

ORIGINAL RESEARCH

Mycosis fungoides-type cutaneous T-cell lymphoma (MF-CTCL) epidemiology and treatment pathway in Spain: new insights for an accurate description

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Abstract

Background: Mycosis fungoides-type cutaneous T-cell lymphoma (MF-CTCL) is a rare lymphoma localized in the skin. Due to its indolent nature and similarity to other skin conditions, diagnosis is often delayed or incorrect. Consequently, accurate calculations of incidence and prevalence are difficult to make. The treatment pathway taken by MF-CTCL patients can differ depending upon local healthcare systems, clinical policies and guidelines.

Aims: This study aims to (1) provide an estimate for the prevalence of treated MF-CTCL patients in Spain, (2) describe the Spanish patient treatment pathways for MF-CTCL, including quantification of the distribution of patients between primary, secondary and tertiary care institutions, and (3) investigate and quantify the treatment preferences of physicians.

Methodology: This study employed primary market research methodologies to facilitate the collection of patient numbers and treatment practices from healthcare professionals (HCPs) and patients.

Limitations: Poor diagnosis of MF-CTCL may mean that actual prevalence levels in the broader population are higher than those estimated by this analysis of treated patients. This study was reliant upon accurate reporting by HCPs of patient numbers and their personal treatment practices. The rarity of the condition means the patient sample size is relatively small and limits possible accuracy of the quantitative analyses of patient-derived data, although this is supplemented by HCP-derived data in the analysis.

Findings: Around 75% of MF-CTCL patients in Spain report that the initial diagnosis by their general practitioner is incorrect. This is usually due to underestimation of severity or type of skin disease. Once they have been correctly diagnosed (usually by a dermatologist) in secondary care, the management of MF-CTCL is led by dermatologists. In 39% of patients, shared care teams are also involved in patient management. Following diagnosis, the majority of patient management is conducted by secondary or tertiary care centers.

Conclusions: Incidence rates have increased in recent years, and possible reasons for this include improving levels of diagnosis. Survival in MF-CTCL has also increased over the last few decades. This trend appears to be reflected in the prevalence reported in this study, which is higher than suggested by some other estimates. However, it is still likely that there are further undiagnosed MF-CTCL patients in Spain due to the challenges of diagnosis at the primary care level.

Keywords: epidemiology, mycosis fungoides, prevalence, T-cell lymphoma.

Citation

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Introduction

Mycosis fungoides-type cutaneous T-cell lymphoma (MF-CTCL) is a type of non-Hodgkin lymphoma characterized by the initial localization of malignant T cells in the skin. It is a rare condition, as indicated by the recent granting of orphan status for a new treatment of this condition by the European Medicines Agency (EMA) Committee for Orphan Medicinal Products (COMP), as

prevalence is below the ceiling for orphan designation of 5 people in 10,000.¹

MF-CTCL is a disease of slow progression that is difficult to classify and often, in its early stages, presents a diagnostic challenge, as many of the signs and symptoms are non-specific or easy to confuse with other conditions. Consequently, many patients are misdiagnosed with other dermatological

conditions such as eczema and psoriasis.² The difficulty in accurately diagnosing patients with MF-CTCL means there is often a considerable delay between first symptoms and a definitive diagnosis; delays of between 0.2–40 years (median 3 years) have been reported.³ This issue is further confounded by the lack of a single diagnostic test; diagnosis currently relies on a range of clinical, histopathological and blood tests.

The incidence of cutaneous T-cell lymphoma (CTCL) has recently been reported to be up to 0.7 per 100,000 per year.⁴ However, higher incidence rates of 2.0 per 100,000 have been reported in Spain, which is similar to rates reported in Arab populations and may be due to a large Arab ancestry in Spain. However, given the low numbers of patients, uncertainties in diagnosis and the indolent nature of the condition, the majority of patients have low-grade malignancies with long survival. There is some uncertainty about the overall prevalence of MF-CTCL, but it is likely to be much higher than currently apparent.⁵

Recent data can be used to estimate prevalence. For example, in 2012, EMA COMP reported a prevalence estimate for all cutaneous lymphomas of up to 2.6 in 10,000 people in the European Union.¹ It is estimated that MF-CTCL represents 55% of all cutaneous lymphomas,⁶ which applied to 2011 census figures would suggest a prevalence of MF-CTCL of up to 6700 in Spain.⁷

As indicated earlier, establishing the true prevalence in a population of a rare disease can be particularly challenging due to lack of epidemiological studies, diagnostic uncertainty and differences between geographies in incidence rates and management practices.⁸ There are also methodological challenges specific to measuring small populations.⁹ In the absence of recent, large-scale prevalence studies, this study was designed to provide an estimate for the prevalence of treated MF-CTCL patients in Spain using primary market research to measure the case loads of healthcare professionals (HCPs) treating MF-CTCL.

