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ORIGINAL RESEARCH

Economic Impact of Etanercept in Patients with Psoriasis and Psoriatic Arthritis in Spain: A Systematic Review

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ABSTRACT

Introduction: Etanercept (ETN), a highly effective biological agent for the treatment of psoriasis (PSO) and psoriatic arthritis (PsA), is widely used in Spain. However, evidence of its economic impact is limited, indicating the need for a systematic review of the economic assessments conducted on the use of ETN in the treatment of both PSO and PsA in Spain.

Methods: A systematic review was carried out in PubMed, Embase, Cochrane Library, Health Technology Assessment reports and not indexed sources up to November 2018. The inclusion criteria were economic evaluations (total and partial) and dose optimization studies published in English or Spanish on the use of ETN to treat PSO and PsA for ETN in Spain.

Results: A total of 402 publications were identified, of which 32 were selected for inclusion in the review; of these 32 publications, 81.3% analyzed PSO (14 full economic evaluations, 5 partial economic evaluations and 7 dose optimization studies) and 18.8% analyzed PsA (1 economic analysis and 5 dose optimization studies). The perspective of the Spanish National Health Service (NHS) was used in 90.0% (n = 18) of the full and partial economic evaluations. The time horizons ranged from 12 weeks to 2 years. Reductions in the Psoriasis Area and Severity Index (PASI) of 50, 75 and 90% (PASI 50, 75 and 90, respectively) were most commonly used as efficacy outcomes in the complete evaluations. The economic impact of ETN ranged from €9110–14,337/PASI 75 at 12 weeks (50 mg/week) to €82,279/PASI 90 at 2 years, depending on the health outcome, time horizon and ETN dose used. Only one study determined the cost of using ETN for the treatment of PSO (€29,430–52,367/QALY for dose 2 × 25 mg/week or 50 mg/week, respectively). Only one partial economic evaluation on PSA was identified (NHS perspective), resulting in an ETN annual cost of €8585/patient-year.

Conclusion: Consistent evidence on the economic impact of ETN for the treatment of PSO and PSA in Spain is lacking, mainly due to the

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highly heterogeneous methodology used and the broad range of outcomes found in the economic evaluations published to date.
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Keywords: Economic evaluations; Etanercept; Psoriasis; Psoriatic arthritis; Spain; Systematic review

INTRODUCTION

Psoriasis (PSO) and psoriatic arthritis (PsA) are autoimmune diseases that are highly relevant both clinically and economically. The overall prevalence of PSO ranges from 0.09 to 11.43%, and PsA coexists with PSO in 1.3–34.7% of these patients [1]. In Spain, the prevalence of PSO stands at 2.31%. This figure has increased over the last decade [2] and is higher in men than in women (2.7% and 1.9%, respectively). It is estimated that 7% of PSO patients in Spain could develop PsA, which would equate to approximately 0.2% of the PSO patient population [3].

Not only do these pathologies have a significant impact on the quality of lives of these patients, even when only a small area of the body is affected, but they also represent a significant cost to health services [1]. In Europe in particular, the annualized cost of PSO and PsA may reach international USD 13,132 and USD 17,050, respectively (USD-purchasing power parity [PPP] 2015, hypothetical currency that makes it possible to compare the purchasing power of different currencies; in this case, the Euro with the USD) [4].

Biological therapies (BT) are a well-established alternative for the treatment of immune-mediated skin diseases [5]. The biological agent etanercept (ETN) is indicated in patients with PSO for whom another systemic therapy is contraindicated and for those who have not responded to or do not tolerate another systemic therapy, as well as in patients with active and progressive PsA, when the response to a previous disease-modifying antirheumatic drug treatment was inadequate [6].

Although ETN is frequently used in the clinical setting in Spain to treat PSO and PsA [7, 8], evidence of the economic impact of its use in the treatment of these immune-mediated diseases is limited. We have therefore performed a critical and systematic review and analysis of the relevant literature in order to draw conclusions on the decision-making process regarding available economic evaluations of the use of ETN to treat PSO and PsA in Spain.

METHODS

Identification

We performed a systematic review of citations in the PubMed, Medline and Embase Ovid databases up to November 2018. The search strategy was structured around recommendations for the performance of systematic reviews in economic evaluations [9], with the key concepts taken into account being population (PSO and PsA patients in Spain), intervention (ETN) and outcomes (economic evaluation/burden of disease). Studies with interventions but no comparator drug were also eligible for inclusion in the review. Subsequently, search terms related to the objective of the study were used (MeSH and free-text, Boolean operators for the performance of simple and combined searches). No restrictions were applied for the year of publication, type of study or language.

