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ORIGINAL RESEARCH

Cost of early-stage mycosis fungoides treatments in Spain

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Aim: To identify the most common therapeutic options for the treatment of early-stage mycosis fungoides in Spain, quantify their associated healthcare resource use and costs.

Methods: After reviewing the literature, a panel of 6 Spanish clinical dermatologists validated the treatments and healthcare resource use through a structured questionnaire. Individual responses were collected, analyzed and presented into a face-to-face meeting in order to reach a consensus. Cost categories considered were: drug acquisition and administration, photo/radiotherapy session and maintenance, clinical follow-up visits and laboratory tests. Costs were expressed in euros from 2018. The Spanish National Health System perspective was considered, taking into account direct health costs and time horizons of 1, 3 and 6 months.

Results: Costs for the skin-directed treatments (SDT) assessed at 1, 3 and 6 months, were: Topical carmustine [€6,593.36, €19,780.09 and €27,592.78]; Phototherapy with psoralens and ultraviolet A light (PUVA) [€1,098.68, €2,999.99 and €3,187.60]; Narrow-band ultraviolet B phototherapy [€1,657.47, €4,842.10 and €4,842.10]; Total skin electron beam therapy (TSEBT) [€6,796.45, €7,913.34 and €7,913.34]. Cost for topical corticosteroids, being considered an adjuvant option, were €17.16, €51.49 and €102.97. Costs for the assessed systemic treatments alone or in combination with SDT at 1, 3 and 6 months, were: Systemic retinoids [€2,026.03, €5,206.63 and €7,426.42]; Systemic retinoids + PUVA phototherapy [€3,066.50, €8,271.26 and €10,046.58]; Interferon alfa + PUVA phototherapy [€1,541.09, €5,167.57 and €6,404.55].

Conclusion: According to the Spanish clinical practice, phototherapies in monotherapy were the treatments with the lowest associated costs regardless of the time horizon considered. TSEBT turned out as the treatment with the highest associated costs when considering 1 month. However, while considering 3 and 6 months the treatment with the highest associated costs was topical carmustine. The results of this analysis may provide critical information to measure the disease burden, to detect unmet medical needs and to advocate towards better treatments for this rare disease.

Keywords: health care costs, health resources, mycosis fungoides, lymphoma, T-cell, cutaneous, surveys and questionnaires, Spain

Introduction

Cutaneous T-cell lymphomas (CTCL) are a heterogeneous group of diseases that represent between 1–4% of cases of non-Hodgkin lymphomas.[1–5] CTCLs are characterized by the primary infiltration of malignant T cells in the skin without evidence of extracutaneous disease at the time of diagnosis.[1,6,7]

Mycosis fungoides (MF) represents between 50–70% of cases of CTCL,[3,8–11] being classified as a rare disease.[12,13] Although prevalence is difficult to

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determine, the age-adjusted incidence of MF is estimated to be between 0.12 and 0.55 cases per 100,000 inhabitants.[14–17] The low incidence rate of CTCLs means it is essential to create multicenter records in order to shed light on the characteristics of patients affected by this group of diseases, to describe their state of health and clinical burden and to have a better understanding of their management and prognosis.[18,19] This has led to the Spanish Academy of Dermatology and Venerology (AEDV) setting up a registry of patients with primary skin lymphomas. It recently published the results from its first year in operation: by December 2017, the registry contained information on 639 patients with primary skin lymphomas from 16 University Hospitals. Among the 348 recorded MF patients, the most common diagnosis was classical MF (77.3%), most of them (83.6%) presented early stages of the disease (IA-IIA).[20]

In most cases, MF initially presents as an indolent condition with slow progression that tends to start with a patch phase, progressing in some patients to infiltrated plaques and finally evolving into a tumoral phase.[1,21–23] The prognosis depends on the disease stage as determined by the International Society for Cutaneous Lymphomas (ISCL) and the European Organization for Research and Treatment of Cancer (EORTC).[6,24]

As the disease progresses, a detrimental effect on survival has been observed among MF patients.[25–29] Although patients with limited T1 stage MF present a similar life expectancy to the control populations,[25,27] generally patients with MF present accumulated survival rates significantly lower compared to the healthy population matched by age and sex.[25]

Treatment strategies for MF can be split into two categories: skin-directed treatments (SDT) and systemic treatments including biological response modifiers, single or multiple chemotherapies, epigenetic therapies, monoclonal antibodies and hematopoietic stem cell transplantation.[11,30,31] Despite the availability of multiple treatment options, none of these may be considered as standard.[32] Patients with limited-stage disease are usually treated with SDT, while patients with advanced stage MF require a broader multidisciplinary approach involving various combinations of SDT, biological response modifiers and systemic chemotherapy.[11,30–32]

MF presents a significant clinical burden for patients with this rare disease. Patients not only feel overwhelmed by the physical symptoms of the disease but also suffer from sleep problems because of itching,[8,33] and experience a significant emotional impact caused by frustration and rejection of their disease.[33,34] MF has an impact on patients' functional capability and the ability to carry out daily activities. It also has a negative effect on patients' productivity, causing work absenteeism or interfering with their productivity.[8]

In financial terms, MF involves a significant burden both to patients as well as to healthcare systems. Although patients with advanced stage MF incur higher healthcare costs than patients at the early stages, it has been shown that MF patients with less severe stages may also require high use of healthcare resources because of numerous visits to outpatient care centers and pharmacy departments.[35–37] In addition, treating MF may be a social economic strain because of transport direct costs and indirect costs associated with loss of productivity,[38] all depending on their geographic location, the type of treatment and the characteristics of the healthcare system.

This, together with the lack of financial studies in Spain on this rare disease, has motivated this study with the aim of identifying the therapeutic alternatives most commonly used in Spain for managing patients with early-stage MF, to determine their associated healthcare resources use and to quantify their associated costs.

