

Annual biologic treatment cost for new and existing patients with moderate to severe plaque psoriasis in Greece

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Aim: The aim of the present study was to estimate the annual per-patient cost of treatment with adalimumab, etanercept, infliximab, and ustekinumab by response status for new and existing patients with moderate to severe psoriasis in Greece.

Methods: An economic analysis was developed from a national health care perspective to estimate the direct cost of treatment alternatives for new and existing patients within a 1-year time horizon. The model included drug acquisition and administration costs for responders and nonresponders. Real-world treatment pattern and resource use data were extracted through nationwide field research using telephone-based interviews with a representative sample of dermatologists. Unit costs were collected from official sources in the public domain.

Results: The mean annual cost of treatment for new patients who responded (or did not respond) to treatment was as follows: adalimumab €10,686 (€3,821), etanercept €10,415 (€3,224), infliximab €14,738 (€7,582), and ustekinumab €17,155 (€9,806). For existing patients the mean annual cost was €9,916, €9,462, €12,949, and €17,149, respectively. Results did not change significantly under several one-way sensitivity and scenario analyses.

Conclusion: Under the base-case scenario, the cost of treatment with etanercept is lower than that of the other biological agents licensed for moderate to severe plaque psoriasis in Greece, for both new and existing patients, irrespective of response status.

Keywords: adalimumab, etanercept, infliximab, ustekinumab, economic evaluation, biologics

Introduction

Psoriasis is a chronic, relapsing, immune-mediated inflammatory disorder, whose most common form, plaque psoriasis (PP), accounts for up to 85%–90% of cases, and is characterized by erythematous scaly patches.^{1,2} Psoriasis affects approximately 2%–3% of the total population on a worldwide scale.³ Nonetheless, its prevalence varies among different populations; a number of factors have been proposed to account for this variability, including climate, genetic susceptibility, and environmental antigen exposure.⁴ The latest data indicate that the prevalence of psoriasis in adults ranges from 0.91% (US) to 8.5% (Norway), while the reported incidence varies from 78.9/100,000 person-years (US) to 230/100,000 person-years (Italy).⁵ The estimated prevalence of the disease in Greece is 2.0%–2.8%.^{6–9}

The severity of PP may vary from a few small, localized patches to coverage of most of the skin and is often associated with cosmetic problems as well as a number of comorbidities, altogether impacting the health-related quality of life of sufferers.^{1,2} While

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considered a nonlife-threatening chronic disease, psoriasis imposes a sizeable social and financial burden to patients, health care systems, and society overall.¹⁰ Patients suffering from psoriasis frequently miss working hours and may experience diminished productivity associated with increased symptom severity or comorbidities.^{11–13} For instance, in the US, Americans with psoriasis lose approximately 56 million working hours, and \$2–\$3 billion per annum is spent on treatment of the disease.¹⁴ Moreover, it has been estimated that the 3-month drug cost per responder is approximately \$10,000–\$13,000 (cost refers to 2011 US\$).¹⁵

Hence, it makes sense to manage psoriasis not only from a humanistic but also from an economic perspective as well. To therapeutically address the significant morbidity and burden associated with psoriasis, several scientific guidelines were developed in Europe and elsewhere.^{16–20} In accordance with the existing guidelines, systemic agents, such as the conventional therapies (cyclosporine, methotrexate, retinoids, and phototherapy) and the biologic agents, including the tumor necrosis factor (TNF) antagonists (adalimumab, etanercept, and infliximab), as well as the interleukin 12/23 antagonist ustekinumab, are recommended for the treatment of moderate to severe PP. Biologics represent established treatment options for moderate to severe psoriasis. The efficacy of these agents is well known and has been previously assessed in the relevant literature, while their use has improved the long-term management of the disease and patient outcomes.^{21–31}

Cost-containment measures implemented across health care systems in the European Union as part of the financial austerity have affected market access to effective therapies for pharmaceuticals in general, including therapies for PP. Greece, in particular, is going through one of the most significant economic crises in its modern history and resources are under severe scrutiny, as the country has been affected by the financial turmoil more than any other European country.³² In this environment, it has been facing several challenges relating to the organization, financing, and delivery of health care services, with a fixed annual public pharmaceutical expenditure in the context of a memorandum signed with its international lenders. Consequently, the National Organization for Health Care Services (EOPYY—«Εθνικός Οργανισμός Παροχής Υπηρεσιών Υγείας» in Greek), the main health care payer in Greece, has to meet an inelastic and predetermined budget, imposing strict constraints. In this context, a clear picture of the financial impact regarding the reimbursed products is considered important to support relevant decision making by EOPYY. To this effect, an economic analysis of the available

biologic treatments for PP in Greece was conducted. The aim of the study was to estimate the annual per-patient cost of treatment with the biologic agents adalimumab, etanercept, infliximab, and ustekinumab in the management of PP in Greece. The current manuscript presents the results of this economic analysis.

