ORIGINAL ARTICLES

Efficiency of Biologic Agents in the Treatment of Moderate to Severe Psoriasis

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Abstract   *Background.* In the treatment of psoriasis, biologic agents are more expensive than conventional therapy while showing similar or superior efficacy. However, their efficiency in terms of cost/efficacy (cost per responder in clinical trial conditions) is unknown.

Objective. To estimate the cost/efficacy ratios of adalimumab, etanercept, infliximab, and efalizumab in the management of moderate to severe psoriasis.

Material and Methods. A model for costs analysis was elaborated by building a decision tree for each of the treatments for which scientific evidence was available. The payer perspective (Spanish national health system) was used, only considering drug costs. The efficacy (proportion of patients who respond according to Psoriasis Area and Severity Index [PASI] 75 criterion) was assigned according to the results of the clinical trials. When more than 1 trial was available per treatment, a meta-analysis was undertaken. In the case of weight-dependent dosing, the weight of the study participants was adjusted by age and sex to the standard Spanish population with correction for increased weight in individuals with psoriasis. Uncertainty was investigated with a sensitivity analysis.

Results and Conclusions. Assigning the efficacy reported in the 15 published clinical trials, the most efficient biologic agent in terms of the cost/efficacy ratio was adalimumab, with one PASI75 response at a cost of €8013.

For the remaining biologic agents and with different regimens, the cost per responder ranged from €9370 to €17 112. The sensitivity analysis confirmed the robustness of these figures.

Key words: psoriasis, efficiency, biologic agents, meta-analysis.

EFICIENCIA DE LOS AGENTES BIOLÓGICOS EN EL TRATAMIENTO DE LA PSORIASIS MODE-RADA-GRAVE

Resumen.   *Introducción.* Los agentes biológicos en el tratamiento de la psoriasis son más caros y, en general, de eficacia similar o superior que la terapia clásica. Sin embargo, se desconoce su eficiencia en términos de coste/eficacia (coste por cada paciente que responde en las condiciones de los ensayos clínicos).

Objetivo. Estimar los cocientes de coste/eficacia de adalimumab, etanercept, infliximab y efalizumab en el manejo de la psoriasis moderada-grave.

Material y métodos. Modelo de evaluación económica, construyendo un árbol de decisión para cada uno de los tratamientos sobre los que existe evidencia científica. Se ha usado la perspectiva del financiador (Sistema Nacional de Salud), considerando sólo los costes del fármaco. La eficacia (proporción de pacientes que responden con el criterio PASI-75) asignada es la que consta en los ensayos clínicos. Cuando había más de un ensayo para cada tratamiento se han realizado metanálisis. Cuando la dosis depende del peso, este último en los sujetos del estudio se ha estandarizado por edad y sexo a la población española, corregido por el incremento de peso de los sujetos con psoriasis. La incertidumbre se ha manejado mediante análisis de sensibilidad.

Resultados y conclusiones. Asignando en los modelos la eficacia de los 15 ensayos clínicos publicados, el agente biológico más eficiente en términos de coste/eficacia es adalimumab, con el que se consigue un respondedor PASI75 a un coste de 8.013 euros. Con el resto de los biológicos y con diferentes pautas el coste/respondedor osciló entre 9.370 € y 17.112 €. El análisis de sensibilidad confirma la robustez de estos hallazgos.

Palabras clave: psoriasis, eficiencia, terapia biológica, metanálisis.

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Introduction

Psoriasis is an inflammatory skin disease of unknown origin that generally follows a chronic, relapsing course. Diagnosis is essentially clinical and involves the identification of erythematous plaques with pearly scales and well-defined borders. The disease is generally characterized by spontaneous remissions and relapses and can last a lifetime or just a few months. It has an estimated prevalence of between 1.5% and 3% in the white population and affects both sexes. It can appear at any age, although it is rare in children under 5 years old. An estimated 125 million people in the world have psoriasis,[1] and the prevalence rate in Spain is 1.4%.[2] Between 5% and 7% of patients with psoriasis and approximately 40% of those with extensive skin disease develop psoriatic arthritis.[3] The most common instrument used to assess psoriasis severity in clinical trials is the Psoriasis Area and Severity Index (PASI). According to the European Medicines Agency, a 75% reduction in the PASI (PASI75) in a clinical trial indicates treatment response in a patient with severe psoriasis.[4]

Psoriasis can be treated with phototherapy or with topical or systemic treatments, depending on the severity of the disease. Systemic treatments have traditionally included methotrexate, acitretin, and cyclosporine A, although new biologic agents have emerged as an alternative for the management of psoriasis in recent years.[3,5-8] These agents can be divided into 2 groups:

1. Agents that target tumor necrosis factor-α (eg, etanercept, infliximab, and adalimumab)
2. Agents that specifically interfere with T-cell activation or function (eg, efalizumab and alefacept)

Biologic agents are more expensive than conventional treatments and show similar or superior efficacy.[8,9] Their efficiency in terms of cost/efficacy (cost per successful treatment), however, is unknown. The general aim of the present study was to generate knowledge on the efficacy of biologic agents in the treatment of psoriasis. The specific aim was to calculate the cost/efficacy ratio for 4 biologic agents (adalimumab, etanercept, infliximab, and efalizumab) in patients with moderate to severe psoriasis.

