Reumatol Clin. 2010;**6(4)**:203–211

Reumatología Clínica

www.reumatologiaclinica.org

Original article

Pharmacoeconomic analysis of Metoject® in the treatment of rheumatoid arthritis in Spain

Carlos Crespo,[a,b,*] Max Brosa,[a] Jordi Galván,[c] Jordi Carbonell,[d,e] Jordi Maymó,[d,e] José Luis Marenco,[f] Javier del Pino-Montes,[g] Alberto Alonso,[h] and Carlos Rodríguez[i]

[a]*Oblikue Consulting, Barcelona, Spain*
[b]*Departamento de Estadística, Universidad de Barcelona, Barcelona, Spain*
[c]*Departamento Médico, Laboratorios Gebro Pharma, Barcelona, Spain*
[d]*Hospital del Mar, Barcelona, Spain*
[e]*Hospital de la Esperanza, Barcelona, Spain*
[f]*Hospital Universitario de Valme, Sevilla, Spain*
[g]*Hospital Universitario de Salamanca, Salamanca, Spain*
[h]*Hospital de Cruces, Bilbao, Spain*
[i]*Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas, Spain*

ARTICLE INFO

Article history:
Receive May 6, 2009
Accepted November 5, 2009

Keywords:
Methotrexate
Cost-effectiveness
Quality of life

ABSTRACT

Objectives: The aim of this study was to compare the clinical and economic consequences of using subcutaneous methotrexate (Metoject®) with respect to oral methotrexate in the management of rheumatoid arthritis (RA) in Spain.
Methods: A cost-effectiveness analysis was performed to compare early treatment of RA using a Markov model. The model allowed us to estimate long term efficacy of RA treatment based on data from the literature and expert opinion, and to combine this data with costs of managing RA in Spain. The perspective of the study was from the National Health System point of view, using a time horizon of 5 years and patient lifetime. All costs were expressed in 2009 euros and a 3% discount rate was applied.
Results: The cost (only pharmacologic costs) per quality-adjusted life year (QALY) gained with Metoject® went from 25,173 to 35,807 € at 5 years and from 19,056 to 25,351 € for patient lifetime. When direct costs in RA treatment were considered, it was observed that cost-effectiveness at 5 years went from 29,682 to 42,175 €/QALY gained, and for patient lifetime from 22,514 to 29,848 €/QALY gained.
Conclusions: Additional costs of Metoject® with respect to oral methotrexate would be offset by their improved effectiveness, expressed in QALY, showing that Metoject® could be a cost-effective treatment option for RA in the Spanish Health System assuming a spanish threshold.

Análisis farmacoeconómico de Metoject® en el tratamiento de la artritis reumatoide en España

Palabras clave:
Metotrexato
Coste-efectividad
Calidad de vida

RESUMEN

Objetivos: El objetivo de este estudio ha sido comparar la eficiencia de utilizar el metotrexato subcutáneo (Metoject®) con respecto al metotrexato oral en el manejo de pacientes con AR en España.
Métodos: Se ha realizado un análisis coste-efectividad/utilidad del tratamiento de la AR temprana utilizando un modelo de Markov. El modelo ha permitido estimar la efectividad a largo plazo del tratamiento de la AR en función de los datos de la literatura y de la opinión de expertos y combinarlo con información de los costes en España. El análisis se ha realizado desde la perspectiva del Sistema Nacional de Salud, utilizando un horizonte temporal de 5 años y de toda la vida del paciente. Todos los costes se expresaron en euros del año 2009 y se ha utilizado una tasa de descuento del 3%.
Resultados: La razón de coste (sólo costes farmacológicos) por año de vida ajustado por calidad (AVAC) ganado con Metoject® fue de 25.173-35.807 € a los 5 años y de 19.056-25.351 € para toda la vida. Al tener en cuenta los costes directos de la AR se observó que el coste-efectividad a los 5 años fue de 29.682-42.175 €/AVAC ganado y para toda la vida fue de 22.514-29.848 €/AVAC ganado.

*Corresponding author.
E-mail address: carlos.crespo@oblikue.com (C. Crespo).

1699-258X/$ - see front matter

Conclusiones: Los costes adicionales de Metoject® respecto a metotrexato oral se verían compensados por su mejora en efectividad, expresada en términos de AVAC, revelando que Metoject® podría ser un tratamiento costeefectivo para la AR en el Sistema Nacional de Salud según el umbral asumido en España.

Introduction

Rheumatoid arthritis (RA) is an aggressive disease that leads to joint destruction and irreversible loss of function in a high percentage of patients. That is why early diagnosis and the rapid establishment of treatment are of utmost importance to induce remission in the first months of RA progression.[1] Although radiological and functional deterioration progresses throughout the course of the disease, the maximum development of radiological damage and functional compromise occurs during the first 2 years of evolution of RA.[2] The clinical course of RA is progressive and leads to a reduced quality of life, as well as increased morbidity and mortality.[3]

The program for control of the global burden of disease from the WHO has identified RA as one of the 10 leading causes of disability in the EU.[4] In Spain, RA affects 0.5% of the adult population (approximately 162,250 people).[5] The estimates for the incidence of RA range from 4.13 per 100,000 adult men to 13-16 per 100,000 adult women.