Further to the diagnosis challenges, variation in prognosis dependent upon stage and a relatively large variety of treatment options mean that the treatment of MF-CTCL provides many clinical challenges. Recent guidelines have encouraged the care of these patients to be managed through specialized centers and to ensure that patient management is reviewed by an appropriate multi-disciplinary team (MDT).⁴ This practice is now common for some other rare conditions, and the healthcare systems of a number of countries have been implementing policies of centralizing the care of patients who require specialized services. In some cases, referral to expert MDTs is mandated.¹⁰

Given the importance of treatment centers, this study aimed to describe the patient treatment pathway for MF-CTCL in Spain; to quantify the distribution of patients between primary, secondary, and tertiary care institutions; and to understand the extent to which management of MF-CTCL patients is concentrated in specialized centers as well as the degree to which shared care is implemented in the management of these

patients. The impact of local management practices upon the choice of treatment prescribed was also considered.

There are many therapeutic alternatives available for the treatment of MF-CTCL, which range from skin-directed therapies (SDTs) including topical therapy, phototherapy, and radiotherapy through to systemic therapy with biologics and chemotherapy. Stem cell transplantation is also an option.

Topical therapies include corticosteroids, mechlorethamine, and carmustine among others. Although these topical treatments are often used in early-stage MF-CTCL, generally there are few clinical studies available that examine their duration of response and relapse rates. Mechlorethamine is in fact the only topical agent for which randomized controlled trials have been performed.⁴

Systemic and combination treatments are used more often as the condition progresses. However, chemotherapy regimens have modest efficacy, and their use is restricted until other options are exhausted.¹¹ There is little evidence that early aggressive combination treatment involving parenteral chemotherapy and radiation therapy improves overall prognosis and, conversely, this may expose patients to considerable toxicity compared to more conservative sequential topical treatment.¹² Guidelines for the treatment of MF-CTCL are based around patient staging, which classifies patients in terms of disease severity and progression. Formal recommendations, such as the European Organisation for Research and Treatment of Cancer (EORTC) consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome, advise that patients with early-stage disease should be treated with SDTs, systemic treatment being reserved for advanced cases or refractory cutaneous disease.⁶ In the very earliest stages of MF-CTCL (Stage IA), patients have a low probability of disease progression; consequently, EORTC recommendations support the application of a 'watch and wait' protocol with these patients.⁶

This study investigated the treatment preferences of physicians in Spain in order to quantify the levels of SDT, systemic and combination treatment regimens currently being prescribed. The study focused on three earlier stages of MF-CTCL: Stage IA, affecting <10% of the body surface area (BSA); Stage IB/IIA, affecting 10–25% of the BSA; and Stage IIB/IIIA, affecting >25% of the BSA.

Methodology

This study employed a mixed market research methodology in order to facilitate the collection of data from a range of sources. These included telephone interviews with clinical experts and online questionnaires completed by HCPs and patients. In addition, patient record forms (PRFs) were completed by HCPs to provide a longitudinal view of patient treatment. For numbers of each respondent types, see Table 1.

All methodologies employed market research techniques and were conducted in accordance with the European Pharmaceutical Market Research Association (EphMRA), British

Table 1. Respondent type and numbers.

Respondent type	Respondent number	Methodology
Clinical expert*	5	60-minute telephone in-depth-interview (IDI)
HCP – dermatologist	52	20-minute online questionnaire
HCP – oncologist	6	
HCP – hematologist	5	
HCP total	63	
PRF	39	Completed by HCP based on reference to patient records (anonymized)
MF-CTCL patient	20	20-minute online patient self-completion (PSC) questionnaire

*Clinical experts were identified based on publication history, roles at an expert centers, and involvement in national and international level expert groups.

HCP, healthcare professional; MF-CTCL, mycosis fungoides-type cutaneous T-cell lymphoma; PRF, patient record form.