In order to identify the maximum number of references possible, the search was extended to the Cochrane Library, MEDES databases in Spanish, National Health Technology Assessment Agencies and journals of interest. A manual search was also conducted on abstracts and posters in communications presented to national and international congresses related to the area of interest that had been published between 2010 and 2018, namely, the American Academy of Dermatology (AAD), the Spanish Academy of Dermatology and Venereology (AEDV), the American College of Rheumatology (ACR), the European Academy of Dermatology and Venereology (EADV), the Spanish Health Economics Association (AES), the European Association of Hospital Pharmacists (EAHP), the European League Against Rheumatism (EULAR), the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), the

Spanish Society of Rheumatology (SER) and the Spanish Society of Hospital Pharmacy (SEFH).

Study Selection

Inclusion criteria were applied to language (publications in English and Spanish only), the country where the analysis was performed (Spain only), pathologies (PSO and PsA) and the type of study (economic evaluations). Publications that were not related to ETN or to the pathologies defined by the study, those that were not developed and conducted in Spain and those that were not economic evaluations (e.g. cost-effectiveness, cost-benefit, cost analysis, cost-consequence and cost-minimization studies) were excluded from the analysis. If there were two publications on the same study, both were selected, and they were jointly presented in the analysis of outcomes obtained.

PRISMA declaration criteria were applied to the identification process for duplicated, rejected and selected references [10].

Data Extraction

A tool was designed to facilitate the process of extracting data exclusively pertaining to ETN for all references published, with the following parameters: pathology, author–year, type of publication, type of economic evaluation, study characteristics, perspective, time horizon, type of costs, measures of effectiveness used and outcomes.

Each complete economic evaluation grouped studies evaluating at least two different alternatives and containing incremental cost data relating to a pre-determined effectiveness variable (e.g. responding patient PASI 75 [75% reduction in the Psoriasis Area and Severity Index] at 12 weeks). Each partial economic evaluation included studies containing cost data for ETN, but the increase in costs was not assessed relative to another alternative with respect to a pre-determined effectiveness variable (e.g. cost analysis studies). In addition, costs studies evaluating the economic impact of the optimization of ETN doses (dose escalation, reduction or spacing) or of switching to biosimilar drugs were grouped and analyzed separately.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

RESULTS

A total of 402 publications were identified, of which 32 were selected for data extraction (26 on PSO and 6 on PsA); of these latter 32 publications, 53.1% (n = 17) were communications to congresses. Of the publications selected, 14 were classified as complete economic evaluations (cost-effectiveness or cost-benefit analysis) in patients with moderate–severe PSO, 18.8% (5 on PSO and 1 on PsA) were classified as partial economic evaluations (cost and cost-minimization analyses) and 37.5% (6 on PSO and 5 on PsA) were classified as dose-optimization studies (Fig. 1).

Study Characteristics

Complete Economic Evaluations

Decision tree modeling was applied in 50% (n = 7) of the complete economic evaluations, with a time horizon of between 12 weeks and 2 years [11–17]. With the exception of a solitary publication which included evaluations of the direct non-healthcare costs and the indirect costs owing to productivity loss [18], the Spanish National Health Service's (NHS) was the perspective mainly used. The main measures of effectiveness used were the percentage of patients obtaining a 50, 75 or 90% improvement with respect to the baseline PASI score (PASI 50, 75 and 90, respectively), quality-adjusted life years (QALY) [19], the percentage of patients who were successfully treated (ETN maintained from the start) after 1 year [13] or the number needed to treat (NNT) [20]. The incremental efficacy results were extracted from pivotal clinical trials of ETN versus placebo [11, 14, 17–19, 21], evidence generated in Spain in a real-life clinical context [22–24] or results taken from previous meta-analyses [25, 26] (Electronic Supplementary Material [SEM] Table S1).

