

Costs of the standard rheumatology care in active rheumatoid arthritis patients seen in a tertiary care center in Mexico City

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Objective: To assess the costs of standard care in patients with active rheumatoid arthritis (RA) seen in a tertiary care center in México City in the context of a clinical trial. To analyze the relationship between costs and utility units obtained by the patients in this scenario.

Patients and methods: This economic evaluation was performed during a clinical trial with a 48-week follow-up in a tertiary care center in México City. The trial compared the efficacy of omega-3 fatty acids versus placebo in patients with active RA who also received standard rheumatology care. The costs of medical consultations, complementary tests and drugs were assessed. Other direct costs were also measured. Hypothetical scenarios with fewer medical consultations and complementary tests than those in the clinical trial were also analyzed. Utilities were assessed by the Health Utility Index. A cost-utility ratio was calculated using the baseline utilities score as comparator. A descriptive statistical analysis was performed.

Results: Ninety RA patients (83 women [92%], age [X ± SD] 43.2 ± 14.2 years with disease duration of 3.3 ± 4.6 years) were included. Data from 88 patients were analyzed. The total direct costs were 152,704.11 US\$ 2005 divided into medical attention (78,386.43 US\$ 2005, 51.33%), drugs (39,339.5 US\$ 2005, 25.76%) and other direct costs (34,978.18 US\$ 2005, 22.91%). In scenarios with fewer medical consultations and complementary tests than those in the clinical trial, the total direct costs ranged from 39,507.4 to 103,880.6 US\$ 2005. Patients improved by a mean of 0.18 utility units on a 0-1 scale equivalent to 0.18 quality adjusted life-years (QALYs). The cost-utility ratios ranged from 2,494.1 to 9,640.38 US\$ 2005 per QALY in the scenarios analyzed.

Conclusions: The direct costs of the standard care of RA in the scenarios analyzed are substantial in the social and

economic context of Mexico. The cost per gained QALY is high.

Key words: Direct costs. Utilities. Rheumatoid arthritis.

Costes de la asistencia reumatológica convencional en los pacientes con artritis reumatoide activa atendidos en un centro de nivel terciario en Ciudad de México

Objetivo: Determinar en el contexto de un ensayo clínico los costes de la asistencia sanitaria convencional en los pacientes con artritis reumatoide (AR) activa atendidos en un centro de nivel terciario de Ciudad de México. Analizar las relaciones existentes entre los costes económicos y las unidades de utilidad en los pacientes con las características señaladas.

Pacientes y métodos: Este análisis económico se realizó en el contexto de un ensayo clínico efectuado con un seguimiento de 48 semanas en un centro asistencial de nivel terciario en Ciudad de México. En el ensayo clínico se comparó la eficacia de los ácidos grasos omega-3 con la del placebo en pacientes con AR activa que también recibían asistencia reumatológica convencional. Se determinaron los costes económicos de las consultas médicas, de las pruebas diagnósticas complementarias y de los tratamientos farmacológicos. También se determinaron otros costes directos. Además, se analizaron varios contextos hipotéticos en los que se hubieran realizado menos consultas médicas y menos pruebas diagnósticas complementarias que las que se llevaron a cabo en el ensayo clínico. La utilidad se evaluó a través del Health Utility Index. Se calculó un cociente coste-utilidad utilizando como factor de comparación la puntuación de utilidad inicial. Se realizó un análisis estadístico de tipo descriptivo.

Resultados: Participaron en el estudio 90 pacientes con AR (83 mujeres [92%], con una edad [X ± DE] de 43,2 ± 14,2 años y con una duración de la enfermedad de 3,3 ± 4,6 meses). En los análisis se utilizaron los datos correspondientes a 88 pacientes. Los costes directos

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Manuscrito recibido el 29-9-2005 y aceptado el 7-2-2006.

totales fueron de 152.704,11 dólares estadounidenses de 2005, correspondientes a la asistencia médica (78.386,43 dólares estadounidenses de 2005, 51,33%), al tratamiento medicamentoso (39.339,05 dólares estadounidenses de 2005, 25,76%) y a otros costes directos (24.978,18 dólares estadounidenses de 2005, 22, 91%). En los contextos hipotéticos en los que se consideró un número menor de consultas médicas y de pruebas diagnósticas complementarias, en comparación con el que tuvo lugar el ensayo clínico, los costes directos totales oscilaron entre 39.507,4 y 103.880,06 dólares estadounidenses de 2005. La mejora de los pacientes tuvo un valor medio de 0,18 unidades de utilidad en una escala de 0-1, equivalente a 0,18 años de vida con ajuste de la calidad (QALY, *quality adjusted life-years*). Los cocientes coste-utilidad oscilaron entre 2.494,1 y 9.640,38 dólares estadounidenses de 2005 por QALY en los contextos analizados.