Methods

The present economic model is a cost-minimization analysis assuming similar efficacy at 1 year (ie, the time horizon of the model) for biologic treatments in scope.²² The model attempted to estimate the direct treatment costs of patients with PP. The main items considered include drug costs and their administration.

Costs associated with monitoring were not considered. The efficacy of biologics for the 1-year perspective was considered roughly equal between treatments, as was the cost for managing adverse events, and thus was not considered in the model.²² The time horizon was limited to 1 year for both new and existing patients, and the perspective of the analysis was that of the payer (EOPYY); other costs that quantify the indirect burden (eg, productivity loss) associated with each therapy were not taken into account in the present analysis.

A model was developed in Microsoft Excel[®] where patients were classified as either responders or nonresponders depending on whether or not they achieved the minimum improvement criterion for PP, namely the Psoriasis Area and Severity Index (PASI) criterion. PASI combines the assessment of the severity of disease into a single score in the range 0 (no disease) to 72 (maximal disease). Clinical improvements are generally reported in terms of the number of people reaching a specified percentage reduction in PASI from their baseline score (for example, PASI 75 is a 75% reduction from baseline score). It is generally recognizable that an achievement of a PASI 75 indicates that severe psoriasis has responded to treatment. Time to assessment of responder status followed the guidance from the respective Summary of Product Characteristics (SPC); ie, at 16 weeks for adalimumab, 12 weeks for etanercept, 14 weeks for infliximab, and 28 weeks for ustekinumab.^{33–36} The model assumed that nonresponders discontinued treatment at the above time points for each respective agent, while responders retained clinical efficacy and continued treatment with the same biologic agent throughout the study time horizon.

Treatment switching was not allowed in the present model. The prices of drugs were set based on the relevant price bulletin issued by the Ministry of Health.³⁷ The cost of drugs was calculated, taking into account the available

pack size of the agents under study, the unit cost per pack, and the required dose per SPC. In the case of ustekinumab, for those patients weighing more than 100 kg the base-case scenario assumed that a double dose was used (90 mg) as described in the respective SPC.^{33–36} As etanercept is licensed for intermittent as well as continuous treatment, the model incorporated the percentage of patients receiving either of those, as well as the time for which responders remained off treatment (treatment holiday), where applicable. Estimates of the time period for which the responders remain on treatment and the dosage schedule for etanercept were collected through a field based survey presented in the Supplementary materials (Table S1). The dosage scheme for the rest of the comparators is presented in Tables S2–S4. The unit costs of parameters used in the model are presented in Table 1. The total therapy cost was based on a per-vial analysis, assuming that there is drug wastage. Considering the annual time horizon of the model, no discount rate was applied. Cost calculations are presented in the appendix.

Due to the lack of detailed data from local registries, the model inputs were based on a nationwide survey of physicians. In particular, field work was performed by a specialized independent agency from June to September 2013 with dermatologists treating patients with PP; the authors had no involvement in the process of data collection. Data were collected by 10-minute telephone interviews conducted by trained interviewers using a structured questionnaire comprised of questions designed to collect information regarding patient demographics and physician treatment patterns. Participants had no prior knowledge of the actual content of the questionnaire, and researchers did neither interfere nor guide the answers throughout the process. The sampling methodology followed was simple random sampling with screener. A screening question was used to screen physicians who prescribe biologic agents for the treatment of PP. Only physicians prescribing biologics for psoriasis were

included in the sample. In accordance with the inclusion criteria, the sample examined in this study comprised only patients with moderate to severe psoriasis. Hence, patients who were diagnosed with other diseases (ulcerative colitis, rheumatoid diseases, etc) were not taken into account. Data analysis was performed independently by the authors using the Excel 2007 software.