Methods

Design

We performed an economic evaluation of the efficiency (cost/efficacy) of 4 biologic agents (adalimumab, etanercept, infliximab, and efalizumab) by building deterministic decision trees and performing sensitivity analysis. The decision trees were built to calculate the direct costs, efficacy (rate of PASI75 responders), and efficiency (cost/efficacy) of each of the 4 treatments according to dose and duration of treatment. Each decision tree was built from data from clinical trials that analyzed the corresponding treatments and compared them to placebo. The simplified model had 2 branches: a treatment branch and a placebo branch (Figure). Costs were analyzed from the perspective of the payer, which in this case was the Spanish national health system, with only direct costs (cost of the biologic agents to the national health system) considered. The time horizon used for each model was the same as the duration of the clinical trials on which the comparisons were based.[9,23] No time-related adjustments (discount rates or future results) were necessary as both cost and efficacy results were obtained within 24 weeks at the most.

Synthesis of Scientific Evidence on Efficacy

To apply efficacy estimators to the model, we first searched for scientific evidence in the Medline and Embase databases, the Cochrane Central Register of Controlled Trials, and the Spanish medical index (Índice Médico Español). Our search included terms related to clinical trials and psoriasis in English and Spanish (*psoriasis, psoria*, clinical trial, randomized trial, controlled trial, ensayo clínico, ensayo aleatorio, ensayo aleatori*,* and *ensayo controlado*) and was restricted to the following drug names: adalimumab, Humira, efalizumab, Raptiva, etanercept, Enbrel, infliximab, and Remicade. We limited the search to articles published in English and Spanish up to March 2008. After analyzing the results, we eliminated duplicate references. The abstracts for the remaining publications were obtained and read independently by 2 of the researchers (AJB and PL), who then excluded studies that did not meet the inclusion criteria and ordered the full articles for those that potentially did. These articles were also read independently by the same 2 researchers, who decided on the basis of the inclusion criteria whether or not to include the study in the final analysis. For a study/article to be included, it had to:

1. Be an original article
2. Be a randomized controlled trial
3. Specifically mention the clinical definition of moderate to severe psoriasis
4. Include at least 1 of the study drugs (adalimumab, efalizumab, etanercept, or infliximab)
5. Include placebo as one of the comparators
6. Include the PASI75 as 1 of the response variables

All sample sizes, treatment regimens, and study durations were considered acceptable.
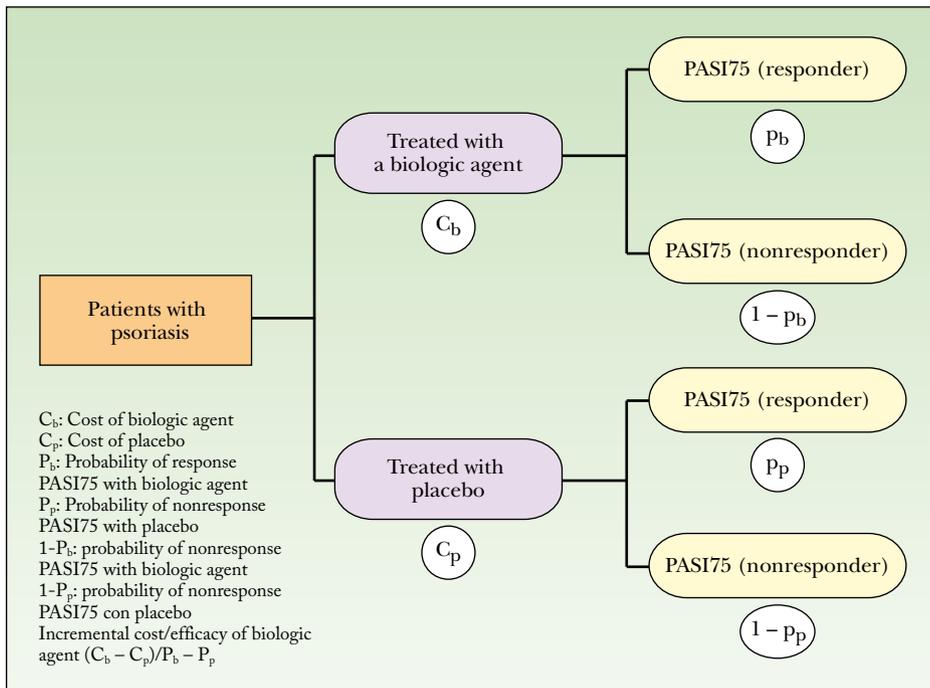
C_b: Cost of biologic agent
C_p: Cost of placebo
P_b: Probability of response PASI75 with biologic agent
P_p: Probability of nonresponse PASI75 with placebo
1-P_b: probability of nonresponse PASI75 with biologic agent
1-P_p: probability of nonresponse PASI75 con placebo
Incremental cost/efficacy of biologic agent $(C_b - C_p)/P_b - P_p$

Figure. Simplified model of Decision Tree.

PASI75 indicates a 75% reduction in the Psoriasis Area and Severity Index.

The branches of each decision tree were assigned the corresponding treatment and placebo efficacy measures. Efficacy was measured as the probability of achieving a PASI75 response based on the scientific evidence provided by the clinical trials analyzed.[9-23] The efficacy of the biologic agent compared to placebo was measured by incremental efficacy, ie, the gain in the proportion of PASI75 responders with the biologic agent compared to placebo, shown in the Figure as Pb-Pp. Expressed in clinical epidemiology terms, incremental efficacy is the absolute reduction of the risk of not achieving a PASI75 response.