Materials and methods

Study design

Firstly, a structured review of medical literature was carried out to determine the available clinical and financial evidence on CTCLs and MF, and to draw up a structured questionnaire with the aim of defining the most commonly used treatment alternatives in Spain for managing patients with early stages of MF, to determine their healthcare resources use and to quantify their associated costs. A panel of 6 clinical dermatology experts from the Spanish setting with a wealth of experience in managing CTCL and MF was put together. After completing and returning the questionnaires, the individual responses were assessed and grouped to obtain data considered in the analysis. A face-to-face meeting was set up to present and validate the responses obtained and to reach consensus on the grouped responses. The identity of the members of the expert panel was kept secret by the team responsible for the research until the face-to-face meeting (Figure 1).

Therapeutic options

From the evidence available, the main treatments used in Spanish clinical practice for early-stage MF are:

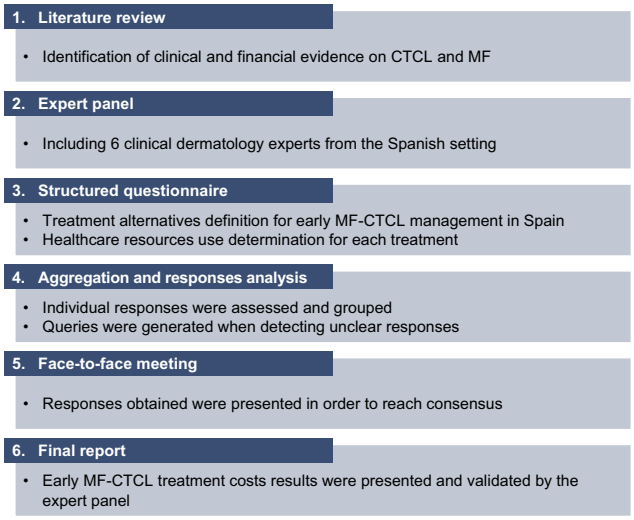

Figure 1 Study diagram.
Abbreviations: CTCL, cutaneous T-cell lymphomas; MF, mycosis fungoides.

phototherapy with psoralen and ultraviolet A light (PUVA), phototherapy with narrowband ultraviolet B light (NB-UVB), total skin electron beam therapy (TSEBT), topical corticosteroids, systemic retinoids, a combination of PUVA phototherapy with systemic retinoids or interferon alfa (IFNα), as well as, to a lesser extent, topical carmustine-based chemotherapy.

Questionnaire

The questionnaire consisted of a total of 72 questions requested as qualitative questions to confirm data from medical literature, quantitative questions, and open-ended questions. The numerical responses were grouped and the average data, standard deviation, median, minimum and maximum data were estimated. The qualitative responses were grouped according to the following criteria: unanimous response (the whole expert panel [100%] in agreement), consensus (at least 83% of the expert panel gave the same response but without being unanimous), majority (response indicated by a majority of the expert panel, that is between 66% and 83%) and discrepancy (all other possible situations: namely, where the same response was not shared by at least 66% of the experts panel). All members of the expert panel provided their informed consent to participate in this study and to complete the questionnaire.

Type of analysis

Treatment cost analysis was carried out from the perspective of the Spanish National Health System. Therefore, the direct healthcare costs were taken into account. The Spanish expert panel considered that adopting one-year time horizon would not be appropriate for this analysis. During one-year timeframe, different MF-CTCL treatments may be used in combination or alternately. Therefore, according to the most commonly established follow-up timeframes and treatment durations, using time horizons of 1, 3 and 6 months would be the best approach to capture and reflect healthcare resource usage within MF-CTCL patients being managed in the Spanish setting.

Costs

Cost categories used for analysis were: pharmaceutical costs, administration-related costs, costs for each session of phototherapy or radiotherapy, costs attributable to their maintenance, and costs associated with follow-up visits and laboratory tests. This analysis has only taken into account costs derived from the healthcare resources differentially required by each treatment, excluding any costs attributable to all treatments assessed. For medicinal products dispensed by community pharmacies, retail prices were used, whereas for medicinal products used in the hospital setting, the reported ex-factory prices were used including the Royal Decree-Law 8/2010 deduction.[39] Vial optimization (ie, residual or non-vial wastage) was taken into account for medicinal products requiring parenteral administration. Unit costs were obtained from tariffs published by the autonomous communities, from the Spanish General Council for the Official College of Pharmacists database and medical literature published in the Spanish setting.[40–47] All costs are given in euros for the year 2018 (Table 1).

Patient characteristics

Clinical experts unanimously confirmed that the mean body surface area and mean weight of an adult patient with early-stage MF should be equivalent to the Spanish adult population, namely 1.81 m^2 and 72.88 kg.[48] In order to be able to estimate the corticosteroids consumption, a baseline body surface area involvement of 11% (range 2%-17%) was considered to be representative for an early-stage MF patient.[49,50] All inputs considered in the current study were available from the literature and validated through an expert panel. Therefore, this study did not require ethical review board or committee approval neither to obtain patient consent.

Use of resources

Skin-directed treatments

Topical carmustine

The human and equipment resources involved in the acquisition, management, compounding, monitoring and dispensing