The treatment of RA should be directed at reducing inflammatory activity and preventing the progression of joint damage.[6] The first-line therapy are usually NSAIDs and glucocorticoids.[7] These drugs act quickly to improve pain and swelling caused by RA. The modifying antirheumatic drugs (DMARDs) are compounds that act more slowly improving not only symptoms but also clinical and radiographic progression. Because the effect observed may take several weeks or months, DMARD are usually prescribed initially along with agents that act more rapidly, such as NSAIDs and glucocorticoids.[7] DMARD have demonstrated the ability to slow or stop the progression of RA and among them methotrexate administered orally or parenterally should be singled out for its efficacy and speed of action.[8] On the other hand, biological response modifiers (biological agents) work by counteracting the effect of inflammatory mediators in the tissue damaged by RA. Initial treatment with anti-TNF plus methotrexate might be justified in patients with recent onset when a particularly aggressive progression is suspected.[9]

The aim of this study was to compare the efficiency of subcutaneous methotrexate (Metoject®) compared to oral methotrexate in the management of patients with RA in Spain.

Methods

Modelling

We performed a cost-effectiveness analysis of treatment with Metoject® against oral methotrexate using a simulation model based on data from the literature and the opinion of a panel of experts specializing in rheumatology for the allocation of economic consequences of each option compared at 5 years and for the lifetime of the patient. This has been adapted to the Spanish environment using a decision tree for the first 24 weeks and a Markov model that simulates the natural history of early RA (Figure 1) and the clinical practice in managing patients who suffer it in Spain.

The model is used to estimate the long-term effectiveness of RA treatment, combining information on costs in the short and long term management of patients with RA in Spain with its prognosis. To this end, the 24-week study of Braun et al[10] was taken as a

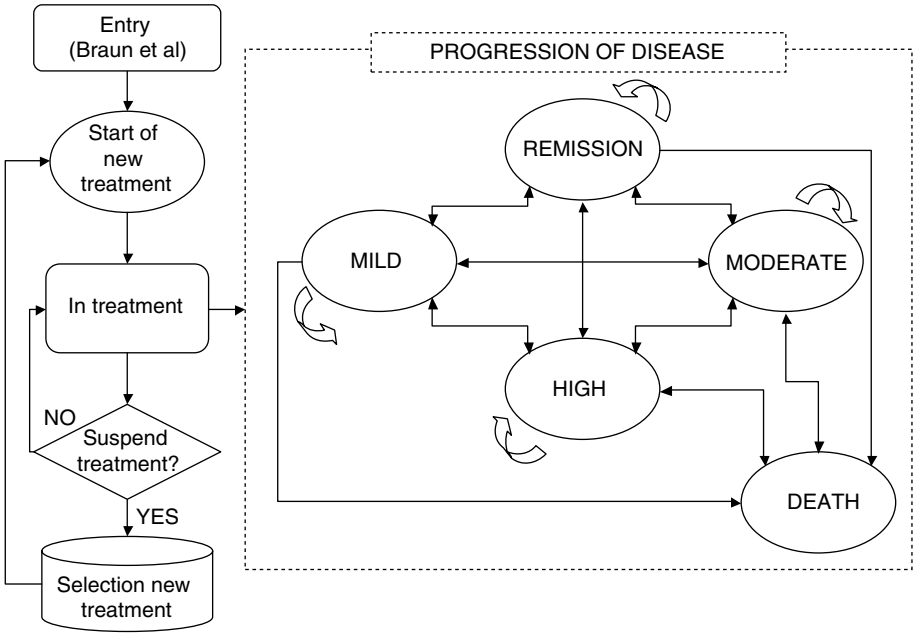


Figure 1. Markov model for RA.

starting point and every six months the likely change of treatment was assessed depending on the drug, the initial state of the disease and whether the patient improved, worsened or remained the same. Also, as recommended by experts, the scheduled treatment sequence after failure was considered, according to Spanish clinical practice, with increasing doses of methotrexate, change of the route of administration, replacement/addition of another DMARD (leflunomide, hydroxychloroquine, sulfasalazine and gold salts), or even the addition of a biological agent. Thus, the hypothetical cohort had the features and the rate of progression of the disease with methotrexate as the first line of treatment equivalent to that of the multicenter clinical trial which compared oral compared and subcutaneous methotrexate.[10] After 24 weeks in the Braun et al[10] study, the effectiveness included in the model was the same for the comparators (methotrexate) and the treatment administered after failure (other DMARDs, methotrexate+biological) extracted from the results at 12 months of the ATTRACT controlled clinical trial of 54 weeks in patients with RA,[11] the cost-effectiveness analysis of the ATTRACT study by Wong et al[12] and the Cochrane review with infliximab[13] and adalimumab.[14] For the long-term (second year, lifetime) a long-term prognosis of patients taken from a pharmacoeconomic model of Wong et al study,[12] Brennan et al[15,16] and an observational study Netherlands[17] was made.

Study subjects

The analysis was developed from a hypothetical cohort of patients with RA (mean age 56 years, 78.9% women) methotrexate naïve, similar to participants in the study of Braun et al.[10]

Parameters

The differential efficacy of methotrexate presentations in Spain, according to their route of administration, comes from the study of Braun et al.[10] In clinical trials the primary efficacy measure is the ACR response rate but is also measured as the Disease Activity Score Index (DAS28) response. The ACR improvement criteria,[18] evaluate the therapeutic response, but do not measure absolute values of activity, but their percentage changes. Due to the nature of the study and taking into account that efficiency is not always measured by DAS28, the analysis is presented based on therapeutic success with ACR20, ACR50 and ACR70. In cases in which response only appears with DAS28, ACR20 response was expected for the moderate DAS28, ACR50 response for mild DAS28 and ACR70 response for DAS28 remission.

With respect to therapeutic approaches in case of progression of the disease, the distribution of therapeutic changes based on the initial treatment were taken from Wong et al[12] and validated and supplemented by the opinion of the panel of Spanish experts in rheumatology. Thus, when a patient's disease progresses, many of them continue to evaluate the treatment and how many treatments change from Spanish clinical practice. Validation and specific data collection was obtained from the panel of Spanish experts using a questionnaire developed ad hoc. The questionnaire for the collection and validation of the data was prepared in advance by the principal investigator before being sent to other researchers who are co-authors of this manuscript. In cases where discrepancies were found in the responses an in-depth interview was carried out where relevant in order to detect changes in one way or another.