Conclusiones: Los costes directos de la asistencia convencional realizada en México sobre los pacientes con AR en los contextos analizados son sustanciales tanto desde el punto de vista social como económico. El coste por QALY ganado es elevado.

Palabras clave: Costes directos. Utilidad. Artritis reumatoide.

Introduction

Rheumatoid arthritis (RA) is a systemic disease that causes pain, stiffness, functional disability and irreversible joint damage¹. It is associated with morbidity, impairment of quality of life and increased mortality^{2,3}. The economic impact of RA on society is high, mainly due to increased use of outpatient medical services, increased hospitalization rates and frequent work disability⁴. In addition, populations with RA generate an excess of costs (incremental costs) when compared with non-arthritic controls⁵⁻⁷ or populations with osteoarthritis⁶⁻⁸. Several works in the last decades^{4,5-10}, and more recent studies¹¹⁻¹⁹ have focused on direct and indirect cost generated by RA. All of them are done in developed countries. However, the RA costs studies are scarce in Mexico²⁰.

Utilities have been proposed to evaluate individual health status. These measurements provide a numerical value that shows patient's preference for a particular health state or health change and they differ from quality of life measures, which express a stated value of health state. Utilities can be combined with life expectancy into quality adjusted life years (QALYs)²¹ which are used in cost-utility analysis. This type of economic evaluation incorporates the preferences or values that individual have for particular health states to compare be-

nefits and costs from health care interventions²². Cost-utility or cost-QALY ratios of different interventions may be calculated and then comparisons between interventions can be made²³.

The purposes of our study were to assess the direct costs of RA in Mexico in the context of a clinical trial and, secondly, to analyze the cost per QALY obtained by Mexican RA patients in this scenario.

Patients and methods

Design

A cost descriptive study nested in a 48-weeks randomized clinical trial.

Setting

Outpatients attending the Rheumatology Department at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, a tertiary care center in Mexico City.

Patients

Consecutive patients attending our outpatient clinic were selected to participate in a randomized, placebo-controlled clinical trial assessing the efficacy of omega-3 fatty acids versus placebo in the treatment of active RA patients besides their standard rheumatology care²⁴. Entry criteria were:

- Age between 18 and 80 years older.
- RA according to the 1987 criteria of the American College of Rheumatology (formerly, American Rheumatism Association²⁵).
- Steinbroker modified functional class I-III²⁶.
- Active disease (three or more of: morning stiffness \geq 60 minutes, \geq 9 tender joints, \geq 6 swollen joints, ESR \geq 30 mm/h).
- All patients gave their consent to participate in the study, and the protocol was approved by the Local Ethics committee.

Methods

The same rheumatologist (BHC) evaluated all patients at baseline and at 4, 8, 12, 16, 24, 32, 40, and 48 weeks. In all the visits disease-related variables were collected including patient and physician global assessments on visual analogue scales (VAS) from 0 = very well to 10 cm = very bad; patient pain assessment VAS from 0 =

no pain to 10 cm = maximum pain; tender joint count of 68 ACR joints; swollen joint count of 66 ACR joints; morning stiffness in minutes, and ESR. The Disease Activity score (DAS)²⁷ was calculated as well as the Health Assessment Questionnaire disability index (HAQ-Di)²⁸. Utilities were assessed by the Health Utility Index²⁹. Medical treatment was prescribed according to the clinical judgment of local rheumatologists. Response was assessed according to the ACR20 criteria.