It is generally known that economic data are truncated at zero and do not follow normal distributions, and consequently hypothesis testing would be invalid if conducted with conventional approaches (ie, 95% confidence intervals). As such, in the present model, bias-corrected uncertainty intervals were calculated using the percentile method of nonparametric simulation.³⁸ Probability distributions were therefore specified around the main model parameters. In particular, all cost components were associated with a gamma distribution and a 10% of coefficient of variation (the ratio of mean/standard deviation) around the mean was used for probabilistic sensitivity analysis (1000 bootstrap replications). Since the variance-covariance matrix was unknown, there was not any correlation pattern among variables in each bootstrap experiment. Of course, due to the probabilistic nature of all parameters, the cost of comparators can be slightly different in each experiment, and the mean of the 1,000 estimates is expected to be a good approximation of the true population mean cost per arm based on the cost assumptions.

In addition, in accordance with the recommended guidelines,³⁹ several one-way sensitivity, and different scenario analyses were undertaken. In particular, the model parameters which varied were the mean weight of patients ($\pm 10\%$, mean 80.7 kg, maximum 89.0 kg, minimum 73.0kg), the dosage schedule for ustekinumab (45 mg for all patients), the holiday period for the intermittent use of etanercept (10 months on treatment/2 months off treatment cycles), and the percentage of etanercept patients starting at 2 \times 50 mg weekly (50%, 75%) for the first 3 months of therapy.

Sensitivity analysis concerning the weight of patients was based on a reasonable assumption of $\pm 10\%$, while the rest of sensitivity analyses were based on expert opinions. Furthermore, as per the relevant Summary of Product characteristics, dosage schedules for infliximab and adalimumab are “fixed”; ie, no variations are allowed. Hence, as this analysis is based on an as per SPC use, no variations in dosage schedules for these two agents were taken into account. On the other hand, for ustekinumab (weight-based dosing) and etanercept (different starting regimens, continuous or

Table 1 Unit costs per item used in the model

| Description | Cost (€) |
|---|----------|
| Drug prices* | |
| Adalimumab (Humira 40 mg/0.8 mL \times 1 prefilled syringe) | 381.39 |
| Etanercept (Enbrel 50 mg/1 mL \times 4 prefilled syringes) | 756.96 |
| Infliximab (Remicade injectable 100 mg/vial, 1 vial) | 426.00 |
| Ustekinumab (Stelara 45 mg/0.5 mL vial, 1 vial) | 2,449.81 |
| Resource use | |
| Subcutaneous injection** | 6.64 |
| Day care hospitalization | 85.00 |

Notes: *Based on the Ministry of Health price bulletin of August 30, 2013;³⁷ **cost of subcutaneous injection was based on cost of personnel time for 22 minutes (€18/hour) by Fragoulakis et al.⁶²

intermittent use), dose variations may be applicable as per the relevant SPC.

Results

The sample of physicians included in the study consisted of 29 dermatologists. 62.1% of participants originated from Athens, 17.2% from Salonika, and the remaining 20.7% from urban areas, Patras, Larisa, and Crete island. Approximately half of the participants (51.7%) were female; 48.3% were male. The majority of participants were employed in the private sector (55.2%), followed by the doctors who work in public hospitals (31.0%). It should be mentioned that due to a recent reform concerning the primary and secondary healthcare system in Greece, a unified health insurance Fund (ie, EOPYY), operating also as a provider of healthcare services was established. Hence, the remaining 14.8% of participants represent contracted EOPYY doctors across the country. In accordance with the survey results, these 29 participants saw 745 patients per month in total during the past 12 months. Every participant saw 26 patients per month on average, while only 10.3% of them examined more than 80 patients per month on biologic treatment in the last year. There was a relatively high concentration of the sample in a limited number of doctors, as 56% of patients in the sample were treated by 20% of physicians. Regarding patients, 78.6% were from Athens, 16.6% were from Salonika, and the remaining 4.7% were from urban areas.

Given that the disease prevalence is about 2.0% and assuming that patients requiring systemic therapy account for approximately 20%–30% of the total moderate to severe disease cases,^{40,41} with a satisfactory long-term response/tolerability to traditional systemic therapies achieved in 40% of patients with moderate to severe psoriasis,⁴² it was estimated that the sample used was representative of the entire psoriasis population on biologics. The mean weight of patients was reported at 80.7 kg on average for the entire sample; 89.1 kg for males (standard deviation 10.8 kg, range 75–125 kg) and 72.3 kg for females (standard deviation 9.7 kg, range 60–110 kg). This is in agreement with data from the literature showing that psoriasis patients are more likely to be overweight compared to the general population.⁴³ The distribution of weight across all patients groups was positively skewed for both sexes (skewness: 1.46/1.94).