With regard to the quality of life, we have used data from different sources since there is no Spanish data that might reflect the values for all necessary health states.[12,17]

We have considered three main types of health care costs: the cost of treatment analysis, the initial cost of managing the various events (ACR20, ACR50, ACR70, death) and the cost of monitoring patients surviving to various events.

Resource use was derived from expert opinion and the Spanish unit costs come from the drug database of the General Council of Official Colleges of Pharmacists[19] for drugs and for the remaining from the database of eSalud healthcare costs.[20] The estimated costs of second line (other DMARDs, anti-TNF) and concomitant medication comes from specific Spanish studies.[21,22]

Perspective, time horizon and discount

The analysis is done from the perspective of the National Health System, using the time horizon of five years and lifetime. All costs are in 2009 euros and a discount rate of 3% was used for both costs and effects.

Cost-effectiveness analysis

Model results are expressed by the acceptability to pay curve, which shows how likely Metoject® is chosen at the expense of oral methotrexate according to different theoretical willingness to pay as assumable by a decision maker.[23] So that when it exceeds the equiprobability threshold (50%) it shows that the alternative studied is more efficient than the alternative compared.

Mortality data and utility introduced in the Markov model was estimated from international studies. Due to the uncertainty of this data, there were several scenarios that combined different uses and mortality data by health status. The baseline scenario refers to values according to the study of Welsing et al[17] for utility and value and the study of Kobelt et al[24] study for mortality. The assessment of quality of life for this baseline case varies depending on the progression of the disease using the values 0.75, 0.71, 0.64 and 0.56 for remission, mild, moderate and high states, respectively. Also, mortality data are also different in terms of these states and we considered that the relative risk of 1.00 is equivalent to the reference, the state 1.30 to mild, 1.65 to moderate and 2.00 to high state.[24] The utilities and mortality used in the baseline case scenario corresponds to the most conservative Metoject® scenario in estimating the quality of life for different health states as the largest studies observed the lowest possible mortality. On the other hand the most favorable scenario for Metoject® (although the most unfavorable for the patients) was built with patients who progress in severity and have the worst quality of life (remission 0.77, mild 0.68, moderate 0.62 and severe 0.52) potential and a lower life expectancy (relative risk of 1.00 for remission, 1.46 for mild, 1.92 and 2.39 for moderate to severe).[16,24]

Budget impact analysis

We have developed an analysis of the potential budgetary impact of extending the use of Metoject® substituting the oral drug treatment in different proportions. We studied a scenario with the current use of Metoject® and the potential cost of more use in this population, using the cost per patient for each option over the next five years. To project patients likely to be treated with methotrexate we carried out a linear regression adjusting for historical data.[25]

Sensitivity analysis

To assess the influence of the uncertainty of the parameters (efficacy, dropout rates, costs, etc.) on the results of the study and validate the robustness of the results obtained, we performed a probabilistic sensitivity analysis using a second order Monte Carlo simulation, so that the cost-effectiveness of each comparison was simulated 1,000 times.

To perform the sensitivity analysis we have selected fixed distribution parameters which were estimated for each distribution based on primary data collected.[26]

Results

Effects on health and costs

Based on the results of the study of Braun et al[10] lasting 24 week it was concluded that Metoject® better controls progress of the disease and that 41% of patients fail to achieve remission (33% oral methotrexate), 21% end with a mild DAS28 (26% oral methotrexate), 16% with a moderate DAS28 (oral methotrexate 11%) and only 22% with a high DAS28 (oral methotrexate 30%). It is noted that the percentage of patients in remission is 8% higher in the Metoject® group with respect to oral methotrexate and that the percentage of patients with high DAS28 is less than those in the Metoject® group, indicating an overall improvement of health status of patients.

The data in the long-term prognosis of patients in each treatment option are from prior cost-effectiveness analysis[12,17] and denote that the majority of patients remain in their state of health (Table 1). Similarly, with respect to therapeutic approaches in the case of disease progression, it is observed that between 84%-95% of the patients maintain treatment. So most times, if the choice to change treatment is made, another DMARD is added and in a few cases (10%-20%) an anti-TNF is chosen to add. On the other hand, in the case of improving the progression of the disease, it has been observed that in clinical practice and in international studies, treatment changes are made with a low frequency (between 5%-23% for methotrexate, between 9% and 35% for DMARD and between 16%-41% for the combination of methotrexate plus DMARDs). When carrying out this change, it can be seen that normally it is based on the substitution of methotrexate or other DMARDs.

With respect to the major costs, it was noted that the use of Metoject® resources is similar to that of oral methotrexate and therefore semi-direct costs only increased drug cost 82 € for the Metoject® group (Table 2, Table 3).

Cost-effectiveness analysis

Metoject® provides the patient with a profit of about 0.103 to 0.145 QALY at 5 years, coming to represent a lifetime profit of approximately 0.308 to 0.396 QALY.

The ratio of costs (drug costs only) for adjusted life years (QALYs) gained with Metoject® versus oral methotrexate was between € 25173-35807 to € 19056-25351 at five years and for the whole life time horizon below the threshold value assumed in Spain (Table 4).[23] By taking into account all direct costs involved in the treatment of RA, it was noted that the cost-effectiveness of Metoject® versus oral methotrexate to five years was € 29682-42175/QALY gained and for life was € 22514-29848/QALY gained (Table 4).

The sensitivity analysis showed that 68%, 77% and 87% of cases treated with Metoject® are below the thresholds of cost-effectiveness of 30,000, 35,000 and 45,000 €/QALY gained, respectively. Thus, Figure 2 shows that Metoject® is an effective medication when equiprobability exceeds the threshold of € 24,000 per QALY gained.