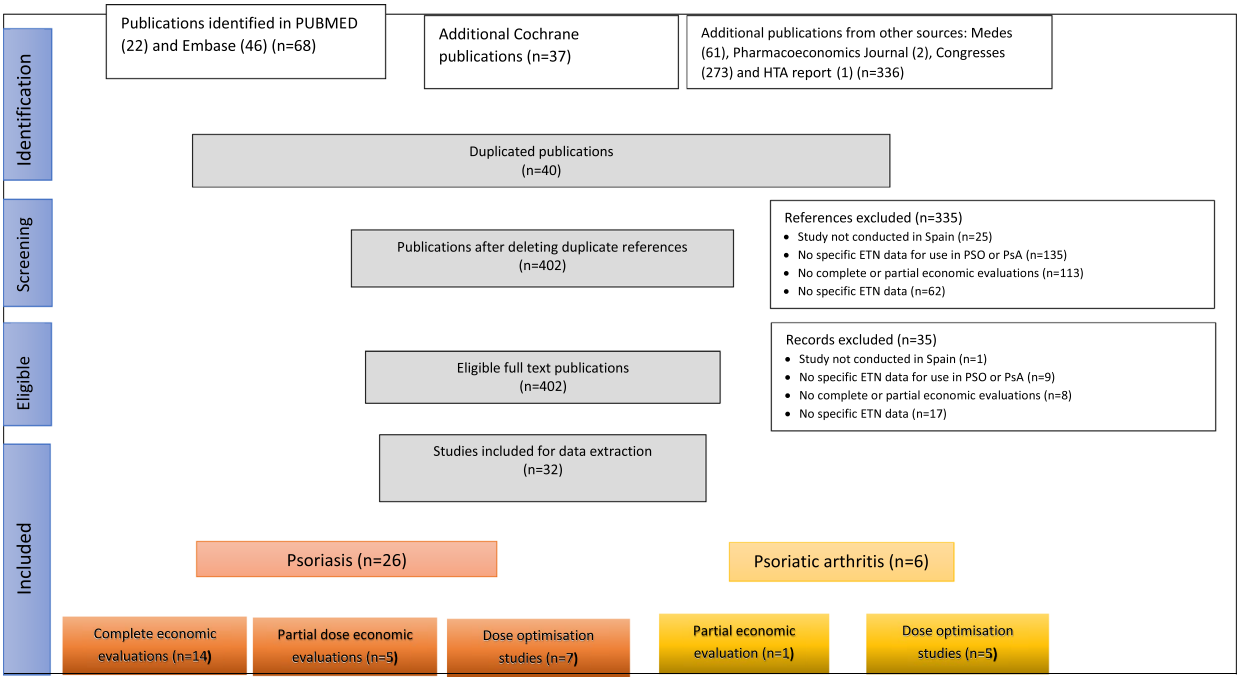

Fig. 1 Flow diagram of the publication selection process based on the PRISMA criteria [10]. *ETN* Etanercept, *HTA* health technology assessment, *PsA* psoriatic arthritis, *PSO* psoriasis

Partial Economic Evaluations

Of the partial economic evaluations for moderate–severe PSO, four (n = 505 patients treated with ETN) were based on observational studies in a real-life clinical context [27–30], and one study used modeling techniques [31]. All of the studies adopted the perspective of the NHS (only pharmacological costs), with the exception of one cost-minimization study which also considered indirect costs owing to loss of productivity [28]. The most commonly administered ETN regimen was 50 mg/week, followed by a regimen of 2 × 25 mg/week or 2 × 50 mg/week.

We identified only one cost-analysis study that assessed—from the perspective of the NHS—the economic impact of ETN in patients with PsA (n = 29 patients treated with ETN) over the course of 1 year [8] (ESM Table S2).

Dose Optimization

The dose-optimization studies in real-life clinical contexts included in our systematic review evaluated the different types of interventions, including dose reduction (n = 4) [32–35], implementation of optimization protocols (n = 4) [36–39], dose spacing (n = 1) [40], optimization/escalation strategies (n = 1) [41], inclusion of multi-disciplinary committees (n = 1) [42] and switching to a biosimilar (n = 1) [43]. The PSO studies [32, 33, 36, 37, 40, 41, 43] all included the pharmacological costs with a time horizon of 1 year, with one exception, namely, a solitary study that used a horizon of 4 years and failed to specify the type of cost included in the analysis [36]. All PsA studies (n = 5) [34, 35, 38, 39, 42] used the perspective of the NHS, with a time horizon of between 6 months and 7 years (ESM Table S3).

Results of Economic Evaluations

Complete Economic Evaluations

A PASI 75 score is considered to be a reasonably satisfactory clinical outcome in the assessment of PSO. Using this criterion, our analysis of data from the original studies showed that the economic impact of ETN during the maintenance and induction phases was €9110–9370 for those

with PASI 75 response rates at 12 weeks (50 mg/week) during the maintenance phase and €12,797 for those with PASI 75 response rates at 12 weeks (2 × 50 mg/week) during the induction phase [11, 12], with the annual cost increasing to €23,034 for those with PASI 75 response rates [22]. Other results found were €20,178/year per patient treated successfully [13]. The impact of ETN when considering a PASI 90 response rate over 2 years as an outcome measure was €89,279. Analysis of the sequence of treatments of ETN with other BTs revealed an impact of €45,672–71,558 for PASI 90 response rates after 2 years when ETN therapy was combined with secukinumab and adalimumab, respectively [16] (Table 1).

A broad range of different clinical outcomes was also found in the selected conference abstracts. The cost-effectiveness using PASI 75 as the clinical outcome over a 1-year time horizon showed an inferior cost-effectiveness ratio (€17,436/PASI 75 at 1 year [14]). Another conference abstract also provided the cost per responder using this clinical outcome, although the time horizon was not specified (€8710/responder PASI 75) [17]. ETN's NNT cost for the first year of treatment (2 × 50 mg/week for 12 weeks followed by 50 mg/week) ranged from €29,277/NNT (PASI 75) to €226,080/NNT (PASI 100), and from €23,787/NNT (PASI 75) to €183,690/NNT (PASI 100) in consecutive years (50 mg/week) [20]. Finally, the only cost-utility study yielded an incremental cost-utility ratio (expresses the correlation between incremental costs and QALYs) of €29,430/QALY gained (ETN 2 × 25 mg/week) and €52,367/QALY gained (ETN 50 mg/week) [19] (Table 1).