Table 1 Unit costs

Concept	Unit cost (€, 2018)			Source
	Base case	Minimum scenario	Maximum scenario	
Pharmaceutical costs				
Acitretin OR (mg)	0.05	0.04	0.06	[40]
Alitretinoin OR (mg)	0.96	0.48	1.43	
Beclomethasone TP (g)	0.05	0.04	0.08	
Betamethasone TP (g)	0.07	0.05	0.09	
Bexarotene OR (mg)	0.14	0.11	0.16	
Carmustine IV (100 mg vial)	1,405.00	1,124.00	1,686.00	
Clobetasol TP (g)	0.08	0.07	0.10	
Diflorasone TP (g)	0.08	0.06	0.09	
Statins OR (tablet)[a]	0.11	0.11	0.12	
Fenofibrate OR (tablet)	0.18	0.18	0.22	
Fluocinolone TP (g)	0.12	0.04	0.24	
Fluticasone TP (g)	0.15	0.12	0.18	
IFNα (MIU)	3.96	3.82	4.11	
Isotretinoin OR (mg)	0.04	0.04	0.04	
Levothyroxine OR (tablet)	0.04	0.02	0.07	
Methylprednisolone TP (g)	0.16	0.14	0.19	
Mometasone TP (g)	0.08	0.08	0.08	
Triamcinolone TP (g)	0.30	0.19	0.39	
Imaging and laboratory tests				
Complete biochemistry	91.41	29.32	182.88	[41]
ANA level	27.39	15.00	38.01	
Calcium/vitamin D level	31.07	12.26	42.88	
Cortisol level	9.58	6.16	14.00	
Creatinine level	2.84	0.48	7.30	
Liver function test[b]	22.92	5.01	63.88	
Thyroid function test[c]	24.95	15.23	43.32	
Hemogram analysis	4.44	3.25	5.36	
Blood triglycerides and cholesterol levels	6.91	1.19	15.10	
Lymphoid phenotype	58.69	24.00	107.06	
Phototest/photopatch	85.81	78.00	94.25	
Chest X-ray	25.97	9.15	84.00	
CT scan of abdomen and pelvis	254.19	62.00	484.88	
Pregnancy test	8.38	5.00	11.30	
Visit and clinical assessments				
Specialist consultation, initial	121.18	26.00	245.99	[41]
Consultations with specialist, successive	86.46	25.52	150.95	
Ophthalmology review	51.55	47.00	56.09	
Following psychiatric review	47.91	26.00	82.00	
Treatment consultations				
PUVA session	87.37	44.00	151.96	[41]
NB-UVB session	136.08	44.00	195.25	
TSEB session	312.09	311.26	312.93	
Other costs				
Parenteral administration (day hospital)[d]	30.51	19.09	41.93	[42]
Annual maintenance of phototherapy equipment	18.29	14.63	21.95	[43]
Hospital pharmacy service pharmacist, compounding pharmaceutical (h)	27.32	24.04	32.78	[44]
Hospital pharmacy service assistant, compounding pharmaceutical (h)	16.60	14.61	19.92	[44]
Ethanol 96 (mL)	0.03	0.02	0.03	[40]
Sterilized/White petroleum jelly (g)	0.10	0.04	0.29	[40]
Vacuflasc® 500 mL sterile flask (unit)	5.51	4.41	6.61	[45]
Needles (unit)	0.12	0.04	0.22	[46]
Absorbent sterile cotton gauze (unit)	0.06	0.05	0.06	[40]
Gloves (unit)	0.04	0.00	0.07	[47]

Notes: [a]Considering equivalent usage distribution between atorvastatin 10 mg/day and simvastatin 20 mg/day. [b]Includes the following assessment: aspartate aminotransferase, alanine amino transferase, gamma glutamyl transferase, alkaline phosphatase, bilirubin, albumin and prothrombin time. [c]Includes the following assessments: thyroxine and thyrotropin [d]Considering the partial attribution method.

Abbreviations: ANA, antinuclear antibodies; IFNα, interferon alfa; IV, intravenous; MIU, million international units; OR, oral; PUVA, psoralens with ultraviolet A light; TSEB, total skin electron beam; CT, computerized axial tomography scan; TG, triglycerides; TP, topical; NB-UVB, narrowband ultraviolet B light.

processes of various topical carmustine-compounded preparations were taken into account. Their usage distribution, their mean daily dose and time until achieving complete response (CR) were also included. Laboratory tests and follow-up visits were also considered (Table S1).[44,51–55]

Phototherapies (PUVA and NB-UVB)

The weekly frequency and number of phototherapy sessions, together with the mean duration until achieving CR were considered for PUVA and NB-UVB. Laboratory tests and follow-up visits were taken into account. For PUVA-based phototherapy, it was agreed that for the base case, no patient would receive maintenance treatment with PUVA after achieving CR (Table S2).[56–61]

Total skin electron beam therapy

The usage distribution, treatment duration and number of sessions until achieving CR of various TSEBT schedules were taken into consideration. Laboratory tests and follow-up visits were also taken into account (Table S3).[62–67]

Topical corticosteroids

The distribution of topical corticosteroids authorized and commercialized in Spain, the amount of product required for topical application and the laboratory tests and follow-up visits were taken into account.[40,68–70] It was estimated that the amount of cream or gel that fits on the tip of a finger (0.5 g) would be enough to treat the surface of both of the patient's hands, equivalent to 2% of body surface area (Table S4).[71]

Systemic treatments alone or in combination with SDT

Systemic retinoids

The usage distribution and dose of systemic retinoids authorized and commercialized in Spain were considered. Additionally, the median duration of treatments, the use of concomitant treatments, together with the laboratory tests and follow-up visits were taken into account (Table S5).[70,72–75]

Systemic retinoids in combination with PUVA phototherapy

The weekly frequency, number of sessions and mean duration until achieving CR of PUVA phototherapy (in combination with systemic retinoids) were considered. In addition, the usage distribution and dose of systemic retinoids authorized and commercialized in Spain, while been used in combination with PUVA phototherapy to treat MF-CTCL, were taken into account. Concomitant treatments, laboratory tests and follow-up visits were also considered (Table S6).[76]

IFNα in combination with PUVA phototherapy

The mean duration until achieving CR, together with the IFNα dose from authorized and commercialized presentations in Spain were taken into account. The clinical evidence identified from medical literature would not allow us to determine the number of PUVA sessions (in combination with IFNα) needed to achieve the CR.[77–79] Thus, it was conservatively assumed that the weekly frequency of PUVA sessions in combination with IFNα would be equivalent to PUVA in monotherapy. PUVA exposure was not considered until patients had reached the end of the third week of IFNα treatment. Laboratory tests and follow-up visits were also taken into consideration (Table S7).[77]

Sensitivity analysis

In order to highlight the difficulties to achieve consensus regarding whether or not to include a maintenance regimen in PUVA-based phototherapy treatment, a sensitivity analysis scenario taking into account that a reduced percentage (10%) of MF patients in the Spanish setting would continue to receive PUVA maintenance therapy after achieving CR has been carried out.