Also, the simulation showed a median cost per QALY of around € 23,836/QALY, with an interquartile range of € 14,627/QALY, values that includes both worst-case (base case) and favorable scenarios (Table 4 and Figure 2).

Budget impact analysis

In terms of the budgetary impact, the methotrexate tributary population is between 120000-160000 patients the first and fifth years, respectively, with 20%-24% of patients treated with Metoject® (Table 5). So that assuming an increased use of Metoject® of 10% per annum on the current scenario, then the direct costs associated with the intervention amounted to 2.5 to 4 million €. As shown in Figure 3,

Table 1
Transition probabilities in the Markov Model

FROM	TO	Remission					Mild DAS28					Moderate DAS28					High DAS28				
		METOJECT®	Oral	DMARD MTX	MET+ DMARD	Anti-TNF	METOJECT®	Oral MTX	DMARD	MET+ DMARD	Anti-TNF	METOJECT®	Oral MTX	DMARD	MET+ DMARD	Anti-TNF	METOJECT®	Oral MTX	DMARD	MET+ DMARD	Anti-TNF
Remission	METOJECT	62.54	0.00	1.46	2.20	0.41	29.05	0.00	1.09	1.65	0.30	1.13	0.00	0.06	0.09	0.02	0.00	0.00	0.00	0.00	0.00
	Oral MTX	0.00	62.54	1.26	2.10	0.71	0.00	29.05	0.94	1.57	0.53	0.00	1.13	0.05	0.09	0.03	0.00	0.00	0.00	0.00	0.00
	DMARD	0.00	0.00	63.38	5.15	1.27	0.00	0.00	24.15	2.69	0.66	0.00	0.00	2.20	0.32	0.08	0.00	0.00	0.08	0.01	0.00
	MET+DMARD	0.00	0.00	0.00	58.98	10.82	0.00	0.00	0.00	23.07	4.43	0.00	0.00	0.00	2.17	0.43	0.00	0.00	0.00	0.08	0.02
	Anti-TNF	0.00	0.00	0.00	0.00	50.00	0.00	0.00	0.00	0.00	31.00	0.00	0.00	0.00	0.00	11.90	0.00	0.00	0.00	0.00	7.10
Mild DAS28	METOJECT	6.57	0.00	0.28	0.15	0.00	69.60	0.00	1.40	2.11	0.39	17.46	0.00	0.59	0.89	0.16	0.35	0.00	0.02	0.03	0.00
	Oral MTX	0.00	6.57	0.28	0.15	0.00	0.00	69.60	1.20	2.01	0.68	0.00	17.46	0.51	0.85	0.29	0.00	0.35	0.01	0.02	0.01
	DMARD			6.78	0.37	0.00	0.00	0.00	65.86	6.13	1.51	0.00	0.00	15.71	2.00	0.49	0.00	0.00	0.50	0.08	0.02
	MET+DMARD	0.55		0.60	5.71	0.00	0.00	0.00	0.00	53.14	20.36	0.00	0.00	0.00	12.83	5.37	0.00	0.00	0.00	0.41	0.19
	Anti-TNF	1.40		0.00	0.00	26.40	0.00	0.00	0.00	0.00	38.80	0.00	0.00	0.00	0.00	30.60	0.00	0.00	0.00	0.00	4.20
Moderate	METOJECT	0.26	0.00	0.02	0.01	0.00	9.56	0.00	0.74	0.40	0.00	72.23	0.00	2.75	4.15	0.77	7.77	0.00	0.48	0.72	0.13
DAS28	Oral MTX	0.00	0.26	0.02	0.01	0.00	0.00	9.56	0.74	0.40	0.00	0.00	72.23	2.37	3.96	1.34	0.00	7.77	0.41	0.69	0.23
	DMARD	0.03		0.34	0.02	0.00	1.12		11.33	0.75	0.00	0.00	64.73	8.88	2.19	0.00	0.00	8.71	1.51	0.37
	MET+DMARD	0.10		0.04	0.26	0.00	3.28		1.41	8.51	0.00	0.00	0.00	47.98	27.82	0.00	0.00	0.00	6.57	4.03
	Anti-TNF	0.00		0.00	0.00	7.20	0.00		0.00	0.00	21.70	0.00	0.00	0.00	55.30	0.00	0.00	0.00	0.00	0.00	15.80
High	METOJECT	0.15	0.00	0.03	0.02	0.00	0.40	0.00	0.07	0.04	0.00	18.67	0.00	2.68	1.44	0.00	64.49	0.00	4.31	6.50	1.20
DAS28	Oral MTX	0.00	0.15	0.03	0.02	0.00	0.00	0.40	0.07	0.04	0.00	0.00	18.67	2.68	1.44	0.00	0.00	64.49	3.71	6.20	2.10
	DMARD	0.02		0.06	0.01	0.00	0.14		0.57	0.09	0.00	2.62		14.53	1.75	0.00	0.00	0.00	66.57	10.93	2.70
	MET+DMARD	0.03		0.01	0.06	0.00	0.22		0.10	0.48	0.00	5.36		2.30	11.25	0.00	0.00	0.00	0.00	47.00	33.20
	Anti-TNF	0.00		0.00	0.00	2.30	0.00		0.00	0.00	4.20	0.00		0.00	0.00	30.90	0.00	0.00	0.00	0.00	62.60

DAS 28 indicates Disease Activity Score; DMARD, Disease Modifying Anti-Rheumatic DruG; MTX: methotrexate.