Costs assessment

Only direct costs were assessed. In each visit, resource utilization was measured following a structured questionnaire. Costs of medical visits, laboratory tests and X-rays were calculated according to a local tabulator for patients with the highest socioeconomic status; these fares may be considered equivalent to the true cost of the visits and complementary tests \pm 20%. The costs of the drugs were calculated using prices at June 1998 in Mexico City. The costs of the medication trial (omega-3 fatty acids or placebo) were not included in the primary analysis but they were considered in the sensitivity analysis (see below). Other direct costs were estimated by a questionnaire administered to 30 randomly selected patients. The questionnaire included items about the expenditures made by patients and people coming with them to medical visits, treatment, complementary tests, etc. (i.e. transportation, food, child care). Lost time was also calculated. The costs of the procedures of the clinical trial were not included. All the costs were originally expressed as Mexican \$ 1998 but they were converted to Mexican \$ 2005 according with the inflation rate in Mexico during the period 1998-2005 (cumulative rate 81.2125%)³⁰. The costs were expressed as US\$ 2005 converting Mexican \$ 2005 in US\$ 2005 according to the change type on December 2005 (1 US\$ = 10.6349 Mexican \$).

Utilities assessment

Utilities were assessed by the Health Utility Index²⁹. It consists in a vertical thermometer or visual analogue scale from 0 (the worst health state) to 100 (the best possible health state). Four cards describing hypothetical health states (well, regular, bad, very bad) of patients with RA were given to the patients. The cards were placed along the thermometer by them. At last, they placed their own health states in a point of the thermometer to score their value. These scores were transformed to a scale from 0 (the worst utility) to 1 (the best utility). A cost-utility ratio was calculated as follows: the numerator of this ratio was the total direct cost of RA in a year per patient and the denominator

was the number of QALYs gained per patient. QALYs were calculated as (utility) \times (years of treatment); since the duration of the study was one year, utilities were equivalent to QALYs.

Sensitivity analysis

Estimations of costs and utilities were done in other scenarios than the clinical trial. These scenarios were hypothetical and some of them may be considered representative of the standard care of the RA in Mexico. So, the analysis was also performed in these situations:

1. Considering 4 medical visits in a year with 3 complete blood cells counts and erythrocyte sedimentation rate, 3 determinations of serum biochemistry (glucose, urea and creatinine), and 3 urinalysis. It was hypothesized according to the described scenario for medical care of mild RA in Mexico²⁰. Additionally, it was considered that X-rays of hands and feet were done once in a year.
2. Considering 5 medical visits in a year with 4 complete blood cells counts and erythrocyte sedimentation rate, 4 determinations of serum biochemistry (glucose, urea and creatinine), 4 liver enzyme assays, and 4 urinalysis. It was hypothesized according to the described scenario for medical care of moderate RA in Mexico²⁰. Additionally, it was considered that X-rays of hands and feet were done once in a year.
3. Including the costs of the medication trial (omega-3 fatty acids or placebo).

Statistical analysis

Descriptive statistics were used. The costs and the difference between the final and the baseline utilities were expressed as mean, median, standard deviation and range.

Results

Ninety patients were included, 83 were females (92%) with age ($X \pm DE$) 43.2 ± 14.2 years and disease duration 3.3 ± 4.6 years. Two patients were excluded at baseline because they withdrew consent, so the follow-up was completed only by 88 patients. The sociodemographic characteristics at baseline are shown in table 1. The patients had high activity (DAS 5.0 ± 0.96), and moderate functional disability (HAQ 1.2 ± 0.6). Eighty-seven (96.6%) were in functional class II or III, and eighty-six (95.5%) had positive rheumatoid factor. The most frequent comorbidity was peptic disease (38 patients, 42.7%).

Seventy-four patients (82.2%) were taking non-steroidal anti-inflammatory drugs (NSAIDs) at baseline.

TABLE 1. Social and demographic characteristics of the rheumatoid arthritis patients at baseline

Variable	n, %	Mean \pm SD	Median, range
Age (years)	90, 100	43.2 \pm 14.2	45, 19-76
Gender			
Male	7, 8		
Female	83, 93		
Years of formal education	90, 100	8 \pm 4.5	8, 0-20
Marital status			
Married	39, 43.8		
Single	35, 35.8		
Others	16, 17.4		
Income, US\$, monthly	90, 100	154.8 \pm 170.6	117.6, 23.5-1176.5

SD: standard deviation.

