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ORIGINAL ARTICLES

Cost-Effectiveness Analysis Comparing Methotrexate With PUVA Therapy for Moderate–Severe Psoriasis in the Sanitary Area of Badajoz

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Abstract. *Objective*. To perform a cost-effectiveness analysis, by using a decision tree model, comparing methotrexate with PUVA therapy for moderate to severe chronic plaque psoriasis in the sanitary area of Badajoz (south-western Spain) over a one-year period.
Material and methods. The following variables and data sources were included: efficacy (a 50% reduction in the PASI) and safety. Data were retrieved from the dermatologic medical literature, mainly general reviews, systematic reviews and randomized clinical trials. Therapy schedules followed current guidelines from work task teams and consensus documents.
Direct costs included unitary costs of medical consults, costs of laboratory tests, pharmacy, phototherapy sessions and costs derived from adverse reactions.
Indirect costs included travel expenses and costs of lost productive work time.
Results. Unitary cost of methotrexate therapy would be 952,79 euros per treatment (direct cost: 796,48; indirect cost: 156,31). Unitary cost of PUVA therapy would be 899,70 euros per treatment (direct cost: 383,36; indirect cost: 516,34). Total cost of a one-year treatment with methotrexate would be 255,202.73 euros. Total cost of a one-year treatment with PUVA would be 266,406.88 euros. The average cost-effectiveness ratios per case successfully treated would be 1,519.06 euros for methotrexate therapy, and 1,085.18euros for PUVA therapy. The incremental cost-effectiveness ratio of PUVA/methotrexate would be 150,65euros for each additional case successfully treated.
Conclusions. One-year treatment for moderate to severe psoriasis in the sanitary area of Badajoz would be more expensive but also more cost-effective with PUVA than with methotrexate. However, indirect costs (borne by patients in the Spanish Health System), are higher for PUVA therapy, a fact that raises an issue of equity. The results should be interpreted taking into account the methodological limitations of a modelling study.

Key words:psoriasis, cost-effectiveness, cost-efficacy, methotrexate, PUVA.

ANÁLISIS DE COSTE-EFECTIVIDAD MODELIZADO COMPARANDO METOTREXATO CON FOTOTERAPIA TIPO PUVA PARA LA PSORIASIS MODERADA-SEVERA EN EL ÁREA DE SALUD DE BADAJOZ

Resumen. *Objetivo*. Realizar un análisis de coste-efectividad modelizado, usando un árbol decisión, comparando metotrexato y fototerapia tipo PUVA para la psoriasis crónica en placas moderadas-severas en el Área de Salud (AS) de Badajoz, durante el período de un año, desde la perspectiva societaria.
Material y métodos. Se consideraron las siguientes variables y fuentes de datos: eficacia y seguridad. Se valoró como eficaz la mejoría del PASI50. Se tomaron datos de la literatura médica dermatológica, fundamen-

In memoriam of my friend Francisco Revenga, who inspired my interest in this and many other subjects.

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talmente revisiones generales, revisiones sistemáticas y ensayos clínicos aleatorizados. Los regímenes de tratamiento se obtuvieron de las recomendaciones de grupos de trabajo y documentos de consenso, recogidos en publicaciones médicas.
Como costes directos se consideraron los costes unitarios por consulta, los de las pruebas de monitorización, los de la medicación y las sesiones de fototerapia y los de las reacciones adversas.
En los costes indirectos se valoraron los costes por desplazamiento, y los de productividad debidos a la pérdida horas de trabajo de la jornada laboral.
Resultados. El coste unitario por tratamiento con metotrexato sería de 952,79 euros (directos: 796,48; indirectos: 156,31). El coste unitario por tratamiento con PUVA sería 899,70 euros (directos: 383,36; indirectos: 516,34). El coste total del tratamiento durante un año con metotrexato sería 255.202,73 euros, y con PUVA 266.406,88 euros. Las ratios medias de coste-efectividad serían, para cada uno de los tratamientos: metotrexato 1.519,06 euros, y PUVA 1.085,18 euros por caso tratado eficazmente. La ratio incremental PUVA/ metotrexato sería: 150,65 euros por cada caso añadido eficazmente tratado.
Conclusiones. El tratamiento de la psoriasis durante un año en el AS de Badajoz con PUVA sería más caro, pero también más coste-efectivo que el tratamiento con metotrexato. Sin embargo, los costes indirectos (soportados por el paciente) del tratamiento con PUVA son más altos, lo que plantea un problema de equidad. Estos resultados deben considerarse a la luz de las limitaciones metodológicas de un estudio modelizado.