Partial Economic Evaluations

The annual cost per patient with moderate–severe PSO who was treated with ETN ranged from €4986 (maintenance phase cost in patients receiving intermittent treatment) to €12,327/patient-year (maintenance phase cost in patients receiving continuos treatment) [30]. For patients who experienced loss of response to the ETN treatment, the annual escalation cost owing to dose duplication ranged from €14,580 (12-week intensification) to €18,908 (31-week intensification)/patient-year [31] (Table 2).

Data extracted from conference abstracts provided a total annual costs for PSO of €15,268/patient-year (year in which the treatment was started) [27] and the only cost analysis data conducted for PsA (using the NHS perspective), which yielded a cost result of €8585/patient-year [8] (Table 2).

Dose Optimization

The total annual cost of a reduced ETN regime for the treatment of PSO varied from €4160 (50 mg/2 weeks) to €8320/patient-year (25 mg/week), whereas the escalated regime increased the annual cost up to €23,773/patient-year [32]. Dose optimization procedures for ETN doses in the treatment of PSO through the implementaion of optimization/escalation strategies and protocols resulted in a saving of €859/patient-year [37] (Table 3).

Conference abstracts showed savings of €2012/patient in 2 years of ETN use to treat PSO by increasing the dosing interval after protocol implementation [36]. Dose spacing in all patients treated with ETN also produced savings of €15,216/year, although this strategy represented only 13% of the total saving caused by dose spacing in BTs (adalimumab 69%; infliximab 10%, ustekinumab 8%) [40]. Further, one study found an increase in treatment cost (difference between the theoretical value and the real value) of €4754/patient-year, owing primarily to the increased number of patients undergoing dose escalation [41].. The only study on switching to biosimilar drugs to treat PSO (reference value of 50 mg/ml ETN vs. biosimilar) yielded an annual saving of 18.7% (€6766.20 monthly saving) [43] (Table 3).

For PsA, a dose regime strategy led to a total saving of €81,949 over 7 years after the dose was changed from 50 to 25 mg/week [38]. When our analysis was limited to results from conference abstracts, the protocol implementation entailed a saving of €793–823/patient-year (€11,480/patient-year before protocol implementation compared to €10,657–10,687/patient-year after protocol implementation) [34, 39], Further, lengthening of the dose interval (from weekly administration to a 10-day administration) produced an annual saving of €1434/patient [35] (Table 3).

Table 1 Results in publications reporting complete evaluations on the use of etanercept to treat psoriasis in Spain

First author/year of publication [reference citation] (year of costs)	Costs at chosen timepoint (dosing regimen or biological agent)	Health outcomes (time period)	Cost/health outcomes relationship
Blasco/2009 [11] (2008)	€2842/patient at 12 weeks (2 × 25 mg/week or 50 mg/week)	PASI 75 2 × 25 mg/week or 50 mg/week (12 weeks): 30.33%	€9370/PASI 75 at 12 weeks (2 × 25 mg/week or 50 mg/week)
	€5683/patient at 12 weeks (2 × 50 mg/week)	PASI 75 2 × 50 mg/week (12 weeks): 44.41%	€12,797/PASI 75 at 12 weeks (2 × 50 mg/week)
	€5683/patient at 24 weeks (2 × 25 mg/week)	PASI 75 2 × 25 mg/weeks (24 weeks): 50.69%	€11,213/PASI 75 at 24 weeks (2 × 25 mg/week)
Carretero/2009 [19] (ND)	€2947 (2 × 25 mg/week)	QALY (1 year) ETN 2 × 25 mg/week: 0.100	€29,430/QALY (2 × 25 mg)
	€7907/patient-year (50 mg/week)	QALY (1 year) ETN 50 mg/week: 0.151	€52,367/QALY (50 mg)
Ferrándiz/2012 [12] (2010)	€2842/patient at 12 weeks (2 × 25 mg/week or 50 mg/week)	PASI 75 2 × 25 mg/week or 50 mg/week (12 weeks): 31.19%	€9110/PASI 75 at 12 weeks (2 × 25 mg/week or 50 mg/week)
	€5683/patient at 12 weeks (2 × 50 mg/week)	PASI 75 2 × 50 mg/week (12 weeks): 44.41%	€12,797/PASI 75 at 12 weeks (2 × 50 mg/week)
	€5683/patient at 24 weeks (2 × 25 mg/weeks)	PASI 75 2 × 25 mg/weeks (24 weeks): 50.69%	€11,213/PASI 75 at 24 weeks (2 × 25 mg/week)
Galván Banquer/i 2013 [22] (ND) Castillo Muñoz/2013 [23] (ND)	€12,807/patient-year (2 × 25 mg/week)	PASI 75 (1 year): 55.6%	€23,034/PASI 75 at 1 year
Puig/2014 [21] (2014)	ND	ND	€8818 (€8271–9459)/PASI 50 at 12 weeks
			€12,735 (€11,699–13,900)/PASI 50 at 24 weeks
			€16,080 (€14,043–18,810)/PASI 75 at 24 weeks