For agents that had been analyzed by just 1 clinical trial, we calculated incremental efficacy and confidence intervals (CIs) as the difference in proportions between the efficacy of the biologic agent and placebo using the Fleiss method.[24] For agents that had been analyzed by more than 1 trial, we performed a meta-analysis, calculating the absolute risk reduction (incremental efficacy) and corresponding CIs, assuming a model of random effects (DerSimonian-Laird method).[25] The degree of heterogeneity between trials was measured using I^2, whose value ranges from 0% to 100%.[26] This parameter reflects the level of inconsistency between different trials included in a meta-analysis. Although there is no categorization of recommended I^2 values, it is generally accepted that values of 25%, 50%, and 75% reflect low, moderate, and high inconsistency, respectively.[26]

As an additional measure of efficacy, we calculated the number needed to treat (NNT) to achieve 1 PASI75 responder. The NNT, together with its corresponding CI, was calculated as the inverse of the absolute risk reduction, ie, the inverse of incremental efficacy.

Allocation of Treatment Costs

We considered differential costs only, ie, the cost of buying the drugs directly from the manufacturer (ex-factory price), and assumed that the rest of the costs would be identical for each of the agents studied. To calculate the cost of each treatment, we noted the dose received by each patient in the clinical trials on which our analysis was based and multiplied this by the ex-factory price for the dose. To calculate ex-factory prices, we used the recommended retail prices (RRPs) listed in the drug database held by the General Spanish Council of Pharmacists and made available on its website.[27] We then converted this price (RRP plus value added tax) to the ex-factory price using the conversion factors established by the Spanish General Directorate for Pharmacy and Health Products.[28] A summary of these prices is shown in Table 1. For drugs supplied in vials, we calculated the number of vials necessary to achieve the required dose (in mg) and counted the full cost of each vial, even if only a part of the last vial was used.

Table 1. Cost of Biologic Agents in Spain, 2008

Biologic Agent	Presentation	Price per Presentation, €		Ex-factory Unit Price	
		RRP + VAT	Ex-factory Price	Price, €	Unit
Adalimumab	Two 40-mg pens	1 116.12	1028.29	514.15	40-mg pen
Infliximab	One 100-mg/20-mL vial	604.43	536.28	536.28	100 mg vial
Etanercept	Four 25-mg syringes	539.25	473.61	118.40	25-mg syringe
	Four 50-mg syringes	1 031.80	947.22	236.80	50-mg syringe
Efalizumab	Four 125-mg vials	1 045.02	959.93	239.98	125-mg vial

Abbreviations: RRP, recommended retail price; VAT, value-added tax.

For example, if a patient needed 347 mg of a drug supplied in 100-mg vials, we calculated the cost of four 100-mg vials.

In the case of weight-dependent dosing (infliximab and efalizumab), we based our calculations on the weight of the patients. Because not all of the studies contained details of patient weight and to make our analysis valid for Spain, we calculated the weight of patients as if they were Spanish using the mean weight of Spanish adults[29] adjusted for age and sex in accordance with the age and proportion of men and women in the studies. This standardized weight was then increased to reflect the weight difference between patients with psoriasis and members of the general population of the same age and sex. To calculate this weight difference, we used the difference in body mass index (BMI) reported for these groups by Herron et al.[30] Because the study by Herron et al contained information on BMI but not on weight, we adjusted the BMI to the standard Spanish population of the same age and sex and calculated the patients' weight using the BMI corresponding to the standard height reported for Spanish adults in accordance with age and sex.[29]

Calculation of Incremental Cost/Efficacy Ratio

To determine the efficiency of each biologic agent with respect to placebo, we calculated the incremental cost/efficacy ratio, in which the numerator was the difference in costs between the treatments being compared (biologic agent vs placebo) and the denominator was the incremental efficacy. In the Figure, this ratio is shown by the formula $(Cb - Cp)/(Pb - Pp)$, where Cb is the cost of the biologic agent; Cp, the cost of placebo; Pb, the probability of response with the biologic agent; and Pp, the probability of response with placebo.

Sensitivity Analysis

Economic evaluation models are characterized by an inherent level of uncertainty resulting from the cost and efficacy estimates used and the assumptions of the model. To analyze the impact of this uncertainty on the efficiency of the biologic agents analyzed in our study, we performed a sensitivity analysis. We considered 3 scenarios: a baseline scenario, a best-case scenario, and a worst-case scenario for each treatment. In the baseline scenario, efficiency ratios were calculated using the central estimate of the incremental cost of each biologic agent as the numerator and the central estimate of the incremental efficacy of the agent as the denominator. In the best-case scenario, the numerator and denominator were the best-case estimates of incremental cost and efficacy, respectively, and in the worst-case scenario, they were the worst-case estimates of cost and efficacy, respectively.

To calculate the best-case and worst-case estimates of incremental cost, we used a variety of approaches depending on the information available. In cases of weight-dependent dosing in which we were missing information on weight (infliximab and efalizumab), we used the mean weight of the Spanish population adjusted to the age and sex of the study patients and the weight difference between patients with psoriasis and members of the general population.[29,30] We calculated the best-case and worst-case estimates by adjusting the CIs for the weight difference between individuals with and without psoriasis reported by Herron et al[30] to the weight of the Spanish population.[29] The baseline, best-case, and worst-case costs of fixed-dose drugs (adalimumab and etanercept) coincided.