Healthcare Business Intelligence Association (BHBI), and Market Research Society (MRS) codes of conduct and guidelines (EphMRA, BHBI, and MRS codes of practice) and adherence to relevant General Data Protection Regulation. Informed consent was obtained from all patients for being included in the study.

The approximately 60-minute in-depth interviews with clinical experts were conducted in line with a structured discussion guide to facilitate collection of key quantitative data (including numbers of patients treated and levels of referral) and in-depth qualitative insights into current and future treatments.

The online HCP questionnaire was designed to take approximately 20 minutes to complete (Supplementary material; available at: <https://www.drugsincontext.com/wp-content/uploads/2020/07/dic.2020-4-8-Suppl.pdf>). The questionnaire covered a range of key areas including patient population, referral policies and behavior, shared care practices, and current and future treatment preferences. Respondents were required to provide data on numbers of patients referred directly from general practitioners (GPs) or via other hospital centers and the number referred on to further hospital centers for assessment or treatment. This provided a quantitative view of the patient flows between primary, secondary, and tertiary care centers and attempted to account for the majority of duplications of patients that might have occurred with a simple count of patient numbers by center. In order to account for potential double counting of patients receiving treatment at more than one center, duplication factors were calculated from inflows and outflows of patients (by referral) from institutions and in shared care arrangements.

HCPs also provided detailed information on their current treatment preferences for MF-CTCL at three levels of severity (Stage IA <10% BSA affected, Stage IA/IIB 10–25% BSA affected, and Stage IA/IIB >25% BSA affected).

Thirty-nine PRFs were collected; HCPs were provided with a structured template into which respondents could input individual patient's data. This approach allowed for collection of key data on patient management while ensuring all protected health information was completely anonymized.

The PRFs provided data on patient demographics, specialty role in diagnosis, involvement of MDTs, current and previous treatment, and reasons for treatment switches.

The online patient self-completion questionnaire was also designed to take approximately 20 minutes to complete, providing insights for development of the patient flow description. Patients provided information on timing of symptom onset, time from symptoms to diagnosis, specialists involved in treatment, type and regularity of clinic attendance, and treatment history. The data from the patient questionnaires were collected in an anonymized form, and only aggregated results presented in order to maintain patient confidentiality.

The analysis triangulated results from these multiple sources to provide insights across a range of hospital institutions and physician specialties. The research was carried out between December 2018 and February 2019.

Results

Patient numbers and distribution between institute types

To determine the number of different types of institutions providing care for MF-CTCL patients, several data sources were used. The number of *general hospitals* was derived from desk research and the HCP interviews in this research. They include the hospitals of some HCPs in this research and those mentioned by respondents as centers involved in referral of MF-CTCL patients.

Table 2. Total estimated numbers of MF-CTCL patients by type of treatment.

	Number of institutions	Percentage of all institutions (%)	Total number of MF-CTCL patients	Percentage of all patients (%)
Centers of excellence	6	6	1128	19
University hospital/center with MF-CTCL expertise	55	50	2626	43
Hospital with dermatology department	48	44	2292	38
Total	109	100	6046	100

MF-CTCL, Mycosis fungoides-type cutaneous T-cell lymphoma.

The number of *specialist dermatology/MF-CTCL centers/university teaching hospitals* was also derived from a combination of desk research and this market research. They include hospitals identified in the research to which MF-CTCL patients were referred. They also include hospitals operating an MDT, which makes treatment decisions for MF-CTCL patients who are referred from other hospitals. These centers do not include the clinical expert institutions/specialist centers/centers of excellence.

Clinical expert institutions/specialist centers/centers of excellence were identified from this research or via desk research/internal databases.

In order to provide an estimate of the total number of MF-CTCL patients under care in Spain and explain how patients are distributed between different treatment center types, HCP and clinical expert respondents provided data on the numbers of patients treated in their own hospitals and the levels of inward and outward referrals. Numbers of patients cared for by clinical experts were derived from interviews in this research.

As expected, there are relatively few centers of excellence (6% of all MF-CTCL treatment centers), but they are responsible for treating a relatively larger proportion of the MF-CTCL patient population (19%). Around 62% of Spanish patients are treated in institutions that are either centres of excellence or university/teaching hospitals. Extrapolation of the numbers of patients treated in the various center types resulted in a total population of treated patients in Spain of 6046 (see Table 2).