Table 2
Use of resources and cost in the management of patients with RA

	Unit cost (€)	METOJECT®		Oral methotrexate/DMARD	
		Ud.	% Pat.	Ud.	% Pat.
Annual patient follow up					
Visits to the rheumatologist (first visit)	92.1	1	100.0	1	100.0
Visits to the rheumatologist (follow up)	55.26	4	91.0	4	95.0
Visits to the orthopedic surgeor (first visit)	59.06	1	9.0	1	9.0
Visits to the orthopedic surgeor (follow up)	35.44	2	7.5	2	7.5
Visits to rehabilitation	5.29	1	28.0	1	28.0
Visits to primary care physician	37.28	7	100.0	5	100.0
Visits to the emergency department	108.17	1	16.0	1	18.0
Hospital stays (rheuma)	374.55	1	18.2	1	15.4
Hematology	11.12	5	100.0	5	92.0
Biochemistry	11.12	5	100.0	5	92.0
Urine	3.68	2	100.0	2	100.0
Computerized tomography	228.47	1	3.1	1	3.1
Magnetic resonance	465.56	1	12.1	1	10.1
Echography	131.76	1	17.0	1	17.0
X rays	43.11	1	75.0	1	75.0
Electromiography	74.22	1	3.6	1	3.6
Annual patient treatment administration					
Nursing visits	16.59	4	97.9	1	91.5
Home nursing visits	29.72	1	25.0	1	17.5
Primary care nursing visits	11.07	48	9.0	6	56.7
Non pharmacologic costs					
Annual		1,008.23€		844.13€	
Semestral		504.11€		422.07€	

% Pat. indicates percentage of patients; DMARD, disease modifying anti rheumatic drug; RA, rheumatoid arthritis; Ud., units.

Table 3
Direct health costs

	Semestral drug cost		Direct semestral cost (non pharmacologic) (€)	Source
	First 6 months, €	Next 6 months, €		
METOJECT®	458.6	470.7	504.1	19, 20, and expert opinion
Oral methotrexato	6.4	6.6	422.1	19, 20, and expert opinion
Other DMARD				
Substitution	435.6	404.4	422.1	19, 20, 22, and expert opinion
Addition	312.7	312.7	422.1	19, 20, 22, and expert opinion
Anti-TNF	5,924.3	5,924.3	1.145.9	19, 20, 21, and expert opinion
Concomitant drugs	268.6	268.6	–	19, 20, 22, and expert opinion

DMARD indicates disease modifying anti rheumatic drug.

increasing the budgetary impact of the introduction of Metoject® on health spending of the estimated target population represents an increase of 1.4% of the cost of pathology.

The sensitivity analysis of the budgetary impact shows that an annual increase in use of Metoject between 10%-30% would lead to a maximum net direct cost budget of 4.1% (Table 5). Also, when considering only the drug impact of the largest Metoject® introduction one can see that the cost amounts to 2.2% to 2.5% in the baseline case and reached 6.6% to 7.4% by assuming an increase of 30% (Table 5).

Discussion

To date existing comparative efficacy data did not suggest methotrexate injection to be greater than oral methotrexate, although the efficacy of the drug is more than proven and is supported by international medical societies, including the Spanish Society of Rheumatology.[27] With the emergence of the study by Braun et al,[10] the greater efficacy of methotrexate given subcutaneously, as Metoject®, than the effectiveness of the drug administered orally because of its superior bioavailability in parenteral administration, shown with a higher degree of evidence. This improved bioavailability as demonstrated by the necessity of early treatment of RA with DMARDs[28,29] is, as shown in our study, most likely to alter the course of the disease. It also notes that the early use of Metoject® provides the patient with a profit of about 0.103 to 0.145 QALY after 5 years, coming to represent a lifetime savings of approximately 0.308 to 0.396 QALY.

Apart from assessing in Spanish clinical practice the effects of the more efficient Metoject® throughout the patient's life, our study suggests that the additional costs of Metoject® with respect to oral

Table 4
Additional cost of METOJECT® by QALY gained in the different scenarios when compared to oral methotrexate

	Δ pharmacologic cost, €	Δ direct cost, €	Δ QALY, €	Cost/QALY (pharmacologic), €	Cost/QALY (direct), €
Baseline case (worst case)					
6 months	422	523	0.012	38,445	45,429
1 year	870	1,026	0.023	37,648	44,429
2 years	1,675	1,975	0.045	37,359	44,037
3 years	2,410	2,840	0.065	37,013	43,612
4 years	3,079	3,627	0.084	36,481	42,975
5 years	3,685	4,341	0.103	35,807	42,175
7.5 years	4,957	5,837	0.146	33,840	39,848
10 years	5,923	6,973	0.186	31,815	37,456
12.5 years	6,632	7,806	0.221	29,968	35,276
15 years	7,127	8,389	0.251	28,408	33,440
Life	7,801	9,185	0.308	25,351	29,848
Favorable scenario					
6 months	442	552	0.0168	26,296	31,076
1 year	868	1,025	0.0337	25,774	30,424
2 years	1,669	1,968	0.0648	25,739	30,354
3 years	2,397	2,826	0.0933	25,679	30,279
4 years	3,057	3,604	0.1200	25,843	30,047
5 years	3,653	4,307	0.145	25,173	29,682
7.5 years	4,893	5,770	0.2028	24,124	28,451
10 years	5,823	6,869	0.2538	22,941	27,062
12.5 years	6,493	7,662	0.2976	21,818	25,745
15 years	6,952	8,206	0.3333	20,857	24,619
Life	7,541	8,910	0.396	19,056	22,514

Δ indicates increase; QALY, quality of life adjusted years.