Forty-four patients (48.8%) took one or more second line drugs (DMARDs). The drugs used as monotherapy were methotrexate (MTX) (35, 79.5%), azathioprine (3, 6.8%), d-penicillamine (3, 6.8%), sulphazalacine (1, 2.3%), chloroquine (1, 2.3%) and cyclophosphamide (1, 2.3%). Twenty-three patients (25.5%) were on combined therapy: MTX + chloroquine (18, 78.2%), MTX + azathioprine (1, 4.3%), MTX + D-Penicillamine (1, 4.3%), MTX + minocycline (1, 4.3%), MTX + sulphasalacine (1, 4.3%), MTX + cyclophosphamide (1, 4.3%). Three patients (3.3%) were taking MTX + chloroquine + d-penicillamine. Twenty-five (27.8%) patients took steroids: prednisone (20, 80%), parametasone (2, 8%), betametasone (2, 8%), and deflazacort (1, 4%). The mean dose of prednisone or equivalent was 5.8 \pm 2.4 mg (median 5, range: 2.5-12.5). Besides, 45 patients received omega-3 fatty acids (18 g/day of eicosapenta-

noic acid and 8.4 g/day of eicosapentaenoic acid), and 45 patients received placebo of omega-3 fatty acids (123.6 g/day of oleic acid, 25.2 g/day of palmitic acid, and 21.6 g/day of linoleic acid) according to the clinical trial in which this study was based.

A significant improvement was observed in all outcome measures except in the ESR along the study with 58/88 (66%) fulfilling ACR20 response criteria. There were not significant differences between patients treated with omega-3 fatty acids and those treated with placebo in any of the study variables. An increased intake of NSAIDs was detected along the study with significant differences between baseline and final (7th visit) [88% vs 94%], $p = 0.006$). The use of DMARD also increased with significant differences ($p < 0.001$). A total of 13/88 patients (17%) were lost to follow up due to adverse events ($n = 4$) or non compliance ($n = 9$).

Costs analysis

The total direct costs were 152,704.11 US\$ 2005; it means 1,735.27 US\$ 2005 per patient and year. The costs of the medical attention were 78,386.43 US\$ 2005 (890.75 US\$ 2005 per patient and year, 51.33%) (table 2). The costs of the drugs were 39,339.5 US\$ 2005 (447.04 US\$ 2005 per patient and year, 25.76%) (table 3). Other direct costs were 34,978.18 US\$ 2005 (397.48 US\$ 2005 per patient and year, 22.91%) (table 4).

Utilities assessment

Baseline utilities were ($\bar{X} \pm$ SD): 0.59 \pm 0.17 (median 0.65, range: 0-0.90) and final utilities were 0.77 \pm 0.13

TABLE 2. Direct costs of medical attention in eighty-eight rheumatoid arthritis patients during a year

	Median per patient (range)	Median cost per patient (range)	Total costs	%
Visits of rheumatologist	8 (1-8)	164.9 (20.6-164.9)	13,731.5	17
Laboratory tests				
Haematology	7 (1-8)	64.4 (9.2-73.6)	5,428.7	7
Biochemistry	7 (1-8)	101.4 (14.5-115.9)	8,400.4	11
Liver function tests	7 (1-8)	324.4 (46.3-370.8)	26,464.2	35
Lactate dehydrogenase	3 (0-7)	17.4 (0-40.5)	1,500.5	2
Lipids profile	2 (1-3)	57.6 (28.8-86.4)	4,837.8	6
Urine tests	2 (0-6)	16.3 (0-49.1)	1,856.6	2
ESR	8 (1-8)	40.9 (5.1-40.9)	3,399.3	4
Sub-total			51,887.4	67
Hands and feet X-Ray	4 (2-4)	151.9 (75.9-151.9)	12,767.5	16
Total			78,386.4	100

Costs are in US\$ 2005.

Biochemistry includes glucose, urea and creatinine.

ESR: erythrocyte sedimentation rate.