Patient treatment pathway

Treatment flow descriptions were constructed using data and responses from three questionnaire types mentioned in the methodology. This provided a more comprehensive perspective of the patient journey from onset of symptoms through diagnosis and treatment.

Around 75% of patients reported incorrect GP diagnosis of their condition, and there was a reported delay of over a year between symptoms and diagnosis. Dermatologists lead

management of MF-CTCL, although shared care teams are involved in the management of 39% of patients; hematologists and oncologists are the specialists most often involved in addition to dermatologists. There was a high level of reported patient/HCP interaction in Spain; 95% of patients reported they attended a regular clinic for the management and review of their MF-CTCL (see Table 3) and early-stage patients reported that they had visited both their GP and dermatologist 3 or more times in the past 12 months (Table 4).

An individual patient's treatment pathway may be influenced by the availability of therapeutic services in the hospital they regularly attend. There is wide availability of the most frequently used treatments for MF-CTCL at patients' 'home' hospitals. However, some of the less frequently used treatments require patients to travel to other institutions. For example, extracorporeal photopheresis is available in only 32% of these 'home' hospitals in Spain and 24% of HCPs reported that they refer patients to other hospitals more distant from patients' homes or to expert centers (21%) in order to receive this form of treatment (see Table 5).

Current treatment preferences

HCPs reported that most early-stage patients were treated with SDM. The results suggest that treatment in Spain is likely to be non-aggressive in early stages of the condition (Stage IA <10% BSA). Around 85% of patients at Stage IA are likely to be assigned to either a 'watch and wait' protocol or SDM, whereas only 15% of patients at this stage receive systemic or combination treatment. Indeed, SDM continues to be frequently used in later-stage patients; 30% of Stage IA/IIB (>25% BSA) patients in Spain receive SDM treatment despite their advancing condition. Combination treatments are the most frequently used regimens for later-stage patients with 33% of these patients in Spain receiving this type of treatment (see Table 6).

HCPs reported that in early-stage patients (Stage IA <10% BSA), SDM treatment is dominated by the use of topical corticosteroids with over half of all patients at this stage

Table 3. Patient flow analysis (combining results from PSC/HCP questionnaires and PRFs).

Treatment stage		Data	Source
Time from symptoms to first HCP consultation		1–11 months (mean=2.7)	PSC n=20
1st HCP consulted = GP		80%	PSC n=20
Incorrect GP diagnosis		94%	PSC n=20
Time from 1st GP appointment to specialist appointment		mean=4.1 months	PSC n=16
Time from symptoms to diagnosis		12–13 months	PSC n=20
First specialist seen	Dermatologist Hematologist Oncologist DK	95% 0% 0% 5%	PSC n=20
Distance between patient location and treatment center	<10 km 11–50 km 100 km+	67% 31% 2%	PRF n=39
Shared care review	Yes No	39% 61%	PRF n=39
Other specialists in shared care	Dermatologist Histopathologist Hematologist Oncologist	29% 0% 13% 26%	PRF n=39
Specialty initiating treatment	Dermatologist Shared care Other specialist	90% 7% 3%	PRF n=39
Current treatment Stage IA <10% BSA	Watch and wait Active treatment	35% 65%	HCP n=63
Current treatment Stage IA/IIB 10–25% BSA	Watch and wait Active treatment	17% 83%	HCP n=63
Current treatment Stage IA/IIB >25% BSA	Watch and wait Active treatment	8% 92%	HCP n=63
Regular clinic attendance		95%	PSC n=20

BSA, body surface area; GP, general practitioner; HCP, healthcare professional; PRFs, patient record forms.

Table 4. Patient visits to HCPs.

		GP	Nurse in GP surgery	Dermatologist	Nurse in hospital dermatology department	Oncologist	Nurse in hospital oncology department	Hematologist	Nurse in hospital hematology department
(n=10) [‡]	Proportion of patients	100%	40%	100%	60%	50%	30%	40%	30%
	Visits per patient*	3.0	4.8	3.1	4.0	3.0	2.7	4.3	2.0

[‡]Patients reporting swollen lymph nodes omitted from this analysis.

*Mean visits of patients visiting specialty; Includes patients who made 12+ visits. Calculated at a value of 12.
GP, general practitioner; HCP, healthcare professional.

Table 5. Availability of treatments relative to patient location.