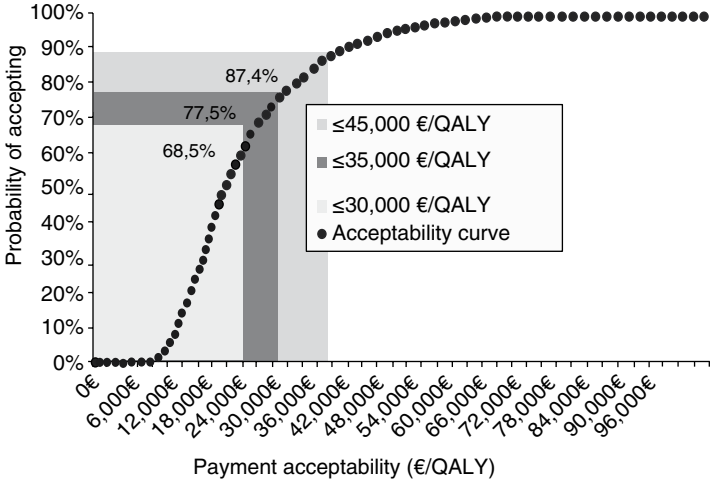
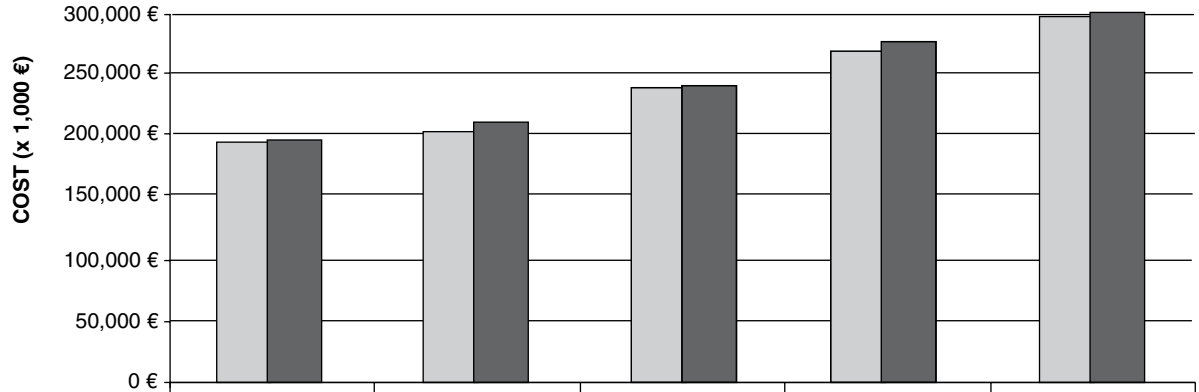


Figure 2. Payment acceptability curve. QALY indicates quality of life adjusted years.

methotrexate are outweighed by its better efficiency, expressed as terms of QALYs. So far, information on the cost-effectiveness of methotrexate in the treatment of RA based on its route of administration had not been studied in depth due to the lack of clinical trials comparing the effectiveness of the drug by subcutaneous or oral administration, although it had been possible to conduct cost-minimization studies. Our research is, in short, a new starting point for potential economic evaluation studies that may allow to be externally validated, using Metoject® in patients with RA as an effective therapy, and therefore faced with the dilemma of choosing of what management path to use.

The budget impact analysis is a technique used to quantitatively assess the expected change in health spending for the care of a condition with the largest introduction of a new health intervention for treatment.[30] In the case of the largest introduction of Metoject® in the National Health System, the impact will be mainly to lower spending due to the progression of disease averted and the differential cost of the new treatment.



	Year 1	Year 2	Year 3	Year 4	Year 5
Actual	189,882,867.36 €	201,331,447.03 €	233,374,638.57 €	265,206,586.83 €	295,081,274.20 €
Expected	192,372,151.43 €	204,055,880.82 €	236,584,001.59 €	268,836,692.15 €	299,058,434.20 €
Net cost	2,489,284.07 €	2,724,433.79 €	3,209,363.02 €	3,630,105.32 €	3,977,160.01 €
% net cost	1.3%	1.4%	1.4%	1.4%	1.3%

Figure 3. Budgetary impact of Metoject®.

Table 5
Sensitivity analysis of the net budgetary impact varying the number of patients expected with METOJECT®

Annual expected increase	Year 1	Year 2	Year 3	Year 4	Year 5
Net pharmacological cost, %					
Baseline cost (10%)	2,489,284 (1.3%)	2,724,434 (1.4%)	3,209,363 (1.4%)	3,630,105 (1.4%)	3,977,160 (1.3%)
5%	1,244,642 (0.7%)	1,362,217 (0.7%)	1,604,682 (0.7%)	1,815,053 (0.7%)	1,988,580 (0.7%)
15%	3,733,926 (2.0%)	4,086,651 (2.0%)	4,814,045 (2.1%)	5,445,158 (2.1%)	5,965,740 (2.0%)
20%	4,978,568 (2.6%)	5,448,868 (2.7%)	6,418,726 (2.8%)	7,260,211 (2.7%)	7,954,320 (2.7%)
25%	6,223,210 (3.3%)	6,811,084 (3.4%)	8,023,408 (3.4%)	9,075,263 (3.4%)	9,942,900 (3.4%)
30%	7,467,852 (3.9%)	8,173,301 (4.1%)	9,628,089 (4.1%)	10,890,316 (4.1%)	11,931,480 (4.0%)
Net pharmacological cost, %					
Baseline cost (10%)	2,145,080 (2.5%)	2,327,343 (2.4%)	2,741,209 (2.4%)	3,097,748 (2.3%)	3,391,907 (2.2%)
5%	1,072,540 (1.2%)	1,163,671 (1.2%)	1,370,605 (1.2%)	1,548,874 (1.1%)	1,695,954 (1.1%)
15%	3,217,620 (3.7%)	3,491,014 (3.6%)	4,111,814 (3.6%)	4,646,623 (3.4%)	5,087,861 (3.3%)
20%	4,290,160 (5.0%)	4,654,686 (4.8%)	5,482,419 (4.7%)	6,195,497 (4.6%)	6,783,815 (4.4%)
25%	5,362,700 (6.2%)	5,818,357 (6.1%)	6,853,023 (5.9%)	7,744,371 (5.7%)	8,479,769 (5.5%)
30%	6,435,240 (7.4%)	6,982,029 (7.3%)	8,223,628 (7.1%)	9,293,245 (6.9%)	10,175,722 (6.6%)