Table 1 continued

First author/year of publication [reference citation] (year of costs)	Costs at chosen timepoint (dosing regimen or biological agent)	Health outcomes (time period)	Cost/health outcomes relationship
Ventayol/2014 [24] (ND)	€40,160/patient persisting at 2 years	N/A	€40,160/patient persisting at 2 years
Alfageme/2016 [18] (ND)	€7026/patient at 12 weeks[a]	PASI 75 (12 weeks): 49%[b]	€14,337/PASI 75 at 12 weeks
Puig/2016 [13] (2015)	€16,286/patient-year (patient treated successfully)	Patients treated successfully: 80.65% Patients treated unsuccessfully (should be treated with another biological drug): 19.35%	€20,178/patients treated successfully at 1 year
Martinez-Sesmero/2016 [14] (2016)	ND	ND	€17,097/PASI 75 at 1 year (only pharmacological costs) €17,436/PASI 75 at 1 year (pharmacological and administrative costs)
Blanch/2016 [15] (ND)	€23,993/patient at 2 years (ETN + SEC) €24,687/patient at 2 years (ETN + UST) €23,191/patient at 2 years (ETN + INF) €23,052/patient at 2 years (ETN + ADA)	NNT: ETN + SEC: 1.91 ETN + UST: 2.54 ETN + INF: 3.19 ETN + ADA: 3.60	€49,375/PASI 90 at 2 years (ETN + SEC) €70,674/PASI 90 at 2 years (ETN + UST) €66,945/PASI 90 at 2 years (ETN + INF) €77,359/PASI 90 at 2 years (ETN + ADA)

Table 1 continued

First author/year of publication [reference citation] (year of costs)	Costs at chosen timepoint (dosing regimen or biological agent)	Health outcomes (time period)	Cost/health outcomes relationship
Puig/2017 [16] (ND)	ETN in monotherapy: €22,677/patient in 2 years Sequence of treatments: €22,194/patient at 2 years (ETN + SEC) €22,836/patient at 2 years (ETN + UST) €22,214/patient at 2 years (ETN + INF) 21,314/patient at 2 years (ETN + ADA)	NNT: ETN + SEC: 1.79 ETN + UST: 2.20 ETN + INF: 3.19 ETN + ADA: 3.60	ETN in monotherapy: €89,279/PASI 90 at 2 years Sequence of treatments: €45,672/PASI 90 at 2 years (ETN + SEC) €56,868/PASI 90 at 2 years (ETN + UST) €64,124/PASI 90 at 2 years (ETN + INF) €71,558/PASI 90 at 2 years (ETN + ADA)
Huete/2017 [20] (ND)	First year of treatment: €12,511/patient-year Successive years of treatment: €10,165/patient-year	NNT: PASI 75: 2.34% PASI 90: 4.59% PASI 100: 18.07%	Cost per NNT in the first year of ETN treatment: PASI 75: €29,277/NNT PASI 90: €57,427/NNT PASI 100: €226,080/NNT Cost per NNT in subsequent years of ETN treatment PASI 75: €23,787/NNT PASI 90: €46,660/NNT PASI 100: €183,690/NNT

Table 1 continued

First author/year of publication [reference citation] (year of costs)	Costs at chosen timepoint (dosing regimen or biological agent)	Health outcomes (time period)	Cost/health outcomes relationship
Rosado/2018 [17] (2017)	ND	ND	€8710 (€6,038[c]–15,619[d])/ responder PASI 75

ADA Adalimumab, *ETN* etanercept, *INF* infliximab, *ND* no data available, *NNT* number needed to treat, *PASI 75, 90, 100* 75, 90, 100% reduction in the Psoriasis Area and Severity Index score, respectively, *PCB* placebo, *QALY* quality-adjusted life year, *SEC* secukinumab, *UST* ustekinumab

[a] Incremental cost as this is compared with PCB, which is given a cost of 0

[b] Incremental effectiveness as this is compared with PCB, which is given an effectiveness of 0

[c] Best-case scenario (upper limit of the 95% confidence interval [CI] for the incremental efficacy of the randomized controlled trial [RCT])

[d] Worst-case scenario (lower limit of the 95% CI for the incremental efficacy of the RCT)