Likewise, it was suggested that a multivariate extreme sensitivity analysis should be carried out in order to estimate treatment costs from scenarios that took into account the extreme parameters (unit cost and use of resources): the most optimistic case possible (minimum scenario) compared with the most pessimistic case possible (maximum scenario). For the healthcare use of resources, the range of variation obtained by the expert panel was taken into account. For costs, the extreme values (minimum and maximum) of the source used, or where this was not available, a variation of ±20% of the base case cost, were considered.

Results

The base case results obtained for time horizons at 1, 3 and 6 months, respectively, are presented below. For each time horizon, the results obtained for minimum and maximum scenarios based on the multivariate extreme sensitivity analysis are shown in brackets.

Skin-directed treatments

Topical carmustine

The treatment cost for carmustine-based topical chemotherapy was €6,593.36 (€2,411.12-€10,814.51), €19,780.09 (€2,411.12-€32,443.54) and €27,592.78 (€2,411.12-€64,887.08) for time horizons of 1, 3 and 6 months, respectively. Pharmaceutical costs were the main component of treatment cost (≥99.79% of the total cost, in all cases) (Table 2).

Phototherapies (PUVA and NB-UVB)

As a base case, the treatment cost for PUVA treatment was €1,098.68 (€538.10-€2,328.99), €2,999.99 (€1,453.29-€6,294.46) and €3,187.60 (€1,453.29-€8,559.67) for time horizons of 1, 3 and 6 months, respectively. The cost of phototherapy sessions represented the main component of treatment cost (between 85.05% and 95.87% of the total cost, depending on the case) (Table 2).

As an alternative scenario, if 10% of MF patients continued receiving PUVA maintenance treatment after reaching CR, PUVA treatment cost would be €1,098.68, €2,999.99 and €3,294.00 for time horizons 1, 3 and 6 months, respectively. Time horizons at 1 and 3 months (4.35 and 13.04 weeks, respectively) were not enough to exceed the mean duration until achieving CR (13.89 weeks).

Therefore, alternative scenario results showed a slight difference to the base case (3.34% increase) only for the 6-month time horizon.

As shown in Table 2, the treatment cost for NB-UVB treatment was €1,657.47 (€651.13-€2,217.01), €4,842.10 (€1,296.46-€6,594.27) and €4,842.10 (€1,296.46-€8,782.89) for time horizons of 1, 3 and 6 months, respectively. Phototherapy sessions costs were the main component of treatment cost (≥97.05% of the total cost, in all cases).

Total skin electron beam therapy

The cost of TSEBT was €6,796.45 (€4,415.84-€9,454.26) considering 1-month time horizon, and €7,913.34 (€5,237.05-€10,923.46) when considering 3 and 6 months time horizons. TSEBT sessions costs represented the main component of the treatment cost (between 86.43% and 97.84% of the total cost, depending on the case) (Table 2).

Topical corticosteroids

Cost of topical corticosteroids was €17.16 (€4.83-€78.09), €51.49 (€14.50-€234.26) and €102.97 (€28.99-€468.53) for time horizons of 1, 3 and 6 months, respectively. Pharmaceutical costs represented the main cost component (between 92.94% and 98.24% of the total cost, depending on the case) (Table 2).

Systemic treatments alone or in combination with SDT

Systemic retinoids

The cost of treatment with systemic retinoids was €2,026.03 (€479.40-€4,172.65), €5,206.63 (€479.40-€10,120.12) and €7,426.42 (€479.40-€19,041.32) for time horizons of 1, 3 and 6 months, respectively. Pharmaceutical costs were the main component of the treatment cost (between 63.75% and 88.50% of the total cost, depending on the case) (Table 3).

Systemic retinoids in combination with PUVA phototherapy

The cost of combined treatment based on PUVA phototherapy together with systemic retinoids was €3,066.50 (€1,698.48-€5,260.62), €8,271.26 (€4,860.29-€13,316.38) and €10,046.58 (€5,938.77-€16,064.16) for time horizons of 1, 3 and 6 months, respectively. Pharmaceutical costs attributed to systemic retinoids together with phototherapy sessions costs represented the main component of the treatment cost (between 70.57% and 96.83% of the total cost, depending on the case) (Table 3).

IFNα in combination with PUVA phototherapy

The cost of combined treatment based on PUVA phototherapy together with IFNα was €1,541.09 (€1,009.75-€2,756.10), €5,167.57 (€3,361.65-€9,742.06) and €6,404.55 (€4,163.87-€12,124.95) for time horizons of 1, 3 and 6 months, respectively. Pharmaceutical and administration costs attributed to IFNα together with phototherapy sessions costs were the main component of the treatment cost (between 84.20% and 97.78% of the total cost, depending on the case) (Table 3).

Discussion

As shown in Figure 2, topical corticosteroids followed by PUVA and NB-UVB phototherapies were, regardless of the established time horizon, the treatments with the lowest associated direct healthcare costs. In contrast, when considering 1-month time horizon, the treatment with the highest direct healthcare cost was TSEBT, a rescue treatment used in early-stage MF patients in the Spanish setting. When considering time horizons for 3 and 6 months, the treatment with the highest direct healthcare costs was carmustine-based topical chemotherapy. In summary, topical corticosteroids and phototherapies remain among the treatments with the least direct healthcare costs associated with the management of early-stage MF patients. In contrast, systemic retinoids, PUVA in combination with systemic retinoids or IFNα, TSEBT and particularly, topical carmustine-based chemotherapy are among the treatments with the highest direct healthcare costs.