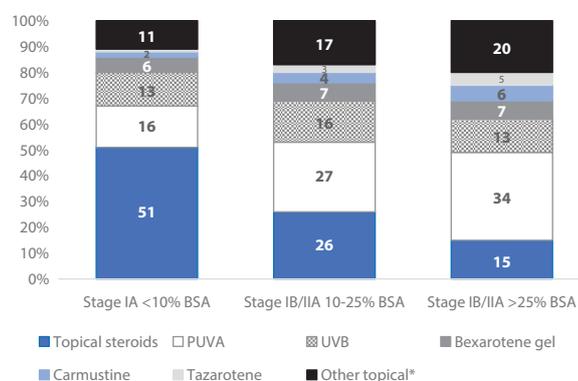
Percentage of HCPs indicating treatments available at home hospital or elsewhere (n=63)	Home hospital (%)	Another hospital – closer to patient's home (%)	Another hospital – farther away from patient's home (%)	Expert center (%)
Treatment type				
Chemotherapy	89	10	8	10
UVB	89	11	6	2
PUVA	87	16	5	2
Radiotherapy	65	21	19	11
ECP	32	24	24	21
TESBT	38	27	21	27

ECP, extracorporeal photopheresis; HCP, healthcare professional; TESBT, total skin electron beam therapy; UVB, type B ultraviolet.

Table 6. Type of treatment regimen by disease stage.

	Stage IA <10% BSA	Stage IB/IIA 10–25% BSA	Stage IB/IIA >25% BSA
Combination treatment	7%	19%	33%
Systemic monotherapy	8%	20%	29%
Watch and wait	35%	17%	8%
SDM	50%	44%	30%

BSA, body surface area; SDM, skin-directed monotherapy.

Figure 1. HCP use of SDM alternatives in Spain (n=63).

*'Other topical' includes: tacrolimus, imiquimod, isotretinoin, and fluorouracil cream.
BSA, body surface area; HCP, healthcare professional; PUVA, psoralen and ultraviolet A; SDM, skin-directed monotherapy; UVB, type B ultraviolet.

receiving this type of treatment (see Figure 1), whereas in later-stage patients, the most common treatment choice is phototherapy with 47% of Stage IB/IIA (>25% BSA) patients receiving UVA or UVB treatment. Topical corticosteroids are used in only 15% of these later-stage patients while other topical treatments, such as carmustine and tazarotene, are sometimes introduced.

HCPs reported that phototherapy is also being often used in early-stage patients in Spain, both as a monotherapy (29% patients) and in 93% of early-stage combination treatments. Despite this widespread use, HCPs reported a range of issues with phototherapy treatment (see Table 7).

Phototherapy was associated with some side effects and treatment limitations; the risk of photo-carcinogenicity and lack of treatment response were both reported by HCPs as problematic for 28% of patients. In addition, phototherapy treatment can present challenges due to difficulties of access. Unavailability of UVA equipment was cited by HCPs as an issue for 19% of patients.

Table 7. HCP reported issues with phototherapy.

	Percentage reporting issue (n=63)
Difficulty in finding psoralens	14%
Unavailability of the equipment for UVA	19%
Maximum cumulative dose of phototherapy	23%
Difficulty going to centers 3–4 times/week	25%
Non-responders or recurrent after PUVA	28%
Time and travel commitment	28%
Risks of photo-carcinogenicity	28%

HCP, healthcare professional; PUVA, psoralen and ultraviolet A; UVA, type A ultraviolet.

Discussion

Prevalence

This study estimated that the number of patients being treated for MF-CTCL in Spain is about 6000. There is considerable variation in the reported incidence and prevalence of MF-CTCL in the literature and, in particular, there are very few studies on prevalence. As a benchmark, in 2012, the French transparency committee referenced an incidence of 0.36 per 100,000 based on US data¹³ and quoted a resulting prevalence for all cutaneous lymphomas of 3200. In comparison, the EMA COMP reported that the number of MF-CTCL patients in Europe was less than 132,000 (<2.6 patients per 10,000); calculating an estimate at 2.6 patients per 10,000 would predict a prevalence of up to 6700 in Spain using population estimates from the 2011 European Population and Housing Censuses.