To calculate the best-case and worst-case estimates of incremental efficacy, we used the upper (best-case) and lower (worst-case) limits of the 95% CI. In the case of drugs for which we had evidence from a single clinical trial, we calculated the difference between proportions using the Fleiss method.[24] For drugs in which evidence

was based on more than 1 clinical trial, we calculated the absolute risk reduction and corresponding CIs using the DerSimonian-Laird method (random effects model).[25] We used the Spanish version of the Critical Appraisal Skill Program[31] (CASPe) for the meta-analysis and Microsoft Word Excel for the economic evaluation.

Results

Sources of Scientific Evidence

In our search for scientific evidence, we identified 15 clinical trials analyzing the efficacy of biologic agents in the treatment of moderate to severe psoriasis that met our inclusion criteria.[9-23] None of the trials had been published in Spanish. Information on doses, dose regimens, and efficacy for each of the biologic agents studied was taken from the reports of the 15 clinical trials analyzed. The trials had been performed in different countries, with results published between 2001 and 2008. Adalimumab was analyzed by 2 articles,[9,10] etanercept by 4,[11-14] infliximab by 4,[15-18] and efalizumab by 5.[15-23] Although several of the studies analyzed a range of doses, in our analysis, we only took into account doses and treatment regimens specified in the corresponding summaries of product characteristics.[32-35] In some of the trials, the placebo group was also treated with the biologic agent during the study period. In such cases, we considered the treatment duration as the time during which the patients received the placebo. The duration of treatment in the different trials ranged from 10 to 24 weeks.

A summary of the characteristics of the trials is shown in Table 2.

Cost/Efficacy of Adalimumab

Two of the 15 clinical trials compared the efficacy of adalimumab with that of placebo at 16 weeks.[9,10] The patients in the study group received 80 mg of adalimumab subcutaneously at week 0, followed by 40 mg every 2 weeks from week 1 to week 15. The cost of treatment per patient was €5141 in the 3 scenarios studied (baseline, best-case, and worst-case). Our meta-analysis of the results of the 2 trials showed that the incremental efficacy of adalimumab over placebo was 64.16% (95% CI, 60.38%-67.94%). The NNT was 2 (95% CI, 2-2). The I^2 was 0%, meaning that there was no inconsistency between the studies analyzed. The incremental cost/efficacy ratio in the baseline scenario was €8013 per PASI75 responder; the corresponding figures for the best-case and worst-case scenarios, respectively, were €7568 and €8515 (Table 3).

Cost/Efficacy of Etanercept

Three different treatment regimens in terms of dose and duration were used in the trials that analyzed etanercept.[11-14] These regimens were 25 mg twice a week for 12 weeks,[11-13] 25 mg twice a week for 24 weeks,[13] and 50 mg twice a week for 12 weeks.[11,12,14]

In our meta-analysis, we analyzed the efficacy of etanercept administered at a dose of 25 mg twice a week for 12 weeks, which was the regimen used by 3 of the trials.[11-13] The cost of treatment per patient was €2842 in the 3 scenarios studied (baseline, best-case, and worst-case) and the incremental efficacy over placebo was 30.33% (95% CI, 25.49%-35.16%). The NNT was 4 (95% CI, 4-3). The I^2 was 0%, meaning that there was no inconsistency between the trials analyzed. Based on the incremental efficacy and cost information, we calculated an incremental cost/efficacy ratio of €9370 for the baseline scenario, €8082 for the best-case scenario, and €11147 for the worst-case scenario (Table 4).

The efficacy of etanercept at a twice-weekly dose of 25 mg for 24 weeks was analyzed by just 1 trial.[13] The cost of treatment per patient for this regimen was €5683 for the 3 scenarios studied (baseline, best-case, and worst-case). The incremental efficacy over placebo was 50.69% (95% CI, 36.47%-64.90%) and the NNT was 2 (95% CI, 2-3). The incremental cost/efficacy ratio was €11 213 in the baseline scenario, €8757 in the best-case scenario, and €15 582 in the worst-case scenario (Table 4).

We used a meta-analysis to examine the efficacy of etanercept administered at a dose of 50 mg twice a week for 12 weeks, a regimen analyzed by 3 trials.[11,12,14] The cost of treatment per patient was €5683 in the 3 scenarios studied (baseline, best-case, and worst-case). The incremental efficacy over placebo was 44.41% (95% CI, 40.34%-48.48%), and the NNT was 3 (95% CI, 3-3). The I^2 was 0%, meaning that there was full consistency between the trials included in the meta-analysis. On the basis of the above data, we calculated an incremental cost/efficacy ratio of €12 797 for the baseline scenario, €11 722 for the best-case scenario, and €14 088 for the worst-case scenario (Table 4).

Cost/Efficacy of Infliximab

We identified 4 clinical trials that analyzed the efficacy of infliximab.[15-18] The dose used in all 4 trials was 5 mg/kg, administered over either 10[15-18] or 24 weeks.[15] The drug was administered at weeks 0, 2, and 6 in the 10-week regimen and at weeks 0, 2, 6, 14, and 22 in the 24-week regimen. Infliximab comes in a 100-mg presentation form (20 mL vial containing 100 mg of powder).[34] When assigning costs to doses, fractional doses of 100 mg were priced as full 100-mg doses.