For topical application treatments, when pharmaceutical costs were divided by their respective time horizon, the results remained equal. Consequently, pharmaceutical costs of topical treatments present a time-proportional cost. For the remaining treatments, costs were allocated based on the number of phototherapy or radiotherapy sessions, or the time until achieving CR, which justifies that certain costs remain equivalent over various time horizons. For example, in the case of phototherapies, costs were allocated based on the mean duration until achieving CR (13.89 weeks [12.64 weeks-18.00 weeks] and 12.81 weeks [8.77 weeks-17.38 weeks] for PUVA and NB-UVB, respectively). For this reason, for the minimum scenario, both phototherapies presented the same cost at 3 and 6 months. However, this equivalence was only maintained for NB-UVB phototherapy in the base case results. The time horizons adopted in the present analysis were established according to the most common follow-up timeframes, treatment durations and time until complete

Table 2 Estimated costs for skin-directed treatments

	Base case		Minimum scenario		Maximum scenario	
	€, 2018	%	€, 2018	%	€, 2018	%
Topical carmustine						
Time horizon: 1 month						
Pharmaceutical costs	6,582.28	99.83%	2,408.77	99.90%	10,791.71	99.79%
Lab tests and follow-up visits costs	11.09	0.17%	2.34	0.10%	22.80	0.21%
Total cost	6,593.36	100.00%	2,411.12	100.00%	10,814.51	100.00%
Time horizon: 3 months						
Pharmaceutical costs	19,746.83	99.83%	2,408.77	99.90%	32,375.13	99.79%
Lab tests and follow-up visits costs	33.27	0.17%	2.34	0.10%	68.41	0.21%
Total cost	19,780.09	100.00%	2,411.12	100.00%	32,443.54	100.00%
Time horizon: 6 months						
Pharmaceutical costs	27,546.37	99.83%	2,408.77	99.90%	64,750.27	99.79%
Lab tests and follow-up visits costs	46.41	0.17%	2.34	0.10%	136.81	0.21%
Total cost	27,592.78	100.00%	2,411.12	100.00%	64,887.08	100.00%
PUVA phototherapy						
Time horizon: 1 month						
Phototherapy sessions costs	949.13	86.39%	477.98	88.83%	1,980.91	85.05%
Lab tests and follow-up visits costs	148.03	13.47%	58.90	10.95%	346.25	14.87%
Associated maintenance costs	1.52	0.14%	1.22	0.23%	1.83	0.08%
Total cost	1,098.68	100.00%	538.10	100.00%	2,328.99	100.00%
Time horizon: 3 months						
Phototherapy sessions costs	2,847.39	94.91%	1,390.84	95.70%	5,942.72	94.41%
Lab tests and follow-up visits costs	148.03	4.93%	58.90	4.05%	346.25	5.50%
Associated maintenance costs	4.57	0.15%	3.55	0.24%	5.49	0.09%
Total cost	2,999.99	100.00%	1,453.29	100.00%	6,294.46	100.00%
Time horizon: 6 months						
Phototherapy sessions costs	3,034.70	95.20%	1,390.84	95.70%	8,205.84	95.87%
Lab tests and follow-up visits costs	148.03	4.64%	58.90	4.05%	346.25	4.05%
Associated maintenance costs	4.87	0.15%	3.55	0.24%	7.58	0.09%
Total cost	3,187.60	100.00%	1,453.29	100.00%	8,559.67	100.00%
NB-UVB phototherapy						
Time horizon: 1 month						
Phototherapy sessions costs	1,632.51	98.49%	631.91	97.05%	2,186.80	98.64%
Lab tests and follow-up visits costs	23.43	1.41%	18.00	2.76%	28.38	1.28%
Associated maintenance costs	1.52	0.09%	1.22	0.19%	1.83	0.08%
Total cost	1,657.47	100.00%	651.13	100.00%	2,217.01	100.00%
Time horizon: 3 months						
Phototherapy sessions costs	4,814.17	99.42%	1,276.00	98.42%	6,560.40	99.49%
Lab tests and follow-up visits costs	23.43	0.48%	18.00	1.39%	28.38	0.43%
Associated maintenance costs	4.49	0.09%	2.46	0.19%	5.49	0.08%
Total cost	4,842.10	100.00%	1,296.46	100.00%	6,594.27	100.00%
Time horizon: 6 months						
Phototherapy sessions costs	4,814.17	99.42%	1,276.00	98.42%	8,747.20	99.59%
Lab tests and follow-up visits costs	23.43	0.48%	18.00	1.39%	28.38	0.32%
Associated maintenance costs	4.49	0.09%	2.46	0.19%	7.32	0.08%
Total cost	4,842.10	100.00%	1,296.46	100.00%	8,782.89	100.00%

(*Continued*)

Table 2 (Continued).

	Base case		Minimum scenario		Maximum scenario	
	€, 2018	%	€, 2018	%	€, 2018	%
TSEBT						
Time horizon: 1 month						
Radiotherapy sessions costs	6,279.56	92.39%	4,303.19	97.45%	8,171.01	86.43%
Lab tests and follow-up visits costs	516.89	7.61%	112.66	2.55%	1,283.25	13.57%
Total cost	6,796.45	100.00%	4,415.84	100.00%	9,454.26	100.00%
Time horizon: 3 months						
Radiotherapy sessions costs	7,395.28	93.45%	5,124.05	97.84%	9,638.17	88.23%
Lab tests and follow-up visits costs	518.06	6.55%	113.00	2.16%	1,285.28	11.77%
Total cost	7,913.34	100.00%	5,237.05	100.00%	10,923.46	100.00%
Time horizon: 6 months						
Radiotherapy sessions costs	7,395.28	93.45%	5,124.05	97.84%	9,638.17	88.23%
Lab tests and follow-up visits costs	518.06	6.55%	113.00	2.16%	1,285.28	11.77%
Total cost	7,913.34	100.00%	5,237.05	100.00%	10,923.46	100.00%
Topical corticosteroids						
Time horizon: 1 month						
Pharmaceutical costs	16.33	95.16%	4.49	92.94%	76.71	98.24%
Lab tests and follow-up visits costs	0.83	4.84%	0.34	7.06%	1.37	1.76%
Total cost	17.16	100.00%	4.83	100.00%	78.09	100.00%
Time horizon: 3 months						
Pharmaceutical costs	49.00	95.16%	13.47	92.94%	230.14	98.24%
Lab tests and follow-up visits costs	2.49	4.84%	1.02	7.06%	4.12	1.76%
Total cost	51.49	100.00%	14.50	100.00%	234.26	100.00%
Time horizon: 6 months						
Pharmaceutical costs	97.99	95.16%	26.95	92.94%	460.29	98.24%
Lab tests and follow-up visits costs	4.98	4.84%	2.05	7.06%	8.24	1.76%
Total cost	102.97	100.00%	28.99	100.00%	468.53	100.00%