Note that the approach adopted in the study is the National Health System and therefore we have excluded other costs that would be considered important from a social point of view, for example, costs associated with the loss of working hours or the cost of the help of relatives. It is known that most of the costs of RA are indirect, and are nearly double than direct costs[31] and that effective treatment of a person who has been diagnosed with RA may also reduce the burden on the individual and society.

One of the main limitations of the study stems from the use of data from different sources regarding costs in the short and long term, prognosis in the long term, performance parameters, quality of life, mortality and utilities as there are no Spanish data that could reflect values for all necessary health states. This disparity in the studies used to establish the model, in the absence of comparative data in the medium to long term could influence the results because the clinical practice of our field can not be the same clinical practice derived from studies which have assumed values, but at all times was validated by the panel of experts. We should also mention that the option of starting treatment with oral methotrexate in our model may not correspond to clinical practice in patients where this treatment is ineffective and then are changed to SC form. However, since there is no evidence of greater efficacy of SC beyond the initial period observed in the study of Braun, the consideration of the change from oral to SC could not be included in the model.

Furthermore, one has to take into account, when evaluating these results, the limitation of it being a theoretical model based on results of clinical trials, especially the study of Braun et al,[10] which could be overestimating the benefits of the methotrexate injection compared with single-arm studies. It should be noted that Braun et al[10] demonstrated that subcutaneous methotrexate is probably more effective than oral weekly dose of 15 mg of methotrexate. This can

be seen in ACR20 and ACR50 but not 70. Therefore, our theoretical study is based on comparative data only in the short term (six months) and a reasonable dose limit, 15 mg weekly. Furthermore, in line with the study of Braun, two recent prospective observational studies conducted in the UK have once again demonstrated that subcutaneous methotrexate is more effective than oral methotrexate and is well tolerated in patients with RA, including in cases where the disease is more chronic.[32,33]

Finally, although the cost per QALY gained from the study falls within the limits arbitrarily accepted in Western countries, it is quite close to the upper margin accepted for it. It would therefore be desirable to have new direct comparative studies in clinical practice that allowed a better adjustment of the valuations of both the effectiveness and costs.

Our research shows that the study of RA should continue trying to address issues not covered, such as treatment compliance or patient satisfaction, or how to reduce uncertainty about the long-term effectiveness and costs (direct/indirect) associated with RA nationwide. Furthermore, although there are some studies that assessed the quality of life of patients with RA in Spain[34] more are still required regarding quality of life with larger numbers of patients, to study in depth the health status and equivalent measures to their preferences as in the case of the EuroQol-5D.

In conclusion, although more data is needed in the medium term to confirm our results, our study suggests that the additional costs of Metoject® with respect to oral methotrexate would be offset by improvements in effectiveness, revealing that Metoject® may be a cost-effective treatment for the Spanish health system under the assumed threshold, with a very limited relative impact on the current cost incurred by these patients.

Financing

The study was financed by Gebro Pharma, but the company did not participate in data gathering, in its interpretation or in the decision to publish.

Disclosures

Jordi Galván works in Gebro Pharma which promotes the study. Max Brosa and Carlos Crespo work for Oblikue Consulting who received payment by the sponsoring company for research assistance.