Differences in prevalence estimates are to be expected as there has been a 2- to 3-fold increase in the worldwide reported incidence of CTCL over the past 20 years.¹⁴ Consequently, more recent publications have reported higher incidence rates. The 2017 EORTC consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome reported an incidence of 0.5 per 100,000 and the National Cancer Registration and Analysis Services Short Report in the United Kingdom reported the incidence to be 0.75 per 100,000.¹⁵ Indeed, in Spain, incidence rates of 2.0 per 100,000 have been reported, explained by the strong Arab ancestry in the Spanish population.¹⁶

In addition to higher incidence rates, there have also been publications reporting an improved survival rate in MF-CTCL over the last few decades.¹⁷ These trends in incidence and survival, together with the indolent nature of the condition, present a challenging scenario for establishing the prevalence of MF-CTCL.

As there is very little published data with which to make prevalence comparisons and given the indolent nature and slow progression and difficult diagnosis of MF-CTCL, any prevalence calculation carries a strong possibility of underestimation. Important factors, which may result in

underestimation, include the potential that a proportion of patients remains undiagnosed, incorrectly diagnosed, or accessing care only infrequently. There are other potential confounding factors. In several studies, a large geographic heterogeneity in rates of CTCL has been observed, with significant clustering, some reporting a range of CTCL case densities of between 0 and >300 cases per 100,000, the clusters occurring in areas with high population density, which also coincide with areas of high dermatologist density.¹⁸ This is consistent with previous research including the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute that found a significant correlation between CTCL incidence and medical specialist density.¹⁹ One possible explanation for this clustering is higher diagnosis rates due to proximity of physicians with knowledge and expertise in diagnosing rarer skin conditions.

In order to quantify the widest possible distribution of patients, this study collected data from HCPs working in a broad spectrum of hospital institutions across Spain; from hospital-based dermatology units to centers of excellence. The results of this study indicate a prevalence rate of 1.29 per 10,000, possibly reflecting the recent upward trends in incidence and survival rates. Increasing prevalence levels of MF-CTCL could have implications for the provision of treatment for these patients (if scarcity of resources limits access and quality of care) as MF-CTCL patients can require complex treatment regimens and are often cared for by a large multidisciplinary group of HCPs that tend to exist in larger institutions. Availability of additional cost-effective treatments will help healthcare systems manage any further increases in the prevalence of MF-CTCL.

Treatment pathway

Our analysis of the patient treatment pathway confirmed that for many patients there is a long delay between symptom development and diagnosis, with patients in Spain reporting a mean delay of over one year. The risk for MF-CTCL to be misdiagnosed as other dermatological conditions was also observed in this study with up to 94% of patients reporting a wrong diagnosis by their GP. This may suggest that, although the

increase in reported incidence rates over the last few decades has potentially been as a result of improved diagnosis at the specialist level, there may be further room for improvement of diagnosis through additional education and awareness in primary care.

Although dermatologists lead management of MF-CTCL, this study suggests that multidisciplinary care of MF-CTCL is also becoming established in Spain with patient record reviews indicating that 39% of patients' care is reviewed by a shared-care team. Involvement of MDTs in patient management may be influenced by the type of treating institution; in Spain, 62% of patients are treated in centers of excellence or university/teaching hospitals – it is probable that these types of centers have easier access to the range of specialty clinicians involved in shared-care.

Whether access to MDT review has an influence on treatment choice is an interesting question that is supported by a parallel study in France, which reported a shared-care involvement as high as 67%.²⁰ The greater access to multidisciplinary expertise and treatment options in France may influence the preferred treatment regimens as it appears that treatment in France was more aggressive even in early stages of the disease. Around 24% of French early-stage patients (Stage IA <10% BSA) receive combination or systemic treatment and this increases to 52% for Stage IB/IIA 10–25% BSA patients. In Spain, the respective rates were 15% (Stage IA <10% BSA) and 39% (Stage IB/IIA 10–25% BSA). Conversely, the level of a 'watch and wait' protocol in early-stage patients (Stage IA <10% BSA) is greater in Spain (35%) than in France (21%).

The role of expert centers is established in the treatment of MF-CTCL in Spain, with 19% of patients being treated in these centers, although they represent only 6% of all institutions. By way of comparison, the focus toward expert referral in this condition is well illustrated in the United Kingdom. Recent guidelines by the British Association of Dermatologists have designated a list of supra-regional centers with MDTs responsible for assessing patients who require specialist treatment options, such as total skin electron beam therapy and extracorporeal photopheresis.