Regarding treatment regimens, the induction schedules were taken into consideration for new patients, as per respective SPC. Existing patients were considered those who were on treatment for 1 year when entering in the model, and the analysis for them reflects the second year on treatment with

a yearly time horizon. The dose of adalimumab was an initial dose of 80 mg, followed by 40 mg given every other week starting 1 week after the initial dose. For etanercept, it was reported that 36.9% of patients started with 50 mg/twice weekly for the first 12 weeks, while the remaining 63.1% started with 50 mg/week. After the first 12 weeks, all etanercept patients were treated with 50 mg/week. In addition, etanercept was given intermittently in 11.2% of patients; the base-case scenario considered that new patients remained on continuous treatment for the first 24 weeks before going on treatment holiday, thus allowing etanercept to approach its maximum efficacy potential.^{2,44–46} Of the intermittent etanercept patients, 88.5% remained on treatment holiday for 12 weeks, while the remaining 11.5% remained off the drug for 8 weeks before reinitiating etanercept at 50 mg/week. For patients on infliximab, the dosing schedule was intravenous infusion of 5 mg/kg on weeks 0, 2, 6, and every 8 weeks thereafter; the total dose was calculated for the mean weight of patients. Treatment with ustekinumab started with dosing on weeks 0, 4 and every 12 weeks thereafter. It was estimated from the field research that 25% of patients undergoing ustekinumab therapy received the dosage of 90 mg every 12 weeks, while the remaining 75% received 45 mg every 12 weeks.

The results of the economic analysis for new and existing patients for the base-case scenario are presented in Table 2. According to these, the annual per-patient cost for new and existing patients is lower with etanercept than with the other agents in the comparison for both responders and nonresponders. For existing patients (ie, patients continuing treatment after the first year) the cost of treatment with etanercept becomes even lower (€9,462) compared to that of new patients (€10,415), as the biweekly regimen is not applicable after the first 12 weeks of treatment and after the

Table 2 Mean annual per patient cost of treatment (€)

| Drug | Mean (95% LCI–95% UCI) | | |
|-------------|---------------------------|----------------------------|---------------------------|
| | New patients | | Existing Patients |
| | Nonresponders | Responders | Responders |
| Adalimumab | 3,821 (3,549–4,086) | 10,686 (9,927–11,429) | 9,916 (9,212–10,606) |
| Etanercept | 3,224 (3,017–3,430) | 10,415 (10,295–10,579) | 9,462 (7,829–11,000) |
| Infliximab | 7,582 (6,640–7,793) | 14,738 (13,280–155,863) | 12,949 (11,619–13,637) |
| Ustekinumab | 9,806 (9,566–10,045) | 17,155 (16,755–17,554) | 17,149 (16,749–17,547) |

Notes: Existing patients are assumed to be those continuing treatment after the first year. Results were based upon 20,000 Monte Carlo iterations.

Abbreviations: LCI, lower confidence interval; UCI, upper confidence interval.

first year a number of patients may go on treatment holiday twice per year (assuming, as per results above, that these patients remain off treatment for 2 or 3 consecutive months and receive treatment for 6 months consecutively). Results did not change significantly under several one-way sensitivity and scenario analyses undertaken, presented in Table 3.

Discussion

Understanding the relative benefits and costs of available treatments for people with moderate to severe PP is important in order to ensure that patients receive an acceptable level of

care within the framework of constrained resources. Since the benefit of adalimumab, etanercept, infliximab, and ustekinumab has been acknowledged by authorities, physicians, medical societies, and payers, their use has become a part of standard medical practice.^{44,45} This economic analysis was undertaken to compare the mean annual cost of treatment of biologic agents approved for the treatment of PP (namely adalimumab, etanercept, infliximab, and ustekinumab) in the Greek setting. The analysis indicated that etanercept was associated with lower annual cost per patient compared to other agents. Cost minimization analysis is used to compare