TABLE 3. Costs of drugs in eighty-eight rheumatoid arthritis patients during a year

Drugs	Number of patients (%)	Costs per patient	Total costs	%
Analgesics	–	–	1,674.1	4.2
NSAIDs				
Diclofenac	25 (28)	342.9	8,572.0	
Nabumetone	4 (4)	212.4	849.6	
Indomethacine	49 (56)	132.6	6,499.1	
Sulindac	8 (9)	359.8	2,878.2	
Naproxen	26 (30)	82.3	2,139.6	
Piroxicam	11 (12)	83.2	915.4	
ASA	18 (20)	8.3	149.3	
Other	6 (7)	26.7	160.5	
Sub-total			22,163.7	56.4
DMARDs				
Methotrexate	72 (82)	53.6	3,861.8	
Chloroquine	45 (52)	29.9	1,347.7	
Sulphasalazine	4 (4)	78.3	313.1	
D-Penicillamine	5 (6)	297.1	1,485.6	
Azathioprine	8 (9)	675.5	5,403.7	
Cyclophosphamide	2 (2)	332.0	663.9	
Minocycline	1 (1)	431.7	431.7	
Sub-total			13,507.5	34.3
Steroids				
Prednisone	59 (67)	29.21	1,723.7	
Deflazacort	1 (1)	270.5	270.5	
Sub-total			1,994.2	5.1
Total			39,339.5	100

Costs are in US\$ 2005.

NSAIDs: non steroidal anti-inflammatory drugs; ASA: acetylsalicylic acid; DMARDs: second line agents.

(median 0.80, range 0.40-1). So, the patients got a mean improvement of 0.18 utility units equivalent to 0.18 QALYs. The cost-utility ratio was 9,640.38 US\$ 2005 per QALY. It is the monetary value of 1 QALY in the scenario in which this study was performed. A cost-effectiveness ratio was also calculated. An ACR 20% response had a cost of 2,629.19 US\$ 2005.

TABLE 4. Other direct costs in eighty-eight rheumatoid arthritis patients during a year

	Cost per patient Median (range)	% patients with costs
Transportation	50.6 (8.2-1,416.99)	100
Food	36.8 (15.3-76.7)	58
Loss of productivity	35.8 (0-306.7)	27
Cost incurred by companionship	83.15 (0-1,159.3)	47
Nurse	30.7	3
Paid stay	513.7 (414.0-613.4)	6
Total	116.0 (12.3-3,375.2)	

Costs are in US\$ 2005.

Sensitivity analysis

The costs lowered in a significant way in the scenarios 1 and 2 (table 5). Considering the costs of the medication trial (scenario 3), the costs increased in 5,218.8 US\$ 2005 (59.3 US\$ 2005 per patient and year).

Discussion

According with our results, the direct costs of medical care for RA outpatients in Mexico in the context of a clinical trial were 1,735.27 US\$ 2005 per patient and year. One half of these costs were related to medical visits and complementary tests and the other half to drugs and other direct costs. However, this study was based in a clinical trial and it may be argued that it does not represent a real scenario. Indeed, the number of medical visits and complementary tests performed was probably higher than in the daily clinical practice. However, the characteristics of the included patients and the pattern of drugs prescription may be representative

TABLE 5. Sensitivity analysis. Costs and cost-utility ratios in the primary analysis and other hypothetical scenarios

	Medical visits	Laboratory	X-rays	Medical attention	Other costs	Total costs per patient	Cost/utility ratio
Primary analysis	13,731.5	51,887.4	12,767.5	78,386.4	34,978.2	152,704.1 1,735.3 (per patient)	9,640.38
Scenario 1	7,422.2	9,986.2	3,191.9	20,600.3	18,907.1	39,507.4 448.9 (per patient)	2,494.1
Scenario 2	9,278.0	28,437.3	3,191.9	40,907.2	23,633.9	103,880.6 1,180.5 (per patient)	6,558.1

Scenario 1: 4 medical visits in a year with 3 complete blood cells counts and erythrocyte sedimentation rate, 3 determinations of serum biochemistry (glucose, urea and creatinine), and 3 urinalysis. Additionally, it was considered that X-rays of hands and

of the medical care to Mexican RA outpatients. Therefore, sensitivity analysis was done considering hypothetical scenarios with a lower number of medical visits and complementary tests than those performed in the clinical trial. These scenarios could be representative of the standard care to Mexican RA outpatients and the annual cost per patient in these situations ranged from 448.9 to 1,180.5 US\$ 2005.

Most economic studies have been focused on the cost of RA in developed countries. In studies performed in the last decade^{5-19,31} the annual direct costs per patient ranged from 2,310 US\$⁸ to 7,691 US\$¹⁰. A review which includes studies performed in several decades⁴ found that the mean direct costs were 5,720 US\$ per patient and year.

In the most of the studies the hospitalization costs were the main component of the total direct costs whereas the medication costs also contributed to the total costs in a significant way¹⁹. In a few studies^{13,16,17} non-medical direct costs were the main component of the total direct costs. In our study, the direct costs of medical attention to RA patients were lower than the most published studies. It may be due to two reasons: first, we only assessed outpatient's costs, and the hospitalization costs including prosthetic surgery were not considered. Second, our study is done in a developing country, and, the results are not comparable with those of the studies in developed countries. Moreover, no patients with biologic treatment were included in this study. In a study based in clinical scenarios, performed by us in the last decade²⁰, the direct costs of the RA in Mexico ranged from 277 US\$ for mild disease to 2,661.4 US\$ per patient and year for severe disease. In the present study, we did not analyze costs by subgroups of patients according to the severity of disease, but the included patients had an active disease and a moderate impairment of their functional capacity. The costs obtained in our study although lower than in other studies, are very high from a patient perspective in Mexico. So, the mean annual income of patients included in this study were 15,789.6 Mexican \$ 1998 equivalent to 2,690.45 US\$ 2005 and the direct cost of the RA (without including admissions to the hospital) represented a 64% of this.

In our study, the patients gained 0.18 QALYs and the cost-utility ratio was 9,640.38 US\$ 2005 per QALY. In the scenarios with a lower number of medical visits and complementary tests than those performed in the clinical trial the cost-utility ratios ranged from 2,494.1 to 6,558.1 US\$ 2005. Several interventions for musculoskeletal conditions have been analyzed from a cost-utility perspective³²⁻³⁷. The total hip arthroplasty vs no total hip arthroplasty in people with hip osteoarthritis in functional class III is cost-saving in white 60 years old women and it has a cost per QALY 5,500 US\$ in white men > 85 years old³². The combined therapy (predniso-

lone, methotrexate and sulphasalazine) in RA is cost-saving vs to the treatment with sulphasalazine alone³³. The use of biologic agents (infliximab, etanercept or adalimumab) in combination with methotrexate has an incremental cost per additional gained QALY between 40,000 and 50,000 €³⁵⁻³⁷. The present cost-utility evaluation has a major limitation due to the lack of a therapeutic strategy to compare with the analyzed intervention (the treatment of RA in Mexico in the context of a clinical trial). Instead of it, we have used as comparator the baseline state of the patients included in the study. Their situation can serve as a model of active disease "without treatment" (in fact, with bad response to the treatment). In this scenario, it is possible to assess the utility of an intervention (the treatment of RA in Mexico). The hypothetical scenarios with a lower number of medical visits and complementary tests than those performed in the clinical trial can be an adequate model of the standard care of the RA outpatients in México. The amount of QALYs obtained by our patients is high when compared to other studies³²⁻³⁷. However, the cost per QALY is also high when related to the economic level of the country. It must be considered that this study was performed before the introduction of leflunomide, and biologic agents in the treatment of RA in Mexico. Indeed, the use of biologic agents in the treatment of RA increases the direct costs in a significant way but it has been addressed only in a few studies^{15,19}. In a longitudinal study performed in the United States on 7,527 RA patients with 25% of them receiving biologic agents¹⁹, the annual drugs costs (6,324 US\$) represented a 66% of the total costs. In this study, the mean total annual direct cost was three-fold higher in patients with biologics than in those without these agents. In recent studies performed in Spain^{16,19} the drugs costs ranged from 56% to 78% of the total costs, and, again, the total costs in patients with biologic agents were three-fold higher than in those without biologics¹⁹.

In summary, the direct costs of the standard care of the RA in the scenarios considered in this study are significant in the social and economic context of Mexico. The cost per gained QALY is high.

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