Table 2. Scientific Evidence Used

Study	Year	Area	Duration, wk	Drug	Dose Regimen	No. of Patients
Saurat et al[9]	2008	Europe, Canada	16	Adalimumab	80 mg + 40 mg/2 wk	108
				Placebo	53	53
Menter et al[10]	2008	USA, Canada	16	Adalimumab	80 mg + 40 mg/2 wk	814
				Placebo	398	398
Leonardi et al[11]	2003	USA	12	Etanercept	2 × 25 mg/wk	162
					2 × 50 mg/wk	164
				Placebo	166	166
Papp et al[12]	2005	USA, Europe, Canada	12	Etanercept	2 × 25 mg/wk	196
					2 × 50 mg/wk	194
				Placebo	193	193
Gottlieb et al[13]	2003	USA	12, 24	Etanercept	2 × 25 mg/wk	57
				Placebo	55	55
Tyring et al[14]	2006	USA	12	Etanercept	2 × 50 mg/wk	311
				Placebo	306	306
Reich et al[15]	2005	Europe, Canada	10, 24	Infliximab	5 mg/kg[a]	301
				Placebo	77	77
Menter et al[10]	2007	USA, Europea, Canada	10	Infliximab	5 mg/kg[b]	314
				Placebo	208	208
Chaudhari et al[17]	2001	USA	10	Infliximab	5 mg/kg[b]	11
				Placebo	11	11
Gottlieb et al[18]	2004	USA	10	Infliximab	5 mg/kg[b]	99
				Placebo	51	51
Leonardi et al[11]	2005	USA, Canada	12	Efalizumab	1 mg/kg wk[c]	162
				Placebo	170	170
Gordon et al[20]	2003	USA, Canada	12	Efalizumab	1 mg/kg/wk[c]	363
				Placebo	183	183
Dubertret et al[21]	2006	Europe, Australia, Mexico, Canada	12	Efalizumab	1 mg/kg/wk[c]	529
				Placebo	264	264
Papp et al[22]	2006	USA, Canada	12	Efalizumab	1 mg/kg/wk[c]	450
				Placebo	236	236
Lebwohl et al[23]	2003	USA, Canada	12	Efalizumab	1 mg/kg/wk[c]	232
				Placebo	122	122

[a] Administered at weeks 0, 2, 6, 14, and 22.
[b] Administered at weeks 0, 2, and 6.
[c] With a starting dose of 0.7 mg/kg.

We conducted a meta-analysis of the 4 trials that analyzed the efficacy of infliximab administered at a dose of 5 mg/kg for 10 weeks.[15-18] The resulting cost per patient was €8044 in the baseline and worst-case scenarios and €6435 in the best-case scenario. Based on the results of this meta-analysis, the incremental efficacy of infliximab over placebo was 76.44% (95% CI, 72.41%-80.48%), and the NNT was 2 (95% CI, 2-2). The I^2 was 16%, indicating

Table 3. Cost/Efficacy of Adalimumab Compared to Placebo (16 Wk)

Trial	No of Pati-ents	Weight %	Costs, €			Efficacy[a]		Incremental Efficacy[a]			Incremental Cost/Efficacy, €[b]		
			Base-line	Best Case	Worst Case	Placebo	Adalimumab	Base-line	Best Case	Worst Case	Base-line	Best Case	Worst Case
Saurat et al[9]	161	8.5	5141	5141	5141	18.87	79.63	60.76	73.75	47.77	8462	6972	10762
Menter et al[10]	1212	91.5	5141	5141	5141	6.53	71.01	64.47	68.43	60.52	7974	7514	8495
Meta-analysis	1373	100.0	5141	5141	5141	7.98	72.02	64.16	67.94	60.38	8013	7568	8515

[a] Percentage of patients that obtained a 75% reduction in the Psoriasis Area and Severity Index Score (PASI75 responders).
[b] Cost per PASI75 responder gained.

Table 4. Cost/Efficacy of Etanercept Compared to Placebo

Trial	No of Pati-ents	Weight %	Costs, €			Efficacy[a]		Incremental Efficacy[a]			Incremental Cost/Efficacy, €[b]		
Dose Regimen: 25 mg Twice Weekly for 12 wk													
			Base-line	Best Case	Worst Case	Placebo	Etanercept	Base-line	Best Case	Worst Case	Base-line	Best Case	Worst Case
Leonardi et al[11]	328	38.1	2842	2842	2842	3.61	33.95	30.34	38.16	22.51	9367	7446	12624
Papp et al[12]	389	46.6	2842	2842	2842	3.11	34.18	31.07	38.15	24.00	9145	7448	11842
Gottlieb et al[13]	112	15.2	2842	2842	2842	1.82	29.82	28.01	40.40	15.62	10146	7034	18197
Meta-analysis	829	100.0	2842	2842	2842	3.14	33.49	30.33	35.16	25.49	9370	8082	11147
Dose Regimen: 25 mg Twice Weekly for 24 Weeks													
Gottlieb et al[13]	112	na	5683	5683	5683	5.45	56.14	50.69	64.90	36.47	11213	8757	15582
Dose Regimen: 50 mg Twice a Wek for 12 Weeks													
Leonardi et al[11]	330	24.9	5683	5683	5683	3.61	49.39	45.78	53.94	37.61	12415	10537	15110
Papp et al[12]	387	29.9	5683	5683	5683	3.11	49.48	46.38	53.83	38.93	12255	10559	14600
Tyring et al[14]	617	45.2	5683	5683	5683	4.90	47.27	42.36	48.42	36.31	13415	11738	15651
Meta-analysis	1334	100.0	5683	5683	5683	4.06	48.43	44.41	48.48	40.34	12797	11722	14088

Abbreviation: NA, nonapplicable.
[a] Percentage of patients that obtained a 75% reduction in the Psoriasis Area and Severity Index Score (PASI75 responders).
[b] Cost per PASI75 responder gained.

a low level of inconsistency between the trials analyzed. The incremental cost/efficacy ratio was €10 523 in the baseline scenario, €7996 in the best-case scenario, and €11 109 in the worst-case scenario (Table 5).