DISCUSSION

In our systematic review the distribution of publications according to pathology was asymmetrical, with the majority focusing on PSO (81.3% [PSO] vs. 18.8% [PsA]). Of the publications identified, 43.8% were complete economic evaluations. The majority of these complete economic evaluations were models based on the results of pivotal clinical trials or prior meta-analyses, with three studies using data in a real clinical context to obtain an incremental cost-effectiveness ratio [22–24]. Although the main measure of effectiveness was the PASI 75 response at 12 and 24 weeks [11, 12, 18, 21] (the end of the induction phase and the time of assessment of the clinical response to PSO treatment, respectively), a wide range of incremental efficacy measurements were also used (PASI 50, PASI 90, PASI 100, QALY, NNT, patients successfully treated, persisting patients) in addition to various ETN administration regimens (2 × 25 mg/week, 2 × 50 mg/week, 50 mg/week)—in some studies not always specified [14–16, 24]—and time horizons (ranging from 12 weeks to 2 years). The NHS perspective was adopted in the majority of studies (there was only one total economic evaluation that included indirect costs) and was restricted almost exclusively to pharmacological costs. The cost of induction in Spain was €9110–9370 and €12,797 per PASI 75 responder at 12 weeks at 2 × 25 mg and 2 × 50 mg weekly doses, respectively [11, 12], and €11,213–16,080 per PASI 75 responder at 24 weeks [11, 12, 21] (even though the studies of Blasco et al. [11] and Ferrandiz et al. [12] differ, both sets of authors reported practically identical results). A study by Alfageme et al. [18] yielded a cost of €14,337 per PASI 75 responder at 12 weeks (doses not detailed).

Other studies reported the annual cost of reaching PASI 75 or for achieving "therapeutic success" per patient-PASI 75 (€23,034/PASI 75 at 1 year to €20,178/patient treated successfully at 1 year) [13, 22, 23], but these results were difficult to group with others due to methodological differences, as was the the case with results for PASI 90 patients at 2 years who also used biological drug treatment sequences [15, 16]. The only ETN cost-benefit analysis presented an incremental cost–benefit ratio for the 2 × 25 mg/week regimen

Table 2 Results of the partial economic evaluations on the use of etanercept to treat psoriasis and psoriatic arthritis in Spain

First author/year of publication [reference] (year of costs)	Direct costs	Indirect costs	Total costs
Psoriasis			
Domínguez/2011 [27] (ND)	Year during which ETN treatment was started (year 1): €15,268/patient-year	N/A	Year during which ETN treatment was started (year 1): €15,268/patient-year
	ETN maintenance year (year 2): €14,420/patient-year		ETN maintenance year (year 2): €14,420/patient-year
Ruano/2013 [28] (2012)	Direct healthcare costs:	€380 ± 157/patient-year	€14,844 ± 6,179/patient-year
	Pharmacological: €14,452 ± 5606/patient-year		
	Consumption of healthcare resources: €251 ± 148/patient-year		
	Direct non-healthcare costs:		
	Transport: €173 ± 293/patient-year		
Puig/2014b [31] (2013)	Escalation of ETN vs. ADA (every 2 weeks):	N/A	Escalation of ETN vs. ADA (every 2 weeks)
	Cost of switching to ADA: €13,602/patient-year		Cost of switching to ADA: €13,602/patient-year
	Escalation of ETN: €14,580/patient-year		Escalation of ETN: €14,580/patient-year
	Difference: €978/year (6.7%)		Difference: €978/year (6.7%)
	Escalation of ETN vs. UST (every 3 months):		Escalation of ETN vs. UST (every 3 months)
	Cost of switching to UST: €13,670/patient-year		Cost of switching to UST: €13,670/patient-year
	Escalation of ETN: €14,580/patient-year		Escalation of ETN: €14,580/patient-year
	Difference of €909/year (6.2%)		Difference of €909/year (6.2%)
	Escalation of ETN vs. UST (every 12 weeks):		Escalation of ETN vs. UST (every 12 weeks)
	Cost of switching to UST: €14,681/patient-year		Cost of switching to UST: €14,681/patient-year
	Escalation of ETN: €15,719/patient-year		Escalation of ETN: €15,719/patient-year
	Difference: €1037/year (6.6%)		Difference: €1037/year (6.6%)
	Escalation of ETN vs. INF (every 2 months):		Escalation of ETN vs. INF (every 2 months)
	Cost of switching to INF: €16,763/patient-year		Cost of switching to INF: €16,763/patient-year
	Escalation of ETN: €17,769/patient-year		Escalation of ETN: €17,769/patient-year
	Difference: €1005/year (5.7%)		Difference: €1005/year (5.7%)
	Escalation of ETN vs. INF (every 8 weeks):		Escalation of ETN vs. INF (every 8 weeks)
	Cost of switching to INF: €17,911/patient-year		Cost of switching to INF: €17,911/patient-year
	Escalation of ETN: €18,908/patient-year		Escalation of ETN: €18,908/patient-year
	Difference: €997/year (5.3%)		Difference: €997/year (5.3%)