References

1. Andréu JL, Silva L, Sanz J, Muñoz P. Optimización del tratamiento clásico de la artritis reumatoide. Reumatol Clin. 2006; 2(Suppl 2):S1-8.
2. Plant MJ, Jones PW, Saklatvala J, Ollier WE, Dawes PT. Patterns of radiological progression in early rheumatoid arthritis: results of an 8 year prospective study. J Rheumatol. 1998;25:417-26.
3. Gabriel SE, Crowson CS, O'Fallon WM. Mortality in rheumatoid arthritis: have we made an impact in 4 decades? J Rheumatol. 1999;26:2529-33.
4. The European Health Report 2005. Public health action for healthier children and populations. ISBN 92 890 1376 1. Oficina regional de la OMS para Europa (WHO Regional Office for Europe), Dinamarca, 2005.
5. Ruiz-Montesinos MD, Hernández-Cruz B, Ariza-Ariza R, Carmona L, Ballina J, Navarro-Sarabia F, et al. Análisis de costes en una cohorte de enfermos con artritis reumatoide atendidos en área especializada de reumatología en España. Reumatol Clin. 2005;1:193-9.
6. Rindfleisch JA, Muller D. Diagnosis and management of rheumatoid arthritis. Am Fam Physician. 2005;72:1037-47.
7. Gaffo A, Saag KG, Curtis JR. Treatment of rheumatoid arthritis. Am J Health Syst Pharm. 2006;63:2451-65.
8. Rodríguez-Valverde V, Cáliz Cáliz R, Álvaro-Gracia Álvaro JM, Marenco de la Fuente JL, Mulero Mendoza J, Tornero Molina J, et al. III Actualización del Consenso de la Sociedad Española de Reumatología sobre terapia biológica en la artritis reumatoide. Reumatol Clin. 2006; 2(Suppl 2):S52-9.
9. Smolen JS, Van der Heijde DM, St. Clair EW, Emery P, Bathon JM, Keystone E, et al. Predictors of joint damage in patients with early rheumatoid arthritis treated with high-dose methotrexate with or without concomitant infliximab. Arthritis Rheum. 2006;54:702-10.
10. Braun J, Kästner P, Flaxenberg P, Währisch J, Hanke P, Demary W, et al. Comparison of the clinical efficacy and safety of subcutaneous versus oral administration of methotrexate in patients with active rheumatoid arthritis: results of a six-month, multicenter, randomized, double-blind, controlled, phase IV trial. Arthritis Rheum. 2008;58:73-81.
11. Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, et al; ATTRACT Study Group. Infliximab (chimeric antitumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. Lancet. 1999;354:1932-9.
12. Wong J, Singh G, Kavanaugh A. Estimating the cost-effectiveness of 54 weeks of infliximab for rheumatoid arthritis. Am J Med. 2002;113:400-8.
13. Blumenauer B, Judd M, Wells G, Burls A, Cranney A, Hochberg M, et al. Infliximab para el tratamiento de la artritis reumatoide (Revisión Cochrane traducida). In: La Biblioteca Cochrane Plus, 2007 Número 3. Oxford: Update Software Ltd. Available from: http://www.update-software.com (translated from The Cochrane Library, 2007 Issue 3. Chichester, UK: John Wiley & Sons, Ltd.).
14. Navarro-Sarabia F, Ariza-Ariza R, Hernandez-Cruz B, Villanueva I. Adalimumab para el tratamiento de la artritis reumatoide (Revisión Cochrane traducida). In: La Biblioteca Cochrane Plus, 2007 Número 3. Oxford: Update Software Ltd. Available from: http://www.update-software.com (translated from The Cochrane Library, 2007 Issue 3. Chichester, UK: John Wiley & Sons, Ltd.).
15. Brennan A, Bansback N, Reynolds A, Conway P. Modelling the cost-effectiveness of etanercept in adults with rheumatoid arthritis in the UK. Rheumatology (Oxford). 2004;43:62-72.
16. Brennan A, Bansback N, Nixon R, Madan J, Harrison M, Watson K, et al. Modelling the cost effectiveness of TNF-alpha antagonists in the management of rheumatoid arthritis: results from the British Society for Rheumatology Biologics Registry. Rheumatology (Oxford). 2007;46:1345-54.
17. Welsing PM, Severens JL, Hartman M, Van Gestel AM, Van Riel PL, Laan RF. The initial validation of a Markov model for the economic evaluation of (new) treatments for rheumatoid arthritis. Pharmacoeconomics. 2006;24:1011-20.
18. Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, et al; American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum. 1995;38:727-35.
19. Base de datos del medicamento. Colegio Oficial de Farmacéuticos. 2009. Available from: http://www.portalfarma.com
20. E-Salud. Base de datos de costes españoles. Oblikue Consulting. Available from: http://www.oblikue.com/bddcostes/
21. Rubió-Terrés C, Ordovas Baines JP, Pla Poblador R, Martinez Nieto C, Sanchez Garre MJ, Rosado Souviron MA, et al. Utilización y coste de los modificadores biológicos de la artritis reumatoide en España (estudio PRAXIS). Farm Hosp. 2007;31:78-92.
22. Mera A, Blanco J, Camaño M. Aproximación al coste de tratamiento farmacológico de la artritis reumatoide en España. An Med Interna. 2003;20:114-21.
23. Sacristán JA, Oliva J, Del Llano J, Prieto L, Pinto JL. ¿Qué es una tecnología sanitaria eficiente en España? Gac San. 2002;16:334-43.
24. Kobelt G, Lindgren P, Singh A, Klareskog L. Cost effectiveness of etanercept (Enbrel) in combination with methotrexate in the treatment of active rheumatoid arthritis based on the TEMPO trial. Ann Rheum Dis. 2005;64:1174-9.

25. IMS. Datos del mercado sanitario. 2004-2008.
26. Briggs A. Handling uncertainty in cost-effectiveness models. Pharmacoeconomics. 2000;17:479-500.
27. Sociedad Española de Reumatología (SER). Actualización de la guía de práctica clínica para el manejo de la artritis reumatoide en España. 2007. Available from: www.ser.es
28. Lard LR, Visser H, Speyer I, Van der Horst-Bruinsman IE, Zwinderman AH, Breedveld FC, et al. Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. Am J Med. 2001;111:446-51.
29. Nell VPK, Machold KP, Eberl G, Stamm TA, Uffmann M, Smolen JS. Benefit of very early referral and very early therapy with disease-modifying anti-rheumatic drugs in patients with very early rheumatoid arthritis. Rheumatolology. 2004;43: 906-14.
30. Brosa M, Gisbert R, Rodríguez JM, Soto J. Principios, métodos y aplicaciones del análisis del impacto presupuestario en el sector sanitario. Pharmacoeconomics-Spanish Research Articles. 2005;2:64-78.
31. Domínguez A. Costes asociados a la artritis reumatoide. Rev Esp Econ Salud. 2003;2.
32. Hameed B, Jones H, Hunt K. Subcutaneous methotrexate is superior to oral methotrexate in the treatment of rheumatoid arthritis. SAT0129. Ann Rheum Dis. 2009; 68(Suppl 3):584.
33. Keidel SM, Chan A. Parenteral methotrexate use in patients with chronic rheumatoid arthritis is effective and produces a lasting response. SAT151. Ann Rheum Dis. 2009; 68(Suppl 3):592.
34. Fernández I, Varela C, Layola M, Ruiz MD, Navorro F. Using HAQ to estimate HUI3 and EQ-5D utility values in Spanish rheumatoid arthritis patients. ISPOR 11th Annual European Congress. 8-11 November 2008, Athens, Greece. Available from: http://www.ispor.org/awards/11euro/PMS47-poster-Varela.pdf