The efficacy of infliximab at 5 mg/kg was analyzed in just 1 clinical trial lasting 24 weeks.[15] The cost of treatment per patient in this case was €13 407 for the baseline and worst-case scenarios and €10 726 for the best-case scenario. The incremental efficacy was 78.35% (95% CI, 71.27%-85.43%) and the NNT was 2 (95% CI, 2-2). The

resulting incremental cost/efficacy ratio was €17 112 for the baseline scenario, €12 555 for the best-case scenario, and €18 812 for the worst-case scenario (Table 5).

Cost/Efficacy of Efalizumab

Five clinical trials, each of which analyzed the efficacy of efalizumab at 12 weeks[19-23] were included in our meta-analysis of efalizumab. The patients received a

Table 5. Cost/Efficacy of Infliximab Compared to Placebo

Trial	No. of Patients	Weight, %	Costs, €			Efficacy[a]		Incremental Efficacy[a]			Incremental Cost/Efficacy, €[b]		
			Basaline	Worst Case	Best Case	Placebo	Infliximab	Base-line	Best Case	Worst Case	Base-line	Best Case	Worst Case
Dose Regimen: 5 mg/kg for 10 wk													
Reich et al[15]	378	37.2	8044	6435	8044	2.60	80.40	77.80	83.52	72.08	10339	7705	11160
Menter et al[16]	522	43.9	8044	6435	8044	1.92	75.48	73.55	78.67	68.44	10936	8181	11753
Chaudhari et al[17]	22	1.6	8044	6435	8044	18.18	81.82	63.64	95.87	31.40	12641	6713	25617
Gottlieb et al[18]	150	17.3	8044	6435	8044	5.88	87.88	82.00	91.11	72.88	9810	7063	11037
Meta-analysis	1072	100.0	8044	6435	8044	3.17	79.31	76.44	80.48	72.41	10523	7996	11109
Dose Regimen: 5 mg/kg (24 wk)													
Reich et al[15]	378	na	13407	10726	13407	3.90	82.25	78.35	85.43	71.27	17112	12555	18812

Abbreviation: NA, nonapplicable.
[a] Percentage of patients that obtained a 75% reduction in the Psoriasis Area and Severity Index Score (PASI75 responders).
[b] Cost per PASI75 responder gained..

Table 6. Cost/Efficacy of Efalizumab 1 mg/kg Compared to Placebo (12 wk)

Trial	No. of Patients	Weight, %	Costs, €			Efficacy[a]		Incremental Efficacy[a]			Incremental Cost/Efficacy, €[b]		
			Basaline	Worst Case	Best Case	Placebo	Efalizumab	Base-line	Best Case	Worst Case	Base-line	Best Case	Worst Case
Leonardi et al[19]	332	16.7	3600	3600	3600	2.35	38.89	36.54	44.38	28.69	9853	8111	12547
Gordon et al[20]	546	20.6	3600	3600	3600	4.37	26.72	22.35	27.78	16.92	16106	12957	21276
Dubertret et al[21]	793	21.9	3600	3600	3600	4.17	31.38	27.21	31.84	22.58	13228	11304	15941
Papp et al[22]	686	22.1	3600	3600	3600	2.97	23.56	20.59	25.07	16.11	17483	14360	22343
Lebwohl et al[23]	354	18.7	3600	3600	3600	4.92	22.41	17.50	24.09	10.90	20575	14941	33029
Meta-analysis	2711	100.0	3600	3600	3600	3.69	27.88	24.49	29.84	19.14	14699	12064	18805

[a] Percentage of patients that obtained a 75% reduction in the Psoriasis Area and Severity Index Score (PASI75 responders).
[b] Cost per PASI75 responder gained.

starting dose of 0.7 mg/kg, followed by 11 weekly doses of 1 mg/kg.

As efalizumab comes in 125-mg vials, the cost of fractional doses was estimated as the cost of a full 125-mg dose. The cost per patient was €3600 in the 3 scenarios studied (baseline, best-case, and worst-case). The incremental efficacy over placebo was 24.49% (95% CI, 19.14%-29.84%), and the NNT was 5 (95% CI, 4-6). The I^2 was 78%, indicating a high level of inconsistency between the trials analyzed. This considerable heterogeneity was largely caused by the highly variable efficacy rates—ranging from

17.50%[23] to 36.54%[19]—reported by the trials (Table 6). The incremental cost/efficacy ratio was €14 699 for the baseline scenario, €12 064 for the best-case scenario, and €18 805 for the worst-case scenario (Table 6).