Abbreviations: PUVA, psoralens with ultraviolet A light; NB-UVB, narrowband ultraviolet B light; TSEBT, total skin electron beam therapy.

response of the treatments assessed. Adopting one-year time horizon would not be appropriate for this analysis, as during one-year timeframe different MF-CTCL treatments could be used in combination or alternately. To establish one-year therapeutic pattern common for all MF-CTCL patients in Spain would be practically unfeasible due to the highly individualized therapeutic approach of this rare disease in the Spanish clinical setting. Therefore, considering horizons of 1, 3 and 6 months would be the best approach to capture and reflect healthcare resource usage within MF-CTCL patients being managed in the Spanish setting. The authors encourage the development of future studies to provide data regarding the time to progression or initiation of subsequent MF-CTCL treatments, especially among early-stage patients. This could enhance the development of further economic studies.

The results of this analysis are always shown together with their respective extreme scenarios. These scenarios, although unlikely to occur, are intended to estimate borderline situations that may arise when considering the extreme ranges for all parameters and assumptions taken into account. The application of extreme sensitivity scenarios allows us to assess the uncertainty associated with these parameters and assumptions. The results from these sensitivity scenarios must be considered with caution, particularly avoiding cross-comparisons. Despite this, in general terms, the results observed in the extreme scenarios are consistent with the conclusions from the base case, namely that topical corticosteroids and both phototherapies remain among the lowest direct healthcare cost associated with early-stage MF treatment. In contrast, TSEBT and topical carmustine-based chemotherapy remain among the

Table 3 Estimated costs for systemic treatments alone or in combination with skin-directed treatments

	Base case		Minimum scenario		Maximum scenario	
	€, 2018	%	€, 2018	%	€, 2018	%
Systemic retinoids						
Time horizon: 1 month						
Pharmaceutical costs	1,495.16	73.80%	367.28	76.61%	2,660.22	63.75%
Lab tests and follow-up visits costs	530.87	26.20%	112.13	23.39%	1,512.43	36.25%
Total cost	2,026.03	100.00%	479.40	100.00%	4,172.65	100.00%
Time horizon: 3 months						
Pharmaceutical costs	4,485.47	86.15%	367.28	76.61%	7,980.66	78.86%
Lab tests and follow-up visits costs	721.16	13.85%	112.13	23.39%	2,139.45	21.14%
Total cost	5,206.63	100.00%	479.40	100.00%	10,120.12	100.00%
Time horizon: 6 months						
Pharmaceutical costs	6,572.46	88.50%	367.28	76.61%	15,961.33	83.82%
Lab tests and follow-up visits costs	853.96	11.50%	112.13	23.39%	3,079.99	16.18%
Total cost	7,426.42	100.00%	479.40	100.00%	19,041.32	100.00%
Systemic retinoids in combination with PUVA phototherapy						
Time horizon: 1 month						
Pharmaceutical costs (retinoids, OR)	1,983.69	64.69%	1,442.15	84.91%	2,474.47	47.04%
Phototherapy sessions costs	522.02	17.02%	119.49	7.04%	1,238.07	23.53%
Lab tests and follow-up visits costs	559.27	18.24%	135.62	7.98%	1,546.25	29.39%
Associated maintenance costs	1.52	0.05%	1.22	0.07%	1.83	0.03%
Total cost	3,066.50	100.00%	1,698.48	100.00%	5,260.62	100.00%
Time horizon: 3 months						
Pharmaceutical costs (retinoids, OR)	5,951.06	71.95%	4,326.45	89.02%	7,423.41	55.75%
Phototherapy sessions costs	1,566.07	18.93%	358.48	7.38%	3,714.20	27.89%
Lab tests and follow-up visits costs	749.56	9.06%	171.70	3.53%	2,173.28	16.32%
Associated maintenance costs	4.57	0.06%	3.66	0.08%	5.49	0.04%
Total cost	8,271.26	100.00%	4,860.29	100.00%	13,316.38	100.00%
Time horizon: 6 months						
Pharmaceutical costs (retinoids, OR)	7,304.31	72.70%	5,310.27	89.42%	9,111.47	56.72%
Phototherapy sessions costs	1,922.18	19.13%	440.00	7.41%	4,558.80	28.38%
Lab tests and follow-up visits costs	814.47	8.11%	184.01	3.10%	2,387.15	14.86%
Associated maintenance costs	5.61	0.06%	4.49	0.08%	6.73	0.04%
Total cost	10,046.58	100.00%	5,938.77	100.00%	16,064.16	100.00%
IFNα in combination with PUVA phototherapy						
Time horizon: 1 month						
Pharmaceutical costs (IFNα)	429.21	27.85%	413.55	40.96%	704.92	25.58%
Administration costs (IFNα)	397.72	25.81%	248.85	24.65%	546.59	19.83%
Phototherapy sessions costs	512.27	33.24%	257.98	25.55%	1,069.15	38.79%
Lab tests and follow-up visits costs	200.37	13.00%	88.15	8.73%	433.61	15.73%
Associated maintenance costs	1.52	0.10%	1.22	0.12%	1.83	0.07%
Total cost	1,541.09	100.00%	1,009.75	100.00%	2,756.10	100.00%
Time horizon: 3 months						
Pharmaceutical costs (IFNα)	1,358.94	26.30%	1,309.36	38.95%	2,632.24	27.02%
Administration costs (IFNα)	1,193.16	23.09%	746.56	22.21%	1,639.76	16.83%
Phototherapy sessions costs	2,410.53	46.65%	1,213.93	36.11%	5,030.96	51.64%
Lab tests and follow-up visits costs	200.37	3.88%	88.15	2.62%	433.61	4.45%

(*Continued*)

Table 3 (Continued).