Table 2 continued

First author/year of publication [reference] (year of costs)	Direct costs	Indirect costs	Total costs
Fernández-Torres/2015 [29] (ND)	€244.60 ± 45.20/PASI 75 in 1 week	N/A	€244.60 ± 45.20/patient-week
Ruiz-Villaverde/2016 [30] (ND)	11,299 (95% CI €10,551–12,046)/patient-year	N/A	11,299 (95% CI €10,551–12,046)/patient-year
	Continuous treatment:		Continuous treatment:
	Cost of the induction phase (year 1): €12,294/patient-year		Cost of the induction phase (year 1): €12,294/patient-year
	Cost of the maintenance phase (year 2): €12,327/patient-year		Cost of the maintenance phase (year 2): €12,327/patient-year
	Intermittent treatment:		Intermittent treatment:
	Cost of the induction phase (year 1): €10,302/patient-year		Cost of the induction phase (year 1): €10,302/patient-year
	Cost of the maintenance phase (year 2): €4986/patient-year		Cost of the maintenance phase (year 2): €4986/patient-year
Psoriatic arthritis			
Acosta/2012 [8] (ND)	€8585/patient-year	N/A	€8585/patient-year

that was higher than those reported in Germany (€18,154/QALY) [44] and Italy (€25,840/QALY) [45], although this could be considered to be an efficient alternative conditioned to the cost-effectiveness thresholds routinely considered in Spain (€25,000–30,000/QALY) [46, 47].

Similar to the complete economic evaluations, the partial economic evaluations primarily focused on treatment of PSO, with only one evaluation (cost analysis) presenting economic impact data on treatment of PsA. The majority of these were observational studies with a time horizon of between 1 and 2 years and restricted to evaluations of the costs of ETN treatment. The perspective in all studies but one was that of the NHS [28], which contrasts with the perspective used in another review on the overall impact of these pathologies in Europe [4] in which the social perspective was primarily used. The annual cost per PSO patient receiving ETN treatment varied widely (€4,986–€15,268/patient-year) [27, 30], resulting in an annual cost of €18,908/patient if an extension of 31 weeks of escalated treatment is considered [31], suggesting that it may be higher than the overall cost of the pathology reported in Europe (13,132 USD-PPP) [4]. In contrast to the above, the annual cost per patient reported by the only publication on the use of ETN in the treatment of PsA in Spain is significantly lower than the referenced study (€8,585/patient-year vs. €10,924–17,050 USD-PPP/patient-year) [4].

A third analysis category, namely study type, includes publications on dose optimization (37.5%), observational and cross-sectional studies with types of procedures (dose escalation, spacing and optimization protocols, switching to biosimilars) and highly heterogeneous cost measures (cost before and after protocol implementation, percentage of saving, actual or theoretical annual cost) that hinder the standardization of the results, although they do highlight the importance of these types of procedures for health professionals.

There are various limitations to our sytematic review which need to be taken into account when interpreting the results. First, given the exhaustiveness of the search strategy, a high proportion of communications to national and international congresses were included—a format which, given its limited extension, routinely includes little information on methodological aspects. This approach led us to not evaluate the quality of the publications

Table 3 Results of the studies on modification of the dosing regimen used to treat psoriasis and psoriatic arthritis in Spain

First author/year of publication [reference] (year of costs)	Effectiveness results	Cost results
Psoriasis		
Fernández-Espínola/ 2013/ [36] (ND)	Variation of average treatment rest time after protocol vs. before protocol: 8.5 weeks Before protocol Baseline PASI: NR Time until reaching PASI 75: NR Time until disease remission: 22.5 weeks (SD 8.8) Number of restarts per patient: 1.8 (SD 0.6) After protocol Baseline PASI: 23.2 (SD 10.1) Time until reaching PASI 75: 30.4 weeks Time until disease remission: 31 weeks (SD 15 weeks) Number of restarts per patient: 2.6 (0.7)	Estimated potential saving due to increasing the dosing interval (more rest) after protocol implementation over 2 years: €2012/patient in 2 years
Baniandres/2015 [32] (2014)	Average dose reduction/patient-year: 13.8% Patient with standard regimen: 54% Dose reduction of standard regimen (2 × 25 mg/week) to: 25 mg/week: 4.2% 25 mg/10 days: 8.3% 50 mg/10 days: 20.8% 50 mg/2 weeks: 8.3% Dose escalation to 100 mg/week over a period of longer than 12 weeks: 4.2%	Saving of ETN (%): 13.8 (total expenditure: €246,046) Average actual cost for ETN, taking into account all modifications (standard, reduction and escalation): €10,252/patient-year Actual annual cost of the standard ETN regimen: €11,886/patient-year Actual annual cost of the reduced ETN regimen: 25 mg/week: €8320/patient-year 25 mg/10 days: €5943/patient-year 50 mg/10 days: €5943/patient-year 50 mg/2 weeks: €4160/patient-year Actual annual cost of escalated ETN regimen: €23,773/patient-year