Table 3 One-way sensitivity analysis (annual per patient cost, €)

| | Mean (95% LCI – 95% UCI) | | |
|---|--------------------------|------------------------|------------------------|
| | New patients | | Existing patients |
| | Nonresponders | Responders | Responders |
| Mean weight of patients at 89 kg* | | | |
| Adalimumab | 3,821 (3,549–4,086) | 10,686 (9,927–11,429) | 9,916 (9,212–10,606) |
| Etanercept | 3,224 (3,017–3,430) | 10,415 (10,295–10,579) | 9,462 (7,829–11,000) |
| Infliximab | 8,008 (7,356–8,489) | 16,016 (14,712–16,977) | 14,227 (12,873–14,855) |
| Ustekinumab | 9,806 (9,566–10,045) | 17,155 (16,755–17,554) | 17,149 (16,749–17,548) |
| Mean weight of patients at 73 kg* | | | |
| Adalimumab | 3,821 (3,549–4,086) | 10,686 (9,927–11,429) | 9,916 (9,212–10,606) |
| Etanercept | 3,224 (3,017–3,430) | 10,415 (10,295–10,579) | 9,462 (7,829–11,000) |
| Infliximab | 6,730 (5,979–7,149) | 13,460 (11,958–14,299) | 11,671 (10,463–12,511) |
| Ustekinumab | 9,806 (9,566–10,045) | 17,155 (16,755–17,554) | 17,149 (16,749–17,548) |
| All ustekinumab patients on 45 mg | | | |
| Adalimumab | 3,821 (3,549–4,086) | 10,686 (9,927–11,429) | 9,916 (9,212–10,606) |
| Etanercept | 3,224 (3,017–3,430) | 10,415 (10,295–10,579) | 9,462 (7,829–11,000) |
| Infliximab | 7,582 (6,640–7,793) | 14,738 (13,280–15,586) | 12,949 (11,619–13,637) |
| Ustekinumab | 7,356 (6,835–7,872) | 12,256 (11,388–13,115) | 12,249 (11,382–13,108) |
| 50% etanercept patients | | | |
| 2x50 mg/week for the first 12 weeks | | | |
| Adalimumab | 3,821 (3,549–4,086) | 10,686 (9,927–11,429) | 9,916 (9,212–10,606) |
| Etanercept | 3,413 (2,841–3,979) | 10,793 (8,949–12,525) | 9,462 (7,843–10,993) |
| Infliximab | 7,582 (6,640–7,793) | 14,738 (13,280–15,586) | 12,949 (11,619–13,637) |
| Ustekinumab | 9,806 (9,566–10,045) | 17,155 (16,755–17,554) | 17,149 (16,749–17,547) |
| 75% etanercept patients | | | |
| 2x50 mg/week for the first 12 weeks | | | |
| Adalimumab | 3,821 (3,549–4,086) | 10,686 (9,927–11,429) | 9,916 (9,212–10,606) |
| Etanercept | 3,981 (3,691–4,262) | 11,361 (11,014–11,585) | 9,462 (7,821–10,981) |
| Infliximab | 7,582 (6,640–7,793) | 14,738 (13,280–15,586) | 12,949 (11,619–13,637) |
| Ustekinumab | 9,806 (9,566–10,045) | 17,155 (16,755–17,554) | 17,149 (16,749–17,547) |
| Etanercept treatment holiday cycles, 10 months on/2 months off** | | | |
| Adalimumab | 3,821 (3,549–4,086) | 10,686 (9,927–11,429) | 9,916 (9,212–10,606) |
| Etanercept | 3,224 (3,017–3,430) | 10,604 (10,374–10,655) | 9,651 (8,023–11,245) |
| Infliximab | 7,582 (6,640–7,793) | 14,738 (13,280–15,586) | 12,949 (11,619–13,637) |
| Ustekinumab | 9,806 (9,566–10,045) | 17,155 (16,755–17,554) | 17,149 (16,749–17,547) |
| 30% patients etanercept intermittent, 6 months on/4 months off | | | |
| Adalimumab | 3,821 (3,549–4,086) | 10,686 (9,927–11,429) | 9,916 (9,212–10,606) |
| Etanercept | 3,224 (3,017–3,430) | 9,847 (9,579–9,860) | 8,894 (7,407–10,386) |
| Infliximab | 7,582 (6,640–7,793) | 14,738 (13,280–15,586) | 12,949 (11,619–13,637) |
| Ustekinumab | 9,806 (9,566–10,045) | 17,155 (16,755–17,554) | 17,149 (16,749–17,547) |

Notes: *Although the mean weight changes, we assumed that the proportion of patients weighting >100 kg remains the same; **refers to the 11.2% of patients receiving intermittent treatment as in the base case scenario.