Palabras clave: psoriasis, coste-efectividad, coste-eficacia, metotrexato, PUVA.

Introduction

Psoriasis affects 1.5% of the population in Spain,[1] and there is no evidence to suggest that prevalence varies from one region to another.

Although the condition can be controlled successfully, it cannot be cured. Effective therapies, rather than prolonging life expectancy, improve patients' symptoms and quality of life, and cure outbreaks of the disease. Efforts are being made to improve both the subjective and objective parameters used to measure clinical improvement. Examples of the former are health-related quality of life scores and patient preferences and an example of the latter is the psoriasis area and severity index (PASI) (recommended by the US Food and Drug Administration as the endpoint for evaluating clinical efficacy).

Numerous studies have analyzed the efficacy, effectiveness, and safety of psoriasis treatments. While some studies have analyzed total cost of treatments in a range of countries, few have analyzed cost-effectiveness. In our review of the medical literature, we found comparative cost-effectiveness studies for methotrexate versus cyclosporine, methotrexate versus Goeckermann therapy, methotrexate versus a modified rotation regimen of cyclosporine and methotrexate, calcipotriol versus UVB phototherapy, and tacalcitol versus a combined regimen of calcipotriol and betamethasone dipropionate followed by calcipotriol alone.[2-6] All these studies were conducted in the United States of America, Holland, Denmark, and France.

Study Objective

The objective of this study was to perform a cost-effectiveness analysis based on a decision tree model comparing methotrexate and psoralen plus UV-A (PUVA) treatment for chronic moderate-to-severe plaque psoriasis from a societal perspective. The study was conducted in the health care area of Badajoz, Spain, over the period of a year.

Treatments Compared

1. Methotrexate. Methotrexate is a DNA synthesis inhibitor with antiproliferative, anti-inflammatory, and immunosuppressive properties. In use since 1958, it is a first-line drug for treating psoriasis, and is used in alternating therapy regimens. It is generally administered orally, although it can also be used subcutaneously or parenterally. The only absolute contraindications to its use are pregnancy and breastfeeding. Dose-limiting acute adverse reactions include gastrointestinal intolerance and leukopenia, followed by renal insufficiency, and drug interactions. The most feared long-term toxic effect is hepatotoxicity (periportal fibrosis and cirrhosis). This risk is greater in patients with predisposing factors such as an excessive intake of alcohol or hepatotoxic drugs, chronic viral hepatitis, and type 1 diabetes mellitus. The American Academy of Dermatology has published

therapeutic guidelines for the management of the disease (last revised in 1998).[7]

2. PUVA. When PUVA treatment became widespread 30 years ago, it offered the first real alternative to the hospitalization of patients with moderate-to-severe psoriasis. PUVA is administered in an outpatient setting and can induce complete and prolonged remission thanks to its immunosuppressive and antiproliferative effects. Its dose-limiting acute toxic effects include photosensitivity, erythema, pruritus, and digestive intolerance to methoxsalen. Prolonged treatment involving many sessions is a predisposing risk factor for skin cancer and eye phototoxicity (cataracts in particular). Two dosing regimens are used: the European system, which is based on the minimum phototoxic dose, and the American system, which is based on skin phototype (Fitzpatrick system).[8]

A consensus group organized by the American National Psoriasis Foundation to study the long-term toxic effects of PUVA treatment concluded that PUVA and methotrexate had the most acceptable benefit–risk ratio of all psoriasis treatments.[9]

The Context

According to the latest census of individual medical card holders conducted in March 2005, the Badajoz health care area serves a population of 251165 inhabitants, with 18 health care centers spread over 4 areas:

1. Central Badajoz and metropolitan area
2. Anexo I, La Paz, Montijo, Oliva de la Frontera, San Roque and Villanueva del Fresno
3. Barcarrota, San Fernando, Jerez de los Caballeros, La Roca de la Sierra, Olivenza, Pueblonuevo del Guadiana, San Vicente, Santa Marta, and Talavera
4. Alburquerque and Alconchel

Specialty care is provided by the Complejo Hospitalario Universitario de Badajoz, which is made up of Hospital Infanta Cristina and Hospital Perpetuo Socorro, both located in the metropolitan area of Badajoz. In the past 2 years, the dermatology department has treated 699 patients with psoriasis; of these 123 (17%) required systemic therapy. This figure is similar to that reported by the Epiderma II study (21%).[15]

Methods

Data Sources

1. Efficacy and safety: data were obtained from the dermatology literature, mainly general reviews, systematic reviews, and randomized clinical trials.[10-12]
2. Treatment regimens: working group guidelines and consensus documents in medical publications.[7,8]
3. Direct costs: *a)* Unit costs per dermatology and ophthalmology visit, obtained from the 2004 Cost Accounting Report published by the Directorate of Finances and General Services of the Department of Health and Consumer Affairs attached to the Public Health Service of Extremadura, Spain. Costs included personnel and department operating expenses, the use of other services, and overheads. We excluded consultancy costs because all the patients had been referred by a primary care physician and treated in outpatient or hospital clinics belonging to the Extremadura public health service. *b)* Costs of monitoring tests (laboratory and radiology tests, and liver biopsy), provided by the corresponding central departments and obtained from the same source as above. *c)* Medication costs, obtained from the Spanish Catalogue of Medicinal Products. *d)* Costs of phototherapy sessions. We calculated the average cost per session on the basis of the fees charged by the 3 main health insurance companies in the province of Badajoz (Asisa, Sanitas, and Adeslas).
4. Indirect costs: *a)* Journey time and cost. Information on journey time, distances from health care centers to hospitals, and transport fares was obtained from the public bus companies that serve the area (Leda and Damas). Costs for transport within the city of Badajoz were not considered. Average cost per journey was determined by calculating the average fare for traveling from each health care centre located outside the city to the hospital for treatment, and weighting this using a population coefficient. *b)* Costs due to lost working time. To calculate this cost, we used the average gross annual salary for Extremadura in 2002, obtained from a survey conducted by the Spanish National Employment Institute. We calculated the average wage per hour on the basis of a 40-hour working week. An identical method had been used in a previous cost-effectiveness study.[3] Any work time lost as a result of travel or treatment was included in the cost calculation. Treatment time was calculated at 30 minutes per patient (per visit or phototherapy session). We did not consider work time lost due to blood analyses or similar tests as these were performed in local health care centers.

Variables

1. Efficacy and safety. Efficacy was measured in terms of clinical improvement. Specifically, we assessed the improvement in the lesions with percentage change in PASI score (PASI%). Treatment was considered successful if a reduction of at least 50% from baseline was achieved in the PASI score (PASI50).

Short-term and medium-term toxicity is generally low if patients are selected carefully and treatment regimens monitored correctly. The main adverse effects are intolerance and analytical alterations without clinical repercussions. When they occur, however, it is often necessary to interrupt treatment either temporarily or permanently. Accordingly, we considered any event that required the interruption of treatment to be an adverse event.

2. Costs. Unit costs per treatment for the period of a year were calculated by adding direct costs (visits, drugs, phototherapy sessions, follow-up tests, and treatment of adverse reactions) and indirect costs (transport and lost working time).

To calculate the cost of the liver biopsy, we multiplied the cost of the test by 5%, which is the percentage of the population at risk (patients with chronic viral or alcohol-induced hepatopathy or type 1 diabetes mellitus) who require at least 1 test a year.

Decision Tree Modeling

We constructed a decision tree (Figure) that estimated event probability using the data obtained from the sources described above. Costs were calculated from the societal perspective (direct plus indirect costs) and the perspective of the Public Health Service of Extremadura (direct costs only).

