Real-world treatment patterns, patient-reported outcomes, and effectiveness of flexible-dosing etanercept in patients with plaque psoriasis in Greece

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Abstract

Etanercept is approved for continuous or intermittent use and flexible dosing in plaque psoriasis (PsO). The objectives of this study were to investigate real-world treatment patterns with etanercept in Greek adults with moderate-to-severe PsO. This non-interventional multicenter study included a retrospective-to-prospective (RP) cohort, previously treated with etanercept for ≥24 months and followed for an additional 6 months, and a biologic-naive, prospective-only (PO) cohort, followed for 6 months after treatment initiation. Parameters assessed included Psoriasis Area and Severity Index (PASI), percentage of body surface area (BSA) affected, Dermatology Life Quality Index (DLQI), and adverse events (AEs). This study enrolled 123 patients (RP, n = 56; PO, n = 67), who mostly adhered to continuous treatment (RP, 68%; PO, 95%). The two cohorts had similar mean baseline-to-endpoint decreases in PASI (-9.5 vs. -10.1) and BSA (-11.9 vs. -12.3). The PO-CTP population had a mean DLQI baseline-to-endpoint score decrease of -5.8, which was statistically significant and clinically meaningful. Flexible treatment regimens are of interest, as environmental factors (e.g., positive effects of sunlight and exacerbations in winter and times of stress) can affect PsO.

In July 2009, etanercept (ETN) became the only biologic approved for PsO with an indication for both continuous and intermittent use; and it can be used in both pediatric and adult patients. ETN also has a flexible-dosing option, with dosage adjusted according to patients’ preferences. Patients are routinely prescribed 25 mg twice weekly (BIW), 50 mg once weekly (QW), or 50 mg BIW for the first 12 weeks of treatment, followed by 25 mg BIW or 50 mg QW thereafter. When treatment is interrupted and later re-started, dosing is resumed at 25 mg BIW or 50 mg QW. Interim ETN dosing has been shown to be effective and well tolerated in patients with PsO. In clinical trials, intermittent use of ETN was not associated with loss of efficacy upon re-starting treatment and did not adversely affect improvements in patient-reported outcomes (PROs). Both continuous and intermittent ETN therapy are well-tolerated long-term and result in improvements of secondary disease manifestations, such as joint pain and nail psoriasis. Real-world studies have also demonstrated the effectiveness and safety of intermittent treatment with ETN in patients with PsO.

A 2010 epidemiological study of PsO in Greece found significantly lower rates of disease exacerbation during the summer, when sun exposure could alleviate the symptoms, that Greek patients with PsO could take advantage of flexible ETN treatment (i.e., discontinuous treatment in the summer). However, data from Greece on the impact of flexible ETN dosing on PsO are very limited. Such data would be of interest to both patients and physicians.

This study was designed to investigate real-world ETN treatment patterns among adult patients with PsO in Greece.

Materials and methods

This study was performed in accordance with the Declaration of Helsinki and was approved by the Institutional Review Boards at each study site: Hospital of Venereal and Skin Disease “Andreas Sygros” 5, Ionos Dragoumi str, Athens PC

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Data availability: Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual anonymized participant data. See https://www Pfizer.com/science/clinical-trials/trial-data-and-results for more information.

Ethics approval: This study was performed in accordance with the Declaration of Helsinki and was approved by the Institutional Review Boards at each study site: Hospital of Venereal and Skin Disease “Andreas Sygros” 5, Ionos Dragoumi str, Athens PC 16121 (reference number 968); Thessaloniki Hospital of Venereal and Skin Disease, 124 Deflon str, Thessaloniki, PC 54643 (2024 con/411 [5d con/356 subj]); University General Hospital “Attiko”, 1 Ramntr str, Hadari PC 14262 (16d con); General Hospital of Athens “Evvagelismos” 45-47 Ypsilantou str, PC 10676 Athens (23769); University General Hospital of Larisa Mezourlo, PC 41110 Larisa (18997); 401 General Military Hospital of Athens 138, Mesogeion Avenue and Katseli, PC 11525, Athens (3). Informed consent was obtained prior to any study-related procedures.

Consent to participate: Patients in this study were enrolled after providing informed consent.

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Patient eligibility and study design

This was a non-interventional, multicenter cohort study of ETN-treated patients with moderate-to-severe PsO in Greece, conducted in a real-world setting of eight major outpatient dermatology clinics. The study included a retrospective portion, intended to capture long-term treatment utilization data, and a prospective portion, designed to collect information on quality of life (QoL) and patient-reported outcomes unlikely to be captured in pre-existing patient files (Figure 1).

To participate in the study, adult patients (aged ≥18 years) were eligible for ETN treatment and willing and able to inject ETN. Key exclusion criteria were pregnancy, breastfeeding, and treatment with an experimental drug or another biologic agent while receiving ETN. Patients were prescribed ETN at the discretion of their healthcare provider (HCP) according to the approved ETN summary of product characteristics (SmPC) and as per usual clinical practice. Any decision to prescribe ETN was made independently of this study and prior to patient enrollment. Patients were enrolled after providing informed consent.

Patients could be included in the retrospective-to-prospective (RP) or the prospective-only (PO) cohort. Patients were eligible for inclusion in the RP cohort if they were being treated with ETN at the time of study initiation, had been treated with ETN for ≥24 months (continuously or intermittently), and had medical records available on file. Patients were eligible for inclusion in the PO cohort if they were biologic-naïve, and if the decision to initiate treatment with ETN had already been taken. Treatment in the PO cohort was initiated at study baseline. Patients in both cohorts were followed prospectively for 6 months after study baseline (Figure 1).

Within each cohort, patients were further categorized into those receiving continuous (CTP) or intermittent treatment pattern (ITP), depending on the duration of ETN discontinuation during the study period (CTP, 15–29 days; ITP, ≥30 days). Discontinuation due to an adverse event (AE) for ≥30 days in duration was considered temporary.

Study objectives

The primary objective was to describe real-life treatment patterns for adult patients with PsO in Greece receiving continuous or intermittent ETN treatment in a flexible-dosing environment, where HCPs can discontinue a patient’s treatment based on their symptoms. Secondary objectives were to capture baseline demographic and disease-related characteristics of Greek patients, to assess clinical parameters (Psoriasis Area Severity Index [PASI] and body surface area [BSA]), and to investigate the impact of short-term ETN treatment (6 months) on patients’ QoL using the Dermatology Life Quality Index (DLQI) questionnaire.

Data collection

Patient data were collected from July 16th 2009, following the addition of the intermittent treatment option in the ETN SmPC, to December 2015. Retrospective data were collected at ETN initiation, at every dosing change, or at least every 6 months for ≥2 years, meaning that the timing of visits varied between patients in the retrospective part of this study (Figure 1). The desirable minimum number of retrospective visits was four. Demographic data were collected at study baseline (Visit n for the RP cohort/Visit 1 for the PO cohort). Prospective data were collected at three pre-specified time points: week 0 (Visit n for the RP cohort/Visit 1 for the PO cohort), week 12, and week 24.

Statistical methodology

The full analysis set (FAS) consisted of patients in the RP cohort who had been treated with ETN for ≥24 months before study baseline, had data available for ≥2 retrospective visits, and had ≥1 prospective visit post-baseline, as well as patients in the PO cohort who had been treated with ≥1 dose of ETN and had data available for ≥1 study visit post-baseline. The safety analysis set consisted of all patients who had been treated with ≥1 dose of ETN during the study, regardless of cohort. Owing to the different time periods over which data were available for collection, no direct comparisons could be made between the RP and PO cohorts, with the exception of initial disease characteristics. Within each cohort and population, parameters assessed included clinical measures (PASI and BSA), PROs (DLQI), and safety (AEs), provided sufficient data were available to allow for meaningful assessments. Descriptive statistics were summarized for all outcomes. P-values for differences between demographic and baseline clinical characteristics were calculated using a t-test for continuous variables and chi-squared test for categorical variables. Changes from the start of treatment in PASI, BSA, and DLQI to pre-specified study visits were assessed using the paired t-test. Missing baseline values were imputed using values prior to the baseline visit within 4 weeks for the RP cohort. There was no adjustment for multiple hypothesis testing. Missing values for any other visits were not imputed. For the DLQI, a sample size of 30 patients was calculated as sufficient, assuming 90% power and 20% dropout rate, to detect a statistically significant difference (assuming a meaningful clinical difference in overall DLQI score of 5 points from initial visit to study end).

Figure 1. Study design.
Results

Demographics and baseline clinical characteristics

Overall, 123 patients were enrolled (SAS; RP, n=56; PO, n=67; Table 1). Initial PASI, BSA, and DLQI scores were documented at the start of ETN treatment (Retro Visit 1 the RP cohort; Visit 1 for the PO cohort) (Figure 1). Scores were not available for all patients in the RP cohort as these data were collected retrospectively. At the time of ETN initiation, there were no significant between-cohort differences in clinical measures. However, patients in the RP cohort were older (mean ± standard deviation [SD]: 50.8±12.1 years) than those in the PO cohort (45.1±13.9 years; p=0.020). At study baseline, mean ± SD ages were 55.8±12.2 years and 45.1±13.9 years, respectively (p<0.001; Table 1).

Table 1. Patient and disease characteristics 1) at ETN initiation, 2) at study baseline, or 3) throughout study (SAS).

| Characteristic                  | RP cohort (SAS) | PO cohort (SAS) | p-value* |
|--------------------------------|----------------|----------------|----------|
| Age, years, mean±SD            | Retro visit 1  | Visit 1        |          |
| 50.8±12.1                      | 45.1±13.9      | 0.020          |
| Initial PASI score, mean±SD    | n = 30         |                |          |
| 13.5±9.2                       | 15.0±10.6      | 0.502          |
| Initial BSA score, %, mean±SD  | n = 11         |                |          |
| 14.0±9.5                       | 15.8±14.4      | 0.693          |
| Initial DLQI score, mean±SD    | n = 4          |                |          |
| 10.0±6.8                       | 9.9±6.7        | 0.966          |
| Time since PsO diagnosis, years, mean±SD | Visit 1 |                |          |
| 16.9±12.1                      | 14.0±11.1      | 0.176          |
| Previous PsO treatment, n (%)  |                |                |          |
| Topical steroid                | 43 (76.8)      | 60 (89.6)      | 0.056    |
| Cyclosporine                   | 37 (66.1)      | 44 (65.7)      | 0.963    |
| Vitamin D analogs              | 27 (48.2)      | 35 (52.2)      | 0.657    |
| Methotrexate                   | 21 (37.5)      | 25 (37.3)      | 0.983    |
| Acitretin                      | 12 (21.4)      | 9 (13.4)       | 0.241    |
| Comorbidities, current, n (%)  |                |                |          |
| Hypertension                   | 18 (32.1)      | 20 (29.9)      | 0.784    |
| PsA                            | 17 (30.4)      | 10 (14.9)      | 0.039    |
| Hyperlipidemia                 | 12 (21.4)      | 6 (9.0)        | 0.051    |
| Diabetes mellitus              | 8 (14.3)       | 9 (13.4)       | 0.891    |
| Dislipidemia                   | 1 (1.8)        | 7 (10.4)       | 0.052    |
| Latent tuberculosis            | 3 (5.4)        | 4 (6.0)        | 0.884    |
| Throughout study               |                |                |          |
| Concomitant medication used, n (%) | 47 (83.9) | 42 (62.7)      |          |
| Methotrexate                   | 18 (32.1)      | 12 (17.9)      | 0.967    |
| Isoniazid                      | 12 (21.4)      | 10 (14.9)      | 0.349    |
| Folic acid                     | 13 (23.2)      | 8 (11.9)       | 0.098    |
| Cyclosporine                   | 5 (8.9)        | 7 (10.4)       | 0.777    |
| Metformin                      | 8 (10.7)       | 6 (9.0)        | 0.743    |

*p-values were not calculated for characteristics collected at study baseline or throughout the study, as the populations were not comparable (RP – ETN treatment for ≥24 months, PO – biologic naive). For the RP cohort, not all clinical/QoL data from time of ETN initiation were available for all patients. Study baseline was Visit n (for the RP cohort)/Visit 1 (for the PO cohort); BMI body mass index, BSA body surface area, DLQI Dermatology Quality of Life Index, ETN etanercept, PASI Psoriasis Area and Severity Index, PO prospective only, SAS safety analysis set, RP retrospective-to-prospective, SD standard deviation.

Table 1. Patient and disease characteristics 1) at ETN initiation, 2) at study baseline, or 3) throughout study (SAS).
tive evaluation (Visit 1), among 56 patients overall with available data, no patients in the CTP population and 11% of patients in the ITP population were receiving >50 mg/week ETN.

In the PO cohort, patients were monitored for a maximum period of 24 weeks, limiting opportunities to change dose or take a treatment holiday. Weekly mean ETN doses were nominally higher for the ITP population, but the low number of patients in this population precludes any meaningful comparisons. No patient in this cohort received a dose of ETN <50 mg/week.

Impact of treatment patterns on ETN effectiveness, QOL, and safety

In the RP cohort, PASI and BSA data were available for 30 and 11 patients, respectively. For the CTP and ITP populations, mean ± standard error of the mean (SE) decreases in PASI from ETN initiation to study end (over ≥30 months) were similar for the CTP and ITP populations (-9.8±2.2 [p<0.001 versus initial score] and -8.9±1.8 [p=0.001], respectively). Greater proportions of CTP versus ITP patients achieved PASI 50/75/90 by study end (Figure 2A). Mean ± SE changes in BSA scores from ETN initiation to study end for the CTP and ITP populations were similar (-12.0±3.4 vs -11.5±8.5). Insufficient BSA data were available for statistical assessment.

In the PO cohort, PASI and BSA data were available for 64 patients, 95% of whom were in the CTP population. The low number of patients in the ITP population (n=3) precluded comparisons with the CTP population. Mean ± SE PASI and BSA scores overall were 15.5±1.3 (n=64) and 16.1±1.8 (n=64) at Visit 1, decreasing to 15.5±1.3 (n=64) and 7.1±1.0 (n=64) at Visit n+12 and study end, respectively, although the ITP population was too small (n=3) for meaningful statistical or clinical assessments. The CTP population had a mean ± SE change in PASI score significantly decreased to study end of -5.8±1.0, which was both statistically significant (p<0.001) and clinically meaningful.

Treatment-emergent AEs were observed in 58.9% (n=33) and 26.9% (n=18) of patients in the RP and PO cohorts, respectively (Table 3). In the RP cohort, the proportion of patients in the ITP population reporting a treatment-emergent AE was more than double that of the CTP population, and a four-fold higher proportion of patients in the ITP population experienced dose reductions or temporary discontinuations due to AEs compared with the CTP population. General disorders and administration site conditions were experienced by 7.1% and 14.9% of patients in the RP and PO cohorts, respectively.

Table 2. Treatment patterns.

| Parameters | Total population (N=64) | CTP (N=38) | ITP (N=26) | Total population (N=64) | CTP (N=18) | ITP (N=26) |
|------------|------------------------|------------|------------|------------------------|------------|------------|
| Weekly ETN dose, mg, mean ± SD* | 58.5±12.2 | 55.0±9.0 | 65.8±15.0 | 77.8±10.7 | 77.6±10.6 | 82.7±15.0 |
| Weekly re-starting ETN dose, mg, mean ± SD* | - | 75.1±23.1 | - | - | 66.7±28.9 |
| Patients with ≥1 dose increases, n (%)* | 20 (35.7) | 6 (15.8) | 14 (77.8) | 2 (3.1) | 1 (1.6) | 1 (33.3) |
| Time to increase in ETN dose, weeks, mean ± SD* | 79.7±22.7 | 121.0±122.8 | 61.9±75.1 | 12.0±0.0 | 12.0±0.0 | 12.0±0.0 |
| Patients with ≥1 dose decreases, n (%)* | 3 (5.4) | 2 (5.3) | 1 (5.6) | 0 | - | - |
| Time to decrease in ETN dose, weeks, mean ± SD* | 153.7±26.5 | 138.5±5.0 | 184±0.0 | - | - | - |

*The standard authorized dose for ETN is either 25 mg BIW or 50 mg QW. ETN 50 mg BIW could be used for only 12 weeks but, then, it should be reduced to standard dose; otherwise, the dose is considered increased after 12 weeks. The dose at re-start treatment should be the standard dose; if it is higher, the dose is considered as increased. A similar definition is used for decrease in dose. Data were calculated across the entire study period. BIW twice weekly, CTP continuous treatment pattern, ETN etanercept, FAS full analysis set, ITP intermittent treatment pattern, PO prospective only, QW once weekly, RP retrospective-to-prospective, SD standard deviation.
Table 3. Treatment-emergent adverse events (SAEs).

| Overall | Total N=123 | RP cohort | CTP N=38 | ITP N=18 | Total N=67 | PO cohort | CTP N=64 | ITP N=3 |
|---------|-------------|-----------|----------|----------|------------|-----------|----------|--------|
| TEAEs, n | 115 | 81 | 35 | 46 | 34 | 26 | 8 |
| Patients with AEs, n (%) | 51 (41.5) | 33 (59.8) | 16 (42.1) | 17 (94.4) | 18 (26.9) | 16 (25.0) | 2 (66.7) |
| Patients with SAEs, n (%) | 3 (2.4) | 2 (3.6) | 1 (2.6) | 1 (5.6) | 1 (1.5) | 1 (1.6) | 0 |
| Patients discontinuing due to AEs, n (%) | 8 (6.6) | 2 (3.6) | 1 (2.6) | 1 (5.6) | 6 (9.0) | 6 (9.4) | 0 |
| Patients with dose reductions or temporary discontinuations due to AEs, n (%) | 25 (20.3) | 21 (37.5) | 7 (18.4) | 14 (77.8) | 4 (6.0) | 4 (6.3) | 0 |

Number of patients reporting

|                          | Overall | RP cohort |
|--------------------------|---------|-----------|
| Off-label use (dose that does not correspond to product label) | 24 (19.5) | 21 (37.5) |
| Upper respiratory tract infection | 7 (5.7) | 6 (10.7) |
| Ineffective drug | 6 (4.9) | 2 (3.6) |
| Overdose | 4 (3.3) | 4 (7.1) |
| Respiratory tract infection | 3 (2.4) | 3 (5.4) |
| Gamma-glutamyltransferase increased | 3 (2.4) | 1 (1.8) |

Medical Dictionary for Regulatory Activities v19.0 coding dictionary applied. AEs adverse events, CTP continuous treatment pattern, ITP intermittent treatment pattern, PO prospective only, RP retrospective-to-prospective, SAEs serious adverse events, SAS safety analysis set, TEAEs treatment-emergent adverse events.

Discussion

This is the first real-world study of ETN treatment patterns in patients with PsO in Greece in patients under continuous or intermittent treatment. No major differences in effectiveness or safety of ETN were noted between the CTP and ITP populations of the RP. Patients in the PO cohort underwent a maximum of three treatment cycles, limiting opportunities to change dose or take a treatment holiday; therefore, very few patients in this cohort received intermittent treatment and it was not possible to draw meaningful conclusions regarding continuous versus intermittent dosing in this cohort.

Since 2008, six EU clinical practice-based real-world data (RWD) studies of ETN treatment patterns, which included continuous and intermittent treatment, have been published including three retrospective analyses from Spain.15-17 Similar to our findings, none of these studies found a difference in effectiveness or safety of continuous versus intermittent treatment with ETN, despite differences in trial design and patient selection.15,16 Similarly, prospective studies from Germany18 and Spain19 reported no significant differences between effectiveness19-20 or PROs14 under CTP or ITP, despite study design differences, including different definitions of CTP and ITP.

This general agreement in outcomes from real-world assessments is interesting in the context of less consistent evidence across prospective, interventional clinical trials: some studies comparing continuous and intermittent ETN regimens in patients with PsO found evidence of a greater benefit of continuous treatment,5,9,12 but others did not.7,9,11,13 This study has limitations inherent to its observational and non-randomized design. In addition, data interpretation in the RP cohort is limited by the lack of clinical records during the retrospective period (in particular, DLQI data). Analysis of the PO cohort is limited by the low number (n = 3) of patients who received intermittent treatment in this cohort. Finally, there may have been a site selection bias since all participating sites were public or academic institutions.

Conclusions

Our data suggest that ETN is an effective and safe option for management of PsO in Greece, both as a continuous and intermittent treatment option.

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