Abbreviations: LCI, lower confidence interval; UCI, upper confidence interval.

two health technologies that have proven to be equivalent in terms of survival and overall therapeutic effect. In such cases, the focus of the analysis shifts to their treatment cost to choose the least costly as the preferable therapeutic option. It must be noted, that in the context discussed here, the equivalence in the efficacy of the treatment regimens considered is not yet fully established by head-to-head trials. Hence, the economic conclusions drawn from the present analysis are based on the premise of comparable efficacy, which is a prerequisite.

The determination of cost was affected mainly by the drug prices and the dosage schedules. In this context, the present analysis focused only on economic implications, without taking into account any off-label dose escalation or differences in efficacy. Thus, our conclusions are driven mainly by differences in the cost and doses of the agents under evaluation. In economic studies such as the present, the choice of time horizon depends on the research question and can range from a few weeks to several years (eg, remaining life expectancy). The time horizon chosen should be long enough to reflect all outcomes of interest associated with the alternative therapies. In the present analysis, as the effectiveness of comparators has been considered equivalent, the focus shifted only in their financial impact in the health care setting for payers; hence, 1 year was considered a reasonable period to study the comparators.

According to the base-case analysis, biologic treatments were prescribed as per label and, in the case of etanercept (the only biologic approved for the treatment of PP with the option for intermittent or continuous use) real-world treatment pattern data were collected by means of a nationwide field research with dermatologists. The cost of these agents for existing patients was lower compared to new patients as the induction schedule was not applicable for the former.

Based on the findings from a recent systematic literature review, dose escalation with the aforementioned comparators may lead to greater efficacy in some cases, while dose reduction may result in reduced efficacy.⁴⁷ We chose to base our analysis on the dosing schedules adopted in Greece based on the approved label for each biologic and on data from a local survey of clinical practice.

In the international literature, many different economic studies or reviews have examined the aforementioned comparators in terms of cost-effectiveness, and such comparisons are becoming increasingly relevant; however, the results remain inconclusive due to several factors, such as the different management of patients across countries, differences in dosage schedule, relative prices, time horizon of

models, perspective of analysis, assumptions concerning the education of patients, sequences of biologic treatment, and conflicts due to funding of research.^{15,48–52} This fact imposes the need to interpret the results of these comparisons with caution. Also, methodological issues set aside, the cost-effectiveness of health technologies might vary from country to country simply due to differences in clinical practice patterns and/or relative prices; hence, extrapolations are not recommended.⁵³ Moreover, long-term data from appropriately designed studies on the comparative efficacy and safety of such treatments are lacking; for a disease requiring life-long treatment, such as psoriasis, the use of short-term data may be misleading. For the above reasons, a straightforward approach is to compare only the treatment cost of the agents under consideration and to declare the least expensive one. This type of analysis, as the one we conducted here, has already been proposed by several national agencies to compare this specific group of agents.⁵⁴

This is the second study conducted in Greece for patients with moderate to severe PP, and its results are somewhat inconsistent with those of the previous one.⁵⁵ The differences in the results can be interpreted on the basis of the different assumptions used for the two models. For example, the previous analysis did not include the additional drug cost for patients receiving 90 mg of ustekinumab (ie, those weighing over 100 kg); furthermore, it assumed that all patients starting on etanercept receive the 50 mg biweekly dose and that all etanercept patients receive continuous treatment (ie, no intermittent dosing schedule). Importantly, the previous model also implemented a hypothetical projection regarding the use of ustekinumab, as this biologic was just becoming available in the Greek market and data on its real-world use were not available for Greece. On the other hand, in our analysis all these parameters were derived from the survey of dermatologists, capturing actual clinical practice, with ustekinumab having been available in the Greek market for over 3 years. This approach may not be as robust as, for instance, a real-world patient registry, but is quite sufficient in giving reasonable indications as the sample of physicians and patients was representative.

To test the robustness of our results, several one-way sensitivity and different scenario analyses were undertaken to show how different treatment approaches may influence the annual treatment cost. These analyses aimed at including the most plausible scenarios applied in daily practice for these biologics when prescribed as per the approved label. In this context, the results presented here may be of value for both decision-makers and Social Funds, as well as physicians

faced with prescribing-related cost-containment measures. Furthermore, results are presented in a format that may allow for the direct calculation of costs upon changes in the prices of the concerned biologics (Table S5).

