilast for the treatment of moderate to severe psoriasis. Clin Exp Dermatol. 2017 Aug;42(6):675–6.

17. Ighani A, Georgakopoulos JR, Zhou LL, Walsh S, Shear N, Yeung J. Efficacy and Safety of Apremilast Monotherapy for Moderate to Severe Psoriasis: Retrospective Study. J Cutan Med Surg. 2018 May 26;22(3):290–6.

18. Kishimoto M, Komine M, Hioki T, Kamiya K, Sugai J, Ohtsuki M. Real-world use of apremilast for patients with psoriasis in Japan. J Dermatol. 2018;(July):1345–8.

19. Ohata C, Ohyama B, Kuwahara F, Katayama E, Nakama T. Real-world data on the efficacy and safety of apremilast in Japanese patients with plaque psoriasis. J Dermatolog Treat. 2018 Oct 8;1–4.

20. Reich K, Bomas S, Korge ; Bernhard, Manasterski M, Schwichtenberg U, Altmann M, et al. First 'Real-World' Insights on Apremilast Therapy for Patients With Plaque Psoriasis From the LAPIS-PSO Study: An Interim Analysis.

21. Ighani A, Georgakopoulos JR, Shear NH, Walsh S, Yeung J. Short-term reasons for withdrawal and adverse events associated with apremilast therapy for psoriasis in real-world practice compared with in clinical trials: A multicenter

retrospective study. J Am Acad Dermatol. 2018 Apr;78(4):801–3.

22. Lee EB, Amin M, Egeberg A, Wu JJ. Adverse events associated with apremilast use and withdrawal for psoriasis in a real-world setting. J Eur Acad Dermatology Venereol. 2018 Oct;32(10):e393–4.

Table 1. Baseline Characteristics of Study Patients*

Characteristic	n= 377
Male	176 (46.7)
Age, mean (SD) years	57.0 (13.8)
Weight, mean (SD) kg	78.7 (16.6)
Height, mean (SD) cm	166.8 (8.5)
Body mass index, mean (SD) kg/m^2 (n = 261)	28.6 (5.6)
<25	85 (32.6)
≥25 to <30	99 (37.9)
≥30	77 (29.5)
Baseline PASI, mean (SD) (n = 292)	10.7 (7.0)
Baseline BSA, mean (SD) (n = 206)	9.6 (7.6)
Baseline PGA, mean (SD) (n = 194)	5.2 (4.1)
Baseline PPGA, mean (SD) (n = 85)	4.2 (5.2)
Baseline DLQI , mean (SD) (n = 184)	11.4 (6.19)
Type of psoriasis	
Plaque	292 (77.5)
Palmoplantar	85 (22.5)
Psoriatic arthritis	41 (10.9)
Previous conventional systemic therapy	
0	93 (24.7)
1	111 (29.4)
2	95 (25.2)
3	47 (12.5)
≥ 4	31 (8.2)
Previous biologic therapy	
0	295 (78.3)
1	32 (8.6)
2	38 (10)
3	8 (2)
≥ 4	4 (1.2)
Number of comorbidities	
0	105 (27.9)
1	113 (30)
2	64 (17)
3	43 (11.4)
≥ 4	52 (13.8)

Comorbidities	
Hypertension	84 (22.3)
Hyperlipidemia	79 (20.9)
Hypercholesterolemia	12 (3.2)
Diabetes mellitus	47 (12.5)
Metabolic syndrome	16 (4.2)
Liver disease	33 (8.6)
Hypothyroidism	9 (2.4)
Lung cancer	20 (3.2)
Latent tuberculosis	19 (5.0)
Hepatitis	33 (8.6)
Cancer in personal history	92 (24.5)
Depression	8 (1.3)
Other comorbidities affecting < 8 patients	196 (31.6)

Data expressed as number (%) of patients unless otherwise specified.