Table 3 continued

First author/year of publication [reference] (year of costs)	Effectiveness results	Cost results
Romero-Jiménez/2015 [40] (ND)	Dose spacing in patients receiving ETN treatment: 37.5% Doses used vs. doses on the ETN SPC: 92.8%	Annual saving after protocol implementation with ETN: €15,216/year
Ríos-Sanchez/2015 [33] (ND)	% patients with PASI 75: 90%	Actual cost: €10,389/patient-year Estimated theoretical cost (theoretical prescribed doses): €11,576/patient-year Estimated actual cost (actual prescribed doses): €9445/patient-year
Romero-Jiménez/2016 [37] (2014)	% patients with dose reduction (increased administration interval): 37.5% Pre-protocol period % patients who reached PASI 75: 60% % standard dose used (95% CI) 98.1 (79.8–116.4) Post-protocol period % patients who reached PASI 75: 63% % standard dose used (95% CI) 92.8 (77.1–108.6)	Pre-protocol period Actual cost of the pre-protocol period/patient-year (95% CI) €11,661 (€9702–13,620)/patient-year Saving corresponding to the pre-protocol period (actual dose vs. standard dose) (95% CI) €225 (€-1734–2184) patient-year[a] Post-protocol period Actual cost of the post-protocol period (95% CI) €11,028 (€8951.60–13,104.40)/patient-year Saving corresponding to the post-protocol period (actual dose vs standard dose) (95% CI) €859 (€-1217–2935.40)/patient-year
Corregidor/2016 [41] (ND)	% patients receiving standard regimen of ETN (50 mg/week): 51.1% % patients receiving optimized regimen: 6.2% % patients receiving the escalated regimen (100 mg/week): 42.7%	Difference between the actual overall cost and the theoretical overall cost: €99,832/year (representing an increase of €4754/patient-year for ETN)
Rosado/2017/) [43] (ND)	Same PASI level as before switching to biosimilar No adverse effect was recorded during the process	Monthly saving of €6766.20 (percentage saving: 18.7%)

Table 3 continued

First author/year of publication [reference] (year of costs)	Effectiveness results	Cost results
Psoriatic arthritis		
Borras-Blasco/2014 [36] (2012)	Average time receiving treatment with ETN 25 mg/week: 0.9 ± 0.2 DAS 28/BASDAI Baseline (ETN 50 mg/week): 2.4 ± 1.2 Start of regimen 25 mg/week: 1.7 ± 0.4 Regimen 25 mg/week ≥ 6 months: 2.1 ± 0.4	Total saving made by switching ETN 50 mg/week to ETN 25 mg/week (7 years): €81,949 in 7 years.
Borras-Blasco/2014a [34] (ND)	NR	Cost corresponding to the pre-protocol period: €11,480/patient-year
Borras-Blasco/2014b [39] (ND)		Cost corresponding to the post-protocol period: €10,687/patient-year (€10,657/patient-year for Borrás-Blasco et al. [36])
Rentero/2016 [42] (ND)	NR	Intervention period: €883.82 per patient in 6 months Pre-intervention period: €824.74 per patient in 6 months
Prada-Ojeda/016 [35] (ND)	NR	Saving entailed by switching from the standard regimen procedure to: 25 mg/week regimen: €3937.96/year 25 mg/10 days regimen: €2503.80/year

BASDAI Bath Ankylosing Spondylitis Disease Activity Index, *DAS* Disease activity Score, *N/A* not applicable, *NR not reported, SD* standard deviation, NHS Spanish National Health Service, *SPC* summary of product characteristics

[a] Statistically significant differences between the pre-protocol period and the post-protocol period ($p < 0.05$)

selected through a valid tool, such as the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) [48]. Second, the cost outcomes obtained were not updated to 2019 values (€, 2019), thus hindering comparability with other results. However, given the diversity of the incremental efficacy variables and the time horizons used (patient-year, patient/PASI 75 at 12 weeks, QALY) in the selected studies, it is difficult to unify the results. Third, the heterogeneity of this review is assumed, given that two pathologies (PSO and PsA) and the different ETN treatment regimens have been reviewed, as well as the different outcome measurements, in an attempt to succinctly collect all available information.

CONCLUSION

To conclude, the economic evaluations conducted in Spain on the use of ETN to treat PSO and PsA should be framed within the context of high heterogeneity, mainly due to substantial

differences in the design of the studies performed to date (e.g. different dosing regimens, different efficacy measurements, different time horizons, etc.), yielding a wide range of costs and leading to a lack of consistent evidence.

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