The advantages of patients receiving expert care from specialist centers in Spain need to be balanced against the benefits of their receiving treatment closer to home. In this study, patient records showed that 31% of patients needed to travel between 11 and 50 km to their treatment centers – and that a small percentage (2–3%) needed to travel over 100 km. This is an important consideration as other authors have documented the 'distance decay association', which identifies that those who live closer to healthcare facilities have higher rates of usage of services after adjustment for need than those who live further away.²¹ Thus, if care becomes more centralized in expert centers, it may result in patients residing distantly from such centers being disadvantaged in terms of access to care. The potentially positive impact on patient outcomes and quality of life of receiving treatment close to where they reside in MF-CTCL warrants further investigation.

This study shows that Spanish patients are very engaged with their HCPs, at least in terms of frequency of contact. Around 100% of patients in this study had met with their GP in the last 12 months in relation to their MF-CTCL, and 60% of patients reported having met with a hospital-based nurse in the last 12 months. As current guidance for early-stage treatment of MF-CTCL recommends a largely palliative approach including potential 'watch and wait' protocols requiring close monitoring, the high level of patient/HCP interaction seen in these Spanish patients would appear to be appropriate and helpful.

Treatment preferences

This study suggests that HCPs in Spain tend to use SDM in larger proportions of early-stage patients compared with other countries. However, there is a high level of agreement between the choice of SDM treatment in Spain with that used in other countries.^{20,22} Topical steroids and phototherapy are reported as the most popular SDM treatment choices in Spain, with 80% of early-stage (Stage IA <10% BSA) patients receiving these treatments.

There is no specific algorithm to guide selection of SDMs in early-stage MF-CTCL, and it is advised that treatments should be tailored according to individual patients needs and the side effects they experience.²³ In this study, we observed that a large selection of alternative SDMs were used in Spain. Corticosteroids were the most widely used topical treatment, but other topicals employed included carmustine, bexarotene gel, tazarotene, tacrolimus, imiquimod, isotretinoin, and fluorouracil cream. The large number of products prescribed could indicate a degree of unmet need and the lack of any formal prioritization between SDM options.

Phototherapy is also widely used both as SDM and in combination treatment. In this study, phototherapy was reportedly used in 29% of Stage IA <10% BSA patients. Phototherapy is considered an effective treatment for MF-CTCL providing a good response. However, there is a longer-term increased risk of skin cancers, and treatment can be complicated by the necessity of patients to travel to a specialized center.²³ Recent recommendations have advised that there is no evidence to support maintenance phototherapy,⁴ which highlights the importance of effective SDM alternatives.

Furthermore, in this study, both the risk of photo-carcinogenicity and the requirements for frequent patient travel to centers providing relevant services were reported as problematic issues for phototherapy treatment. Given the preference for non-invasive, palliative SDTs in early-stage patients and the issues that phototherapy can present, it is hoped that the availability of additional topical treatments will provide physicians and patients with further options for a less aggressive, palliative approach to early-stage treatment.

Conclusion

The trend toward improved diagnosis by dermatology centers and increasing survival rates for MF-CTCL patients may be reflected in the prevalence rates reported in this study. However, it is still likely that there are many undiagnosed MF-CTCL patients due to the challenges of diagnosis at the primary care level. Patients are frequently referred to expert centers, and MDTs are sometimes involved in treatment decisions – whether this leads to improved outcomes for patients at all stages of the condition is not addressed in this study but could warrant further investigation. The current recommendation for early-stage patients is based on the use of SDTs and aimed at maintaining quality of life. This type of regimen can be adequately supported by institutions close to patients' homes, particularly as regular monitoring of such patients is advised.

Providing access to effective SDT treatment options for early-stage patients will help support the recommended treatment strategies for these types of patients while freeing resources for centers of expertise to manage more complex patients.

The large range of treatments used may reflect a level of unmet need. Indeed, although phototherapy is widely used in monotherapy and in combination, HCPs report many issues both in relation to side effects and treatment access. The availability of newer treatments may help address some of these needs.

This study has provided useful insights into the treatment pathway of a complex and rare condition. The study has quantified the number of treated patients in Spain and identified issues that may impact treatment choices and patient access to resources. We believe this study design is a useful model to analyze other rare diseases, where diagnosis, treatment pathways, and management choices are complex.

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