Summary of Cost/Efficacy Analysis

The findings of our cost/efficacy analysis are summarized in Table 7. Incremental efficacy based on the central estimate of efficacy (baseline scenario) ranged from a

minimum of 24.29% (efalizumab) to a maximum of 78.35% (infliximab 5 mg/kg at 24 weeks). The most efficient agents were infliximab and adalimumab, both of which had an incremental efficacy of over 60% in terms of PASI75 responders. Efficiency in terms of incremental cost/efficacy in the baseline scenario ranged from €8013 (adalimumab at 16 weeks) to €17 112 (infliximab at a dose of 5 mg/kg at 24 weeks) per PASI75 responder gained. The most efficient biologic agent in terms of cost/efficacy, thus, was adalimumab (€8013 per PASI75 responder gained). Adalimumab was also the most efficient biologic agent according to our sensitivity analysis, both in the best-case scenario (€7568 per PASI75 responder) and in the worst-case scenario (€8515 per PASI75 responder).

Discussion

According to the findings of the present study, the biologic agent with the greatest cost/efficacy ratio in the short term (clearance period) was adalimumab, which achieved a PASI75 response for a mean cost of €8013, with minimum and maximum costs of €7568 and €8515, respectively. The least efficient option was infliximab administered at 5 mg/kg for 24 weeks. In this case the mean cost of achieving a PASI75 response was €17 112, with a minimum cost of €12 555 and a maximum cost of €18 812. Although infliximab had a 14% greater efficacy than adalimumab, this efficacy was achieved at twice the cost. Efalizumab was the least efficacious and the second most costly option, making it the second least efficient option. Finally, etanercept was the second least efficacious option

but the second or third most efficient option depending on the dose (Table 7).

Our study has both strengths and limitations. One of its strengths is that the results are based on all the available scientific evidence on the efficacy of biologic agents in the treatment of moderate to severe psoriasis. We included in our analysis all the randomized clinical trials comparing biologic agents to placebo published in English-language research journals up to March 2008. When a particular treatment was analyzed by more than 1 trial, we performed a meta-analysis using highly robust, conservative methods. Our search can be considered comprehensive because we located the same articles as those included by Brimhall et al[36] in a meta-analysis of the safety and efficacy of biologic agents in psoriasis that was published after we had performed our search. Furthermore, the efficacy indicators obtained in our meta-analyses were also consistent with those used by Brimhall et al. The results of the studies included in each of the meta-analyses were highly consistent with each other, with the exception of those for efalizumab at 1 mg/kg. This is because the analysis included a study—that by Leonardi et al[19]—with questionable validity. On the one hand, it is striking that the 1-mg/kg dose regimen proved to be more efficacious that the 2-mg/kg regimen, and on the other, the efficacy results for the 2-mg/kg dose regimen were similar to those seen with 1-mg/kg doses in other studies.[20-23] These differences explain why there was a large degree of inconsistency across the studies included in our meta-analysis of the efficacy of efalizumab and also call into question the findings of Leonardi et al.[19]

Table 7. Summary of Cost/Efficacy Results of Biologic Agents Compared to Placebo

Biologic Agent	Dose Regimen	Duration of treatment, wk	Baseline Scenario		Incremental Cost/Efficacy per PASI75 Responder Gained		
			Incremental Efficacy	NNT	Baseline Scenario	Best-Case Scenario	Worst-Case Scenario
Adalimumab	80 mg + 40 mg/2 wk	16	64.16	2	8013	7568	8515
Etanercept	2 × 25 mg/wk	12	30.33	4	9370	8082	11147
Etanercept	2 × 25 mg/wk	24	50.69	2	11213	8757	15582
Etanercept	2 × 50 mg/wk	12	44.41	3	12797	11722	14088
Infliximab	50 mg/kg[c]	10	76.44	2	10523	7996	11109
Infliximab	50 mg/kg[c]	24	78.35	2	17112	12555	18812
Efalizumab	1 mg/kg/wk[c]	12	24.49	5	14699	12064	18805

Abbreviations: NNT, number of patients needed to treat to achieve a 75% reduction in the Psoriasis Area and Severity Index (PASI75).
[a] Administered at weeks 0, 2, and 6.
[b] Administered at weeks 0, 2, 6, 14, and 22.
[c] With a starting dose of 0.7 mg/kg.

One possible limitation of our study is that it did not take into account the cost of adverse effects, essentially because the scientific evidence on adverse effects is more limited than that on efficacy. In their meta-analysis, Brimhall et al[36] found that, compared to placebo, efalizumab and infliximab were significantly associated with a risk of developing 1 or more adverse effects, but they found no such association for serious adverse effects. They did not analyze adalimumab in their study. It should be noted, however, that a recent report by the National Institute for Health and Clinical Excellence in the United Kingdom also concluded that the risk of adverse effects was greater with adalimumab than with placebo but with no differences for serious adverse effects.[37] It is thus reasonable to assume that our findings would have been similar had we analyzed the cost of adverse effects.

Another possible limitation is the fact that we only considered the cost of the actual drugs and not the costs associated with their administration. In the case of adalimumab, etanercept, and efalizumab, these costs are negligible as they are administered subcutaneously, but in the case of infliximab, they could be high as the drug needs to be administered intravenously in a hospital. Treatment with infliximab needs to be initiated and supervised by a qualified physician, with a recommended infusion time of 2 hours, after which the patient must remain in observation for 1 to 2 hours due to the risk of acute reactions related to the infusion.[34] This means that treatment with infliximab incurs additional costs related to premedication, nursing and physician care, infusion material, and indirect hospital costs. If these costs are considered, then the efficiency of infliximab in terms of cost/efficacy would decrease considerably.