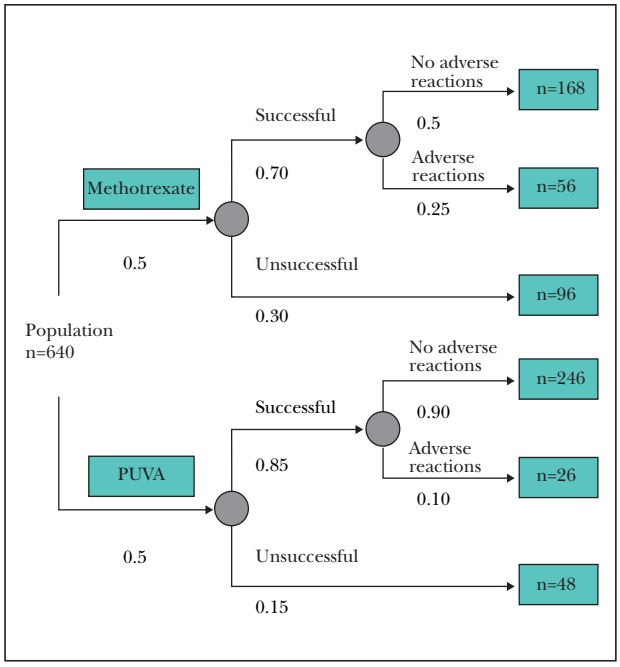

Figure 1. Decision Tree.

Target Population

In accordance with the prevalence of psoriasis in Spain, we estimated that 3767 inhabitants in the study area would have psoriasis. As 17% of the patients who had visited the dermatology department in the past 2 years had clinical and/or subjective signs of psoriasis that justified systemic therapy, we calculated that 640 patients would be candidates for methotrexate or PUVA treatment. Because neither of the 2 treatments have absolute contraindications (except pregnancy and breastfeeding), we assumed that half of the group could be candidates for one or other of the treatments.

Treatment Regimens and Monitoring

Methotrexate

The average treatment regimen includes the following drugs and doses:

1. Methotrexate: 7.5-30 mg/wk; average of 15 mg/wk for 16 weeks (240 mg/treatment). Considering a relapse period of 5 weeks, we calculated that each patient would require 2.5 methotrexate treatments per year. This is the equivalent of a total cumulative dose of 600 mg/y.
2. Folic acid: 5 mg/d for 16 weeks: total dose, 1400 mg/y.
3. Ranitidine: 300 mg/wk: total dose, 15 600 mg/y.

Recommended monitoring tests (laboratory and imaging studies) include: *a)* tests performed prior to treatment: blood count (3 series), liver function tests (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-glutamyltransferase, bilirubin, and albumin), kidney function tests (creatinine levels, creatinine clearance, urea, and urine test), and chest radiographs. We excluded type III procollagen and methotrexate blood level tests as these are not available at our hospital. *b)* Toxicity monitoring tests: blood count every week for first 2 weeks, every 2 weeks for the following month, and every month thereafter (15 tests in total per year). *c)* Liver biopsy, performed on patients without risk factors who received a cumulative dose of 1.5 g (reached after 120 weeks or 28 months in mean dose regimen) and on patients with risk factors who received a cumulative dose of 250 to 300 mg (reached after 2 to 4 months). *d)* Number of journeys: number of visits to dermatology department (15 per year in the absence of complications).

Psoralen Plus UV-A Treatment

The average PUVA treatment regimen includes:

1. Psoralen: mean dose of 0.6 mg/kg/session. This is the equivalent of 1920 mg/y for a patient with an average weight of 70 kg (40 mg/session, 48 times a year).

2. UV-A light therapy: incremental exposure regimen that varies according to patient's skin photoype (2 sessions/wk for 8 weeks depending on the protocol followed). Each treatment session can last for up to 15 minutes. Given that PUVA is contraindicated during the summer, we calculated an average frequency of 2 treatment sessions per year.
3. Pre-treatment monitoring tests: liver function, antinuclear and anti-Ro antibody tests, eye examination. Post-treatment tests: eye examination every 6 months. No further tests are required if there are no complications.
4. Number of journeys: number of visits to dermatology unit per year, 3 (before treatment, during treatment, and 8 weeks after treatment); number of visits to ophthalmology unit per year, 2; number of treatment sessions per year: 24 x 2 = 48; total number of journeys a year: 54.

