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ORIGINAL RESEARCH

The European Lambert–Eaton Myasthenic Syndrome Registry: Long-Term Outcomes Following Symptomatic Treatment

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ABSTRACT

Introduction: Lambert–Eaton myasthenic syndrome (LEMS) is characterized by autoantibodies against voltage-gated calcium channels (VGCC) at the neuromuscular junction causing proximal muscle weakness, decreased tendon reflexes, and autonomic changes. The European LEMS registry aimed to collate observational safety data for 3,4-diaminopyridine phosphate (3,4-DAPP) and examine long-term outcomes for patients with LEMS.

Methods: Thirty centers across four countries participated in the non-interventional European LEMS registry. Any patients diagnosed with LEMS by means of clinical assessment and abnormal neurophysiological testing, or clinical assessment and positive for VGCC antibodies were eligible to participate. Patients were monitored using standard assessments for LEMS-related clinical manifestations.

Results: Among 96 evaluable participants, 50 (52.1%) were being treated with 3,4-DAPP, 21 (21.9%) with 3,4-diaminopyridine (3,4-DAP), and 25 (26.0%) with other treatments (e.g., pyridostigmine, corticosteroids, immunoglobulins, and azathioprine); 74 participants (77.1%) were exposed to 3,4-DAPP at any time. Quantitative myasthenia gravis scores were similar across treatment groups. Muscle strength was generally good and maintained during follow-up. Cerebellar ataxia, defined as a negative Romberg's test and at least one other positive ataxia test, was observed in 30 (56.6%) patients. Most participants had reduced reflex tone and limited functioning. Sustained or improved functioning was observed in participants administered 3,4-DAPP. Inconsistent and sporadic functional improvement and regression was observed with 3,4-DAP and other treatments. Fifty-five treatment-related adverse events (AEs) were reported by 32 (33.3%) participants. Eight (8.3%) participants reported nine treatment-related serious AEs. No new safety signals were identified.

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Conclusion: No new safety signals were observed following long-term management of LEMS with 3,4-DAPP.

Keywords: Amifampridine; Lambert–Eaton myasthenic syndrome; Paraneoplastic; Quality of life; Observational study; Real world; Safety

Key Summary Points

Why carry out this study?

The potassium channel blocker 3,4-diaminopyridine (3,4-DAP) improves neurotransmission in patients with Lambert–Eaton myasthenic syndrome (LEMS), a rare movement disorder, but compounded product often fails to meet Good Manufacturing Practice standards for consistency of active ingredient.

The European LEMS registry aimed to investigate the management of LEMS in a real-world setting with a particular focus on the efficacy and safety of the 3,4-DAP salt 3,4-diaminopyridine phosphate (3,4-DAPP), which is administered as a standardized tablet formulation.

What was learned from this study?

Long-term symptomatic management of LEMS with 3,4-DAPP did not result in any new safety signals.

Additional insight was gained into the natural history of LEMS, confirming a stable disease course with no notable changes in muscle strength, ataxia, reflexes, or autonomic nervous system symptoms over time, and malignancies associated with small cell histology potentially underlying paraneoplastic disease.

INTRODUCTION

Lambert–Eaton myasthenic syndrome (LEMS) is a rare autoimmune disorder that affects 3–4 in every one million people [1, 2]. LEMS can be autoimmune or paraneoplastic in origin, with patients with autoimmune LEMS tending to present in their mid-30s, whereas paraneoplastic LEMS tends to occur in patients in their 50s or 60s, most commonly in conjunction with a diagnosis of small cell lung cancer (SCLC) [3]. Among patients with SCLC, 0.5–3% will develop LEMS [4].

LEMS is generally characterized by autoantibodies against presynaptic voltage-gated calcium channels (VGCC; P/Q type) at the neuromuscular junction causing proximal muscle weakness, decreased tendon reflexes, and autonomic changes [2, 4–6]. Accordingly, patients with LEMS often present with a multitude of symptoms, including neuromuscular, cranial, and autonomic symptoms, as well as fatigue [4, 6, 7]. In particular, more than 90% of patients experience leg weakness and more than 80% report general fatigue.