Neither did we take into account the cost of diagnostic tests, such as laboratory workups, Mantoux tests, and chest radiographs, which, in addition to other tests, are generally requested on initiating treatment with a biologic agent. Nonetheless, even though these costs might vary from one agent to the next, they would do so only slightly and would not thus alter our findings.

The method we used to assign weight to patients in studies that analyzed biologic agents with weight-dependent dosing could also be considered with reservation. The problem we encountered was that not all of the studies we included in our analysis provided information on weight, and furthermore, the weight and height of individuals can vary from one country to another, as is the case, for example, with Spain and the United States of America (USA). Furthermore, one of the aims of our study was to calculate cost/efficacy ratios for Spain. To overcome this limitation and make our findings applicable to Spain, we standardized the weight of patients from each study to that of the Spanish population based on the age and sex of the patients analyzed. In our opinion, this was the best possible method we could have used and it also means that our results will be valid for the Spanish population. As far as the method we used to calculate the weight of patients with psoriasis is concerned, it should be noted that several studies have demonstrated an association between psoriasis and obesity.[30,38] Nonetheless, whether obesity is actually caused by psoriasis or is indeed a risk factor for the disease is still a matter of debate.[39] Because there is no information available on the weight of patients with psoriasis in Spain, we estimated this weight based on the results of a study by Herron et al,[30] who compared the BMI of the general population to that of patients with psoriasis in Utah, USA. Assuming that the weight difference between patients with psoriasis and the general population would be the same in Spain as in Utah, we standardized the difference in accordance with age and sex to the Spanish population. The weights assigned to the patients—adjusted in accordance with the proportion of men and women in each study and their age—were approximately 78 kg in the best-case scenario, 80 kg in the baseline scenario, and 83 kg in the worst-case scenario. These estimated weights are very similar to those reported by a survey of 598 patients with moderate to severe psoriasis conducted in 5 European countries (UK, Germany, France, Italy, and Spain) in 2007.[40] In that survey, the mean weights were 78.1 kg for patients with moderate psoriasis and 80.1 kg for those with severe psoriasis. It is therefore unreasonable to consider that our cost results for biologic agents with weight-dependent dosing might have been biased by our approach.

Another possible limitation of our study is that we calculated costs and results in accordance with the duration of each study. Accordingly, in some cases we had cost and efficacy data for 10 weeks while in others we had this information for 12, 16, and 24 weeks. We could not correct for this through analysis as the efficacy results for each clinical trial corresponded to the moment at which the investigators estimated that the drug would have produced its maximum effect. Furthermore, treatment efficacy curves are not linear in time and were not described in the clinical trials analyzed. Treatment with infliximab at a dose of 5 mg/kg for 24 weeks, for example, was 2% more efficacious than the same treatment over 10 weeks but 67% more costly. In such a case, we could have calculated the incremental cost/efficacy ratio for 14 additional weeks of treatment but not that for each additional week. Given the information we had available from the trials, therefore, we were unable to calculate a methodologically valid incremental cost/efficacy ratio by week of treatment. Because the trials analyzed focused on the period of maximum treatment effect, however, we believe that our analysis helps to provide a better understanding of cost/efficacy ratios in a scenario in which the aim is to maximize clinical results using

evidence-based treatment regimens from clinical trials. Nonetheless, in a cost-containment scenario, cost/efficacy ratios based on clinical trial results should be considered in conjunction with cost/effectiveness studies, using data from routine clinical practice.

Conclusions

Following our analysis of the cost/efficacy of 4 biologic agents used to treat moderate to severe psoriasis based on the best available scientific evidence and the doses specified in the corresponding summaries of product characteristics authorized by the Spanish Agency for Medicines and Health Care Products (AEMPS), it can be concluded that the most efficient biologic agent in terms of cost per PASI75 responder is adalimumab administered for 16 weeks (€8013), followed by etanercept administered at 25 mg twice a week for 12 weeks (€9370), and infliximab administered at 5 mg/kg for 10 weeks (€10 523). The advantage of adalimumab was particularly evident as it proved to be more efficient than all of the other drugs studied (in all regimens) in the baseline, best-case, and worst-case scenarios.

Conflicts of Interest

This study was funded by Abbott Laboratories.

A Garcia is a member of the advisory board on psoriasis for Abbott and Merck Serono and C Ferrandiz has received consultancy fees, speaker fees, and fees for participating in clinical trials from Merck Serono, Wyeth, Schering-Plough, Abbott, Centocor, and Janssen-Cilag. The other authors have reported no potential conflicts of interest with regard to the content of this study.

Appendix

On February 19, 2009, when this manuscript was in press, the European Medicines Agency recommended suspending the marketing authorization for Raptive for a number of safety reasons including the risk of progressive multifocal leukoencephalopathy.

The European Medicines Agency has also withdrawn the marketing authorization for efalizumab as it considers that its therapeutic benefits do not outweigh the risks.

It should also be noted that continuous treatment and treatment at a dose 0.8 mg/kg in children aged 8 and above have been included as treatment options in the summary of product characteristics for etanercept.

[http://www.emea.europa.eu/humandocs/Humans/EPAR/raptiva/raptiva.htm]

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