Regarding the limitations of the present study, it must be noted that modeling-based analyses, such as the one employed here, involve by definition a simplification of the process they try to emulate, and the present one is no exception. Much of the data entered in the model resulted from a nationwide survey that was based on questionnaire-driven interviews conducted with dermatologists across the country. Even though the sample size of dermatologists appears relatively small, it may be considered a representative one as it includes input from both public hospital and EOPYY physicians across Greece managing a satisfactory sample of patients with moderate to severe psoriasis. This approach has known limitations, such as participant recall bias and misunderstanding of questions. Nonetheless, it must be noted that this type of data collection represents a reasonable, second-best approach in the absence of local real-world data, such as those derived by registries, and was conducted by an independent company specializing in this type of research.

Moreover, our model did not include the cost related to treatment failure (eg, increased hospital visits, reduced productivity), as this was considered out of scope for the purpose of the study. In terms of the safety profile of the biologics considered, even though available data may favor etanercept over the other anti-TNFs regarding certain adverse events such as tuberculosis, nontuberculosis opportunistic infections, and lymphoma^{56–60} which, although rare, may be associated with increased management costs, our analysis assumed a comparable safety profile and thus did not include adverse event-related costs; this approach is consistent with previous economic analyses conducted.^{51,61–63}

Another limitation of the study is that treatment switching between biologic agents is not considered in the present model. Nonetheless, it must be noted that in clinical practice both agents may be used in a sequence, an approach which has not been evaluated in the Greek model due to limitations concerning the data availability. This is a common issue in small countries like Greece, since there is no available registry/database which could be used for analytical purposes. In addition, in the present analysis the cost of nonresponders has been estimated until treatment discontinuation; thus, no further costs have been incorporated in the model for this type of patient.

Despite the above limitations, the model used incorporates real-life data and, under its specific scope, presents

useful results of practical value for both the payer and the prescriber on the cost of treatment of PP with biologics in Greece.

Conclusion

The cost of treatment with etanercept may be lower than that with other biologic agents licensed for the treatment of moderate to severe PP in Greece. Further analysis with real-world data on effectiveness, safety, and utility is needed to confirm the accuracy, completeness, and appropriateness of the results in the local setting. Results presented must be viewed strictly in the light of the setting and time undertaken, the data, and the assumptions utilized and may change if some of these also change over time.

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VF conducted the analyses, interpreted the results, and wrote the manuscript. ER and EV supervised the study and interpreted the results. NM supervised the study and is the guarantor for the overall content.

Nothing contained in this paper is intended to guarantee the appropriateness of any medical treatment or to be used for therapeutic purposes or as a substitute for a health professional's advice.

The authors or Pfizer Hellas have no access to any personal information of the participating physicians. Each one of the recruiters of IPSOS Company declared that the interviews were conducted in compliance with the law 2472/97.

Disclosure

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Supplementary materials

Table S1 The treatment schedule of etanercept for responders

| Year | Weeks | Dosing schedule for etanercept | | |
|------|---------------------|---|---|---|
| 1 | 1–12 | 36.90% patients 2×50 mg/week | 63.10% patients 1×50 mg/week | |
| | Response assessment | | | |
| | 13–24 | 100% patients 1×50 mg/week | | |
| 2 | 25–52 | 88.80% patients Continuous 50 mg/week | 9.91% patients Intermittent 50 mg/week (cycles of 3 months off, 6 months on after week 24) | 1.29% patients Intermittent 50 mg/week (cycles of 2 months off, 6 months on after week 24) |
| | 53–104 | 88.80% patients Continuous 50 mg/week | 9.91% patients Intermittent 50 mg/week (cycles of 3 months off, 6 months on, continuing from Year 1) | 1.29% patients Intermittent 50 mg/week (cycles of 2 months off, 6 months on, continuing from Year 1) |

Notes: Response is assessed after 12 weeks of treatment; therefore, nonresponders were assumed to have received treatment for a total of 12 weeks and then stopped treatment.

Table S2 The treatment schedule of adalimumab for responders

| Year | Weeks | Dosing schedule for adalimumab | |
|------|---|--------------------------------|------|
| 1 | 0 | 80 mg | 100% |
| | 1, 3, 5 ... 51 (dosing every 2 weeks) | 40 mg | 100% |
| 2 | 53, 55, 57 ... 103 (dosing every 2 weeks) | 40 mg | 100% |

Notes: Response is assessed after 16 weeks of treatment; therefore, nonresponders were assumed to have received treatment for a total of 16 weeks and then stopped treatment.