Table 2. Causes of apremilast discontinuation

0–3 months					
Total patients	377	Adverse events	30	Adverse event	
		Loss of effectiveness	17	Diarrhea	10
Treatment interruption, No. of patients	52	Patient decision	3	Digestive intolerance	10
		Contraindications	1	Headache	7
		Other	1	Nausea	5
				Epigastric pain	3
				Myalgia	3
				Dyspnea, dysphagia	2
				Asthenia	2
				Cutaneous eruption	1
				Depression	1
				Progression of lymphoma	1
				Nervous tremor	1
4-6 months					
Total patients	325	Adverse events	18	Adverse event	
		Loss of effectiveness	43	Gastric intolerance	6
Treatment interruption, No. of patients	70	Disease remission	1	Diarrhea	5
		Poor adherence	1	Headache	4
		Other	7	Asthenia	3
				Depression	2
				Weight loss	1
				Pneumonia	1
				Breast cancer	1
				Nausea	1
7–9 months					
Total patients	255	Adverse event	9	Adverse event	
		Loss of effectiveness	25	Diarrhea	4
Treatment interruption, No. of patients	35	Patient decision	1	Epigastric pain	2
				Urticaria	2
				Headache	1
				Leg swelling	1
				Digestive intolerance	2
				Anorexia	1
				Depression	1

10–12 months					
Total patients	220	Adverse event	3	Adverse event	
		Loss of effectiveness	5	Diarrhea	2
Treatment interruption, No. of patients	11			Digestive intolerance	2
		Disease remission	1		
		Other	2	Tachycardia	1
Survival after 52 weeks	209			Asthenia	1

Table 3. Demographic characteristics of patients and effectiveness and safety outcomes for apremilast in real-world settings.

	Our series (n=377)	Mayba et al (n=81)	Vujic et al (n=48)	Wong et al (n=59)	Ighani et al (n=34)	Papavid et al (n=50)	Kishimoto et al (n=44)	Ohata et al (n=50)
Age, mean (SD) years	57.0 (13.8)	49.0 (12.9)	51 (21–77)	50	53.5 (12.7)	55.0 (25-82)	58.5 (14.9)	58.6 (16.1)
Male, *n* (%)	176 (47)	36 (44)	33 (69)	26 (44.1)	20 (58.8)	35 (70)	31 (70.5)	30 (60)
Mean PASI , *n* (SD or range)	10.3 (7.1)*	NA	10.7 (4.7)	16.1 (10.1–39.2)	13.1 (6.3)	10.8 (9–49)	NA	10.1 (8.3)
Previous systemic therapy, *n* (%)	256 (75.3)	54 (67)	41 (85.4)	NA	21 (61.8)	26/33 (78.8)	29 (65.9)	15 (30)
Previous biologic therapy, *n* (%)	76 (21.7)	15 (19)	3 (6.3)	8 (13.5)	4 (11.8)	7/33 (21.2)*		5 (10)
PASI-75 week 12–16, *n* (%)	58 (24.4)*	NA	9 (18.8)	28 (47.5)	19 (55.9)	16/27 (59.3)	NA	14/42 (33.3)**
Mean reduction in PASI week 12–16, *n* (%)	49.6%*	NA	NA	65.2	70.2	60.2	NA	47.6 **
Adverse events, *n* (%)	177 (47)	50 (61.7)	31 (64.6)	27 (46)	23 (67.6)	15 (30)	55.9	38 (76)
Drug survival rate,%	54.9 (week 52)	75 (week 52)	50 (12.5 weeks)	NA	NA	67.6 (week 24) and 53.4 (week 52)	NA	70 (28 week)
Discontinuation due to lack or loss of efficacy, *n* (%)	90/377 (23.9)	5 (6.2)	18 (37.5) primary failure	16 (27.1)	1 (2.9)	7 primary failures (14) 1 secondary failure (2)	9 (20.5)	2 primary failures (12.5)

			5 (10.4) secondary failure					6 secondary failures (37.5)
Discontinuation due to adverse events, *n* (%)	60/377 (15.9)	13/81 (16)	2/48 (4.2)	3/59 (5.1)	5/34 (14.7)	6/50 (12)	4 (9)	3/50 (6%)

NA, not available; PASI, Psoriasis Area Severity Index; PASI-75, 75% or greater reduction in PASI score; SD, standar deviation

*Based on 292 patients with plaque psoriasis

** Values achieved at the end of the study.