	Base case		Minimum scenario		Maximum scenario	
	€, 2018	%	€, 2018	%	€, 2018	%
Associated maintenance costs	4.57	0.09%	3.66	0.11%	5.49	0.06%
Total cost	5,167.57	100.00%	3,361.65	100.00%	9,742.06	100.00%
Time horizon: 6 months						
Pharmaceutical costs (IFNα)	1,676.07	26.17%	1,614.91	38.78%	3,289.64	27.13%
Administration costs (IFNα)	1,464.48	22.87%	916.32	22.01%	2,012.64	16.60%
Phototherapy sessions costs	3,058.02	47.75%	1,540.00	36.98%	6,382.32	52.64%
Lab tests and follow-up visits costs	200.37	3.13%	88.15	2.12%	433.61	3.58%
Associated maintenance costs	5.61	0.09%	4.49	0.11%	6.73	0.06%
Total cost	6,404.55	100.00%	4,163.87	100.00%	12,124.95	100.00%

Abbreviations: IFNα, interferon alfa; OR, oral; PUVA, psoralens with ultraviolet A light.

treatments with the highest direct healthcare costs. The sensitivity scenarios pointed out a high sensitivity of the results obtained in the present study to those parameters related to application patterns, treatment duration and time to achieve complete response.

The results of this analysis have shown that the most commonly used treatments in Spanish clinical practice during the early stages of MF represent a considerable direct healthcare cost. To our knowledge, this study is the first financial analysis carried out with the aim of identifying the therapeutic alternatives most commonly used in Spain for managing the early stages of MF, to determine their healthcare resources use and quantify their associated costs. The lack of national studies with similar objectives has prevented us from creating comparative arguments. However, the conclusions observed in this study are in line with previous publications carried out in other healthcare environments,[35–37] which evidence that MF patients, even in the early stages, require considerable use of healthcare resources due to the high frequency of visits to outpatient care centers and pharmacy departments.

Given the low incidence of this rare disease, limited literature has been found regarding its management in the Spanish setting or regarding the use of healthcare resources. Despite the inherent nature and limitations of any consultative methodology using a reference expert panel, the participation and involvement of the Spanish clinical experts involved in this study have become an essential factor in achieving the proposed objectives. One of the limitations of the present study is the lack of a recommended daily dose defined by WHO Collaborative Centre for Drugs Statistics Methodology for topical treatments. This has forced us to apply certain assumptions during the estimation of topical corticosteroid

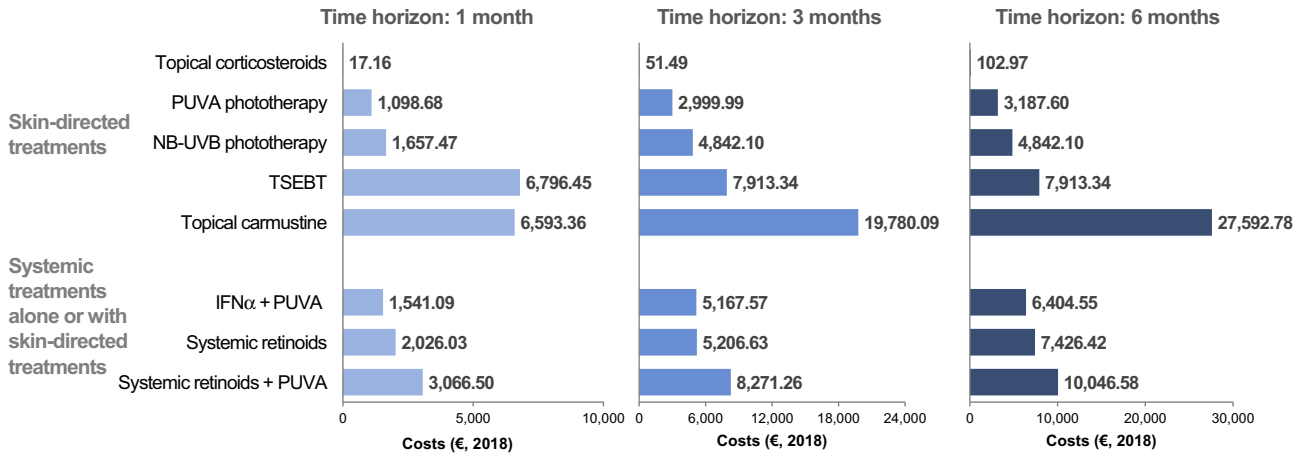

Figure 2 Cost of the main alternative treatments in managing the early stages of MF in Spain.
Abbreviations: IFNα, interferon alfa; PUVA, psoralens and ultraviolet A light; TSEBT, total skin electron beam therapy; NB-UVB, narrow-band ultraviolet B light.

usage per application. Likewise, to estimate the cost of topical carmustine-based chemotherapy, it was necessary to consider the acquisition, management, compounding, control and dispensing processes of various topical carmustine preparations in Spain. Given the lack of specific publications on these pharmaceutical compounding procedures, it was considered that the human resources involved in these activities would be equivalent to those indicated by Berlana et al,[44] a multicenter cost analysis carried out in the Spanish setting, which details the human and equipment resources involved in the preparation, management and compounding for medicinal formulations other than topical carmustine. Nevertheless, considering the price per vial of carmustine, the associated compounding activities represent a limited portion (<5%) of the estimated total costs of topical carmustine-based chemotherapy. Not to consider the costs associated to the adverse events management represent a study limitation, especially due to differential safety profile of the treatments evaluated. Therefore, the estimated direct health costs here presented could be underestimated, especially for the systemic treatments and for the TSEBT. Additionally, the results of this analysis would be underestimated due to not including the indirect costs associated to these treatments, especially for the phototherapies and the TSEBT. This is particularly relevant for MF-CTCL patients, taking into account their disease impact in terms of productivity loss.[38] The authors encourage the development of future studies to provide data regarding the societal impact associated to the available treatments for MF-CTCL, especially considering the slowly progressive and chronic features of the disease, together with the emotional and functional impact of the disease.[9,33,34] Further studies should explore the potential impact in terms of productivity loss and health-related quality of life burden associated to the available treatments for the management of MF-CTCL.