Table S3 The treatment schedule of infliximab for responders

| Year | Weeks | Dosing schedule for infliximab | |
|------|-----------------------------|--------------------------------|------|
| 1 | 0, 2, 6 | 5 mg/kg | 100% |
| | 14, 22, 30, 38, 46 | 5 mg/kg | 100% |
| 2 | 54, 62, 70, 78, 86, 94, 102 | 5 mg/kg | 100% |

Notes: Response is assessed after 14 weeks of treatment; therefore, nonresponders were assumed to have received treatment for a total of 14 weeks and then stopped treatment.

Table S4 The treatment schedule of ustekinumab for responders

| Year | Weeks | Dosing schedule for infliximab | |
|------|----------------------|--------------------------------|-----|
| 1 | 0, 4, 16, 28, 40, 52 | 45 mg | 75% |
| | | 90 mg | 25% |
| | | | |
| 2 | 64, 76, 88, 100 | 45 mg | 75% |
| | | 90 mg | 25% |

Notes: Response is assessed after 28 weeks of treatment; therefore, nonresponders were assumed to have received treatment for a total of 28 weeks and then stopped treatment.

Table S5 Cost calculations used in the analysis of the annual per patient cost of treatment

| | Total dose (mg) | Weighted mean dose (mg) | Total vials (mean) | Drug cost (€) | Administration cost (€) | Total treatment cost (€) |
|---|-----------------|-------------------------|--------------------|---------------|-------------------------|--------------------------|
| Etanercept | | | | | | |
| Responders new patients | | | | | | |
| 36.90% patients 2x50 mg/week up to week 12 | 3,135 | 2,756.40 | 55 | 10,408.20 | 6.64 | 10,414.84 |
| 63.10% patients 1x50 mg/week up to week 12 | 2,535 | 2,756.40 | 55 | 10,408.20 | 6.64 | 10,414.84 |
| Responders existing patients | | | | | | |
| 88.80% patients continuous | 2,600 | 2,490.58 | 50 | 9,462.00 | 0 | 9,462.00 |
| 1.29% patients intermittent (8-week holiday) | 1,800 | 2,490.58 | 50 | 9,462.00 | 0 | 9,462.00 |
| 9.91% patients intermittent (12-week holiday) | 1,600 | 2,490.58 | 50 | 9,462.00 | 0 | 9,462.00 |
| Nonresponders – 1st year | | | | | | |
| 36.90% patients 2x50 mg/week up to week 12 | 1,200 | 821.40 | 17 | 3,217.08 | 6.64 | 3,223.72 |
| 63.10% patients 1x50 mg/week up to week 12 | 600 | 821.40 | 17 | 3,217.08 | 6.64 | 3,223.72 |
| Adalimumab | | | | | | |
| Responders new patients | 1,120 | NA | 28 | 10,678.92 | 6.64 | 10,685.56 |
| Responders existing patients | 1,040 | NA | 26 | 9,916.14 | 0 | 9,916.14 |
| Nonresponders | 400 | NA | 10 | 3,813.90 | 6.64 | 3,820.54 |
| Infliximab | | | | | | |
| Responders new patients | 3,230 | NA | 33 | 14,058.00 | 680.00 | 14,738.00 |
| Responders existing patients | 2,826 | NA | 29 | 12,354.00 | 595.00 | 12,949.00 |
| Nonresponders | 1,615 | NA | 17 | 7,242.00 | 340.00 | 7,582.00 |
| Ustekinumab | | | | | | |
| Responders new patients | | | | | | |
| 75% of patients 45 mg/dose | 225 | 281.25 | 7 | 17,148.67 | 6.64 | 17,155.31 |
| 25% of patients 90 mg/dose | 450 | 281.25 | 7 | 17,148.67 | 6.64 | 17,155.31 |
| Responders existing patients | | | | | | |
| 75% of patients 45 mg/dose | 225 | 281.25 | 7 | 17,148.67 | 0 | 17,148.67 |
| 25% of patients 90 mg/dose | 450 | 281.25 | 7 | 17,148.67 | 0 | 17,148.67 |
| Nonresponders | | | | | | |
| 75% of patients 45 mg/dose | 135 | 168.75 | 4 | 9,799.24 | 6.64 | 9,805.88 |
| 25% of patients 90 mg/dose | 270 | 168.75 | 4 | 9,799.24 | 6.64 | 9,805.88 |

Note: Existing patients are assumed to be those continuing treatment after the first year onwards; calculations are based on a 52-week per year time horizon.

Abbreviation: NA, not applicable.

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