First-line treatment of patients with LEMS aims to improve neurotransmission, while immunosuppressant therapy may be used to reduce anti-VGCC antibody production and activity in patients with an inadequate response to symptomatic therapy [3, 8, 9]. For example, the potassium channel blocker 3,4-diaminopyridine (3,4-DAP) improves neurotransmission by prolonging presynaptic depolarization, enhancing calcium transport into the nerve ending [3, 4], and is recommended as a first-line treatment for patients with LEMS [8]. Treatment with 3,4-DAP has been shown to improve isometric muscle strength, neurologic disability score, and quantitative myasthenia gravis (QMG) score in patients with LEMS [10–12]. Furthermore, 3,4-DAP offers improved symptomatic outcomes compared with the cholinesterase inhibitor pyridostigmine, which may be offered as adjunctive therapy [8, 13].

However, 3,4-DAP has generally been provided as a compounded product, which has not met Good Manufacturing Practice standards for consistency of active ingredient [14]. In

contrast, the 3,4-DAP salt 3,4-diaminopyridine phosphate (3,4-DAPP) offers a standardized tablet formulation for treating patients with LEMS that is more stable than 3,4-DAP base [12, 15]. 3,4-DAPP has also demonstrated efficacy and safety for the symptomatic treatment of LEMS in a randomized, placebo-controlled study [16, 17].

The European LEMS registry aimed to collate observational safety data on treatments offered to patients with LEMS, particularly 3,4-DAPP, which was approved in the year before the registry was initiated [18]. The registry also aimed to examine long-term outcomes for patients with LEMS [18].

This analysis disseminates the final results from a registry study investigating how LEMS is managed in a real-world setting with a particular focus on the efficacy and safety of 3,4-DAPP, expanding on a preliminary report of the baseline demographics and clinical characteristics of participants in the European LEMS registry [18].

METHODS

Thirty centers across four countries (Germany, Italy, Spain, and the UK) participated in the non-interventional European LEMS registry as part of the post-approval monitoring program for 3,4-DAPP. Any patient diagnosed with LEMS by means of clinical assessment and abnormal neurophysiological testing, or clinical assessment and positive result for VGCC antibodies, not participating in a clinical study of 3,4-DAPP, was eligible to participate. Recruitment began on 5 May 2010 and the last patient was enrolled on 2 August 2016. The study was completed in August 2019. Full study methodology and an interim analysis of the baseline characteristics for patients enrolled in the European LEMS registry was published previously (and is available open access) [18].

The protocol, patient information sheet, and consent form were approved by ethics committees, subject to all applicable local laws. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and in accordance with the Helsinki Declaration of 1964, as revised in 2013 (see Table S1 in the supplementary material).

Patients were classified according to their LEMS treatment(s) at baseline: 3,4-DAPP, 3,4-DAP, other LEMS treatments (e.g., pyridostigmine, corticosteroids, long-term immunosuppressive drugs, intravenous immunoglobulin, etc.) or no designated LEMS-specific treatment, although most subjects had been receiving LEMS-specific or LEMS-related treatment(s) for varying durations and at varying doses at the time of enrollment into the study. Baseline was defined as assessments performed ± 1 month relative to the time of enrollment of a patient into the registry.

Patients were monitored using standard assessments currently used to monitor LEMS-related clinical manifestations and to stage disease progression across the life-long course of the disease, including neurophysiological testing (including incremental and decremental responses to repetitive nerve stimulation), QMG total score, muscle strength, reflexes, ataxia assessments, autonomic nervous system (ANS) function, daily functioning, and EQ-5D health status. Patients were assessed at enrollment, then annually or biannually thereafter.

Descriptive statistics are presented. When statistical data are presented as pooled data, this refers to data combined from all available patients across the four treatment groups. Adverse events were recorded using Medical Dictionary for Regulatory Activities (MedDRA) version 12.1.

RESULTS

Baseline Characteristics

Overall, 105 patients were enrolled, of which 96 (91.4%) were evaluable. Duration of participation ranged from 0.7 to 105.8 months. In total, 36 (37.5%) patients discontinued prematurely. Fifteen (15.6%) patients died during the follow-up period (including 6 deaths directly related to progression of a neoplasm), while 18 (18.8%) were lost to follow-up and 3 (3.1%) discontinued for other reasons (Supplementary Fig. S1).

Mean (standard deviation, SD) age at diagnosis was 55.9 (13.9) years with patients enrolled in the registry at a mean age of 60.0 years. The majority of patients were Caucasian (n = 69; 71.9%), 49 (51.0%) were