Treatment alternatives identified in this study are congruent with clinical data and treatment information on MF patients reported by AEDV's primary cutaneous lymphomas patient registry,[20] and also concur with the treatments recommended for early-stage MF management in the main clinical practice guidelines.[11,30–32] Additionally, the therapeutic options assessed in this study are consistent with the first results shown by the AEDV's primary cutaneous lymphomas. The SDTs assessed in this analysis represent 90.8% (topical corticosteroids), 86.1% (phototherapies), 8.3% (TSEBT) and 6.0% (topical chemotherapies) of the treatments used for MF patients recorded by the AEDV. With regard to the systemic treatments assessed in this analysis, the use of systemic retinoids and IFNα was described by 6.9% and 12.1%, respectively, of MF patients recorded by the AEDV.[20] This is aligned with the indications from the expert panel consulted during this study, in which the use of combined therapies including systemic treatments for patients with early-stage MF is usually suggested for those non-eligible patients or those with a poor response to SDTs.

Based on the clinical expert panel, topical corticosteroids constitute the basis of MF management, being offered through all stages, especially during the initial ones. However, when topical corticosteroids are used in combination with other treatments, they are not considered as treatments per se, and the combination is, in general, perceived as a "monotherapy treatment". Long-term use of topical steroid may lead to atrophy and development of striae. This risk increases with the potency of topical corticosteroid and may lead to systemic absorption.[80] Despite that, topical corticosteroids are often used as a symptomatic relief for the skin manifestations caused by the disease or the concomitant therapies. Therefore, topical corticosteroids were taken in the present analysis into account due to their wide use in clinical practice, particularly among early-stages MF patients. The lack of a standardized dose for their topical application forced us to include additional considerations (eg, amount of product required for each topical application, baseline body surface area involvement and its evolution through time). Therefore, the interpretation of topical corticosteroids results should be interpreted with caution.

The lack of clear, agreed or homogeneous treatment algorithms together with the range of treatment options available means that treating MF-CTCL becomes a highly individualized process. This, together with the few comparative studies available, leads the decision-maker to choose a specific treatment based on the stage of the disease, the clinical criteria, patient characteristics, the safety profile, patient preferences and resources available in each healthcare center. For this reason, having financial studies available is essential in order to include opportunity cost and cost-benefit elements among the arguments for assessing these treatments. Consequently, and taking advantage of the recently generated evidence from the AEDV registry of primary cutaneous lymphomas patients,[18,20] we would strongly encourage adding evidence related to healthcare resources use in prospective or retrospective studies already developed in our setting. This would not only allow us to corroborate the results of

the current study, but also to promote the development of further pharmacoeconomic evidence regarding CTCLs.

Conclusions

Despite the available information regarding the clinical features and comorbidities of MF-CTCL, there are limited data on the treatment patterns, clinical burden and financial implications of this rare disease. Results of this analysis show that topical corticosteroids, despite being considered as an adjuvant option especially for patients with generalized skin lesions, and phototherapies remain the treatments with the lowest direct healthcare costs for managing early-stage MF patients. In contrast, systemic retinoids in monotherapy, PUVA in combination with systemic retinoids or IFNα, TSEBT and particularly, topical carmustine-based chemotherapy are among the treatments with the highest direct healthcare costs. The results of this analysis show that the treatments mostly used in Spanish clinical practice during the early stages of MF represent considerable associated healthcare costs. This information may be of interest to all those healthcare professionals interested in quantifying the financial implications for healthcare systems resulting from MF treatments, to identify unmet medical needs, to encourage those treatments that offer the most benefits, expectations and quality-of-life for patients and to assess the degree of efficiency of healthcare systems. In this respect, in order to encourage an efficient healthcare resources distribution, regardless of the disease or clinical circumstances, it is essential to determine the cost of alternative treatments.

Abbreviations

AEDV, Spanish Academy for Dermatology and Venerology; EORTC, European Organization for Research and Treatment of Cancer; IFNα, interferon alfa; ISCL, International Society for Cutaneous Lymphomas; CR, complete response; CTCL, cutaneous T-cell lymphomas; MF, mycosis fungoides; PUVA, psoralens with ultraviolet A light; SDT, skin-directed treatments; TSEBT, total skin electron beam therapy; NB-UVB, narrowband ultraviolet B light.

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Author contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

PLOR, OS, MTE, RMIB, RFdM and FG are, respectively, employed by Hospital 12 de Octubre, Hospital Universitari de Bellvitge, Hospital Clínic, Hospital de Basurto, Hospital Universitario Nuestra Señora de Candelaria and Parc de Salut Mar-Hospital del Mar. NLM and APM are employees of Oblikue Consulting, an independent contract health economic organization which received consultancy fees from Actelion Pharmaceuticals España S.L. and Helsinn Healthcare SA to conduct this research. The funding body was not involved in the study design, collection and interpretation of data, or in the decision to publish. PLOR has reported consultancy, participation to advisory boards and research support from Actelion Pharmaceuticals, Kyowa Kirin International, Takeda, and 4SC. PLOR also reports personal fees from Actelion and Helsinn, during the conduct of the study; personal fees from 4SC, Takeda, Miragen, Innate Pharma, Kyowa, Ricordati Rare Diseases, non-financial support from Meda, and a patent with PLCG1, outside the submitted work. OS reports personal fees, non-financial support from Takeda, personal fees from Kiowa kirim and Actelion, outside the submitted work. FG, NLM and APM received fees related to this study from Actelion Pharmaceuticals España S.L. and Helsinn Healthcare SA, during the conduct of the study. The authors report no other conflicts of interest in this work.

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