Results

Efficacy

Methotrexate

Although methotrexate is among the oldest and most widely used systemic therapies for psoriasis, a recent systematic review of the literature concluded that its efficacy cannot be determined due to the lack of well-designed studies.[10] It has been estimated, however, that its efficacy (measured by number of patients with a 50% reduction in the PASI score) may be at least 70% in the first 2 to 4 months,[11] although some clinical trials have reported a lower rate.[13,14]

Psoralen Plus UV-A Treatment

Although a recent systematic review of 23 randomized controlled studies dealing with the efficacy of PUVA warned about the considerable heterogeneity of the corresponding study designs and protocols,[15] it is estimated that between 70% and 90% of patients with chronic moderate-to-severe psoriasis achieve improvements of 50% in PASI score from baseline.[11]

Safety

Methotrexate

Adverse effects have been observed in 25% of patients who received recommended doses of methotrexate.[14] The effects reported include gastrointestinal intolerance, leukopenia, and mild-to-moderate liver disease (mostly asymptomatic). They can be minimized with the concomitant administration of folate and ranitidine. When these effects do occur, however, it is often necessary to withdraw the drug and conduct a series of tests, although additional medication is not required. In our analysis of adverse events, we excluded intoxication due to accidental overdose, severe lung disease (rare in psoriasis treatment), and long-term outcomes due to hepatic fibrogenesis or immunosuppression.

Psoralen Plus UV-A Treatment

PUVA has a very low dose-limiting toxicity. The most common adverse effect is digestive intolerance to psoralen, which generally requires dose reduction and drug administration with meals. While mild erythema is not uncommon, acute phototoxicity is rare if the incremental exposure regimen is adjusted to the patient's skin phototype. In the event of phototoxicity, the patient must generally be protected from light, and administered an emollient and an H1 antihistamine for 2 days. We excluded long-term toxicity (photoaging and skin cancer) from adverse effects as it fell outside the time frame contemplated by the study.

Costs

Direct unit costs, costs related to adverse events, and indirect costs for both treatments are shown in Table 1. The total

Table 1. Unit Costs Per Treatment in Euro (€)

	Methotrexate	*PUVA*
Visits	510	187.18
Medication	83.44	9.78
Monitoring	164.21	18.4
Sessions	-	168
Liver biopsy	38.83	-
Total direct costs	796.48	383.36
Adverse reactions	92.69	3.68
Travel	40.65	146.34
Lost working time	115.66	370
Total indirect direct costs	156.31	516.34
Unit cost per treatment	952.79	899.7

Table 2. Total Cost of Treatment With Methotrexate for a Year in Euro (€)

Methotrexate		
Successful	168 × 952.79	160 068.2
Successful with adverse reactions	56 × 1045.48	58 546.88
Not successful	96 × 381.12	36 587.13
Total	255 202.73	

Table 3. Total Cost of Treatment With Psoralen Plus UV-A (PUVA) for a Year in Euro (€)

PUVA		
Successful	246 × 899.7	221 326.2
Successful with adverse reactions	26 × 903.38	23 487.88
Not successful	48 × 449.85	21 592.8
Total		266 406.88

costs per year of treatment with methotrexate and PUVA are shown in Tables 2 and 3, respectively. Unsuccessful treatments also incur a cost which is generally lower than that of successful treatments as they have to be interrupted following the first course of treatment.

Average Cost-Effectiveness Ratios

Methotrexate: €255 202.73/168 (number of successfully treated patients) = €1 519.06 per patient treated successfully.

PUVA: €266 953.14/246 (number of successfully treated patients) = €1 085.18 per patient treated successfully.

Incremental Cost-Effectiveness Ratio (Psoralen Plus UV-A/Methotrexate)

Incremental ratio: €266 953.14–€255 202.73/246-168 = €150.65 for each additional patient treated successfully.

Discussion

Several studies have calculated the direct and indirect costs of psoriasis.[12] One such study in Spain, EPIDERMA II, a multicenter study conducted between 2003 and 2004, analyzed a group of 797 patients with psoriasis, of whom 717 completed the study; 61% had mild psoriasis (PASI<10), 17% moderate psoriasis (PASI 10-20), and 9% severe psoriasis (PASI>20). The estimated average annual cost per patient was €890.50 for direct costs and €188.50 for indirect costs (not including transport). The total average direct costs for patients who received systemic therapy, however, were almost double those for patients who only received topical treatment. The figures for moderate and severe psoriasis were €1265 and €2169.30, respectively. These figures are somewhat lower than ours, which included indirect transport costs. About 13% of the costs calculated by the EPIDERMA II study corresponded to oral medication (unspecified) and phototherapy. The indirect costs of moderate and severe psoriasis were 2 and 5 times higher than those of mild psoriasis, respectively. The majority of patients with severe psoriasis had been treated at hospital.

Our calculations are based on data from the medical literature that show that PUVA is probably safer and more efficient than methotrexate. This assertion cannot be confirmed, however, due to the lack of medical evidence.[10,11,16]

According to the present study, in ideal circumstances, in which any patient with moderate-to-severe psoriasis is a candidate for methotrexate or PUVA treatment (only pregnancy and breastfeeding are absolute contraindications), PUVA would be a more cost-effective option than methotrexate as it has a higher average cost-effectiveness ratio. This finding contrasts with those of a US cost-comparison study of psoriasis treatments that found methotrexate to be the most cost-effective systemic therapy.[12] That study analyzed cost-effectiveness using 2004 Medicare fees for drugs and monitoring tests.

Although in our study the unit cost per treatment was higher for methotrexate than for PUVA, the total annual cost was lower as methotrexate had a higher efficacy rate. The opportunity cost is ultimately lower for PUVA than for methotrexate, however, as alternative treatments are not required for patients who do not respond.

The fact that indirect costs, borne entirely by patients in our local health care system, are 3.3 times higher for PUVA than for methotrexate, raises an issue of equity. The considerable geographic spread of patients and different distances from the hospital where treatment is administered are some of the structural reasons behind this problem. One possible solution would be to provide transport subsidies to affected patients.

Conclusions

1. The unit cost per treatment in the Badajoz health care area is higher for methotrexate than for PUVA. The total cost of treatment over 1 year, however, is higher for PUVA than for methotrexate.
2. PUVA treatment is more cost-effective than methotrexate treatment.
3. Direct treatment costs, which are borne by the Extremadura Public Health System and the patient, are higher for methotrexate than for PUVA. Indirect costs, in contrast, borne exclusively by the patient, are slightly higher for PUVA. This raises an issue of equity, which we have not analyzed in this study.

Methodological Limitations of the Study

1. Because our study is based on modeled data rather than data obtained from a prospective controlled clinical trial, we used a range of different sources to calculate average efficacy rates and costs.

2. Psoriasis is a chronic, generally progressive, disease that has an unpredictable course of fluctuating severity. A time frame of 1 year may therefore not be enough to correctly assess cost-effectiveness and guide clinical decisions. Nonetheless, this time frame has been previously used in at least 1 study.[12] A Markov model would certainly be a more suitable method.
3. We only evaluated treatment efficacy using percentage changes in PASI scores (50% reduction in PASI score); we did not use overall or quality-of-life improvement scores.
4. We did not take into account costs related to long-term toxic effects (treatment of skin cancer associated with PUVA, and lymphomas and hepatotoxicity associated with methotrexate treatment, etc).
5. We only used systematic reviews and studies published in English. A number of systematic reviews have warned about the lack of evidence regarding the efficacy and safety of PUVA, and methotrexate in particular. The lack of rigorous data is due to poor study designs, heterogeneous treatment protocols and management, and poorly defined efficacy endpoints and indicators.
6. We did not consider other reasons for choosing one treatment over the other, such as the coexistence of arthritic psoriasis (for which methotrexate would be more efficient) or a history of immunosuppressive treatment (where PUVA would be more efficient).

Conflicts of Interest

The authors declare no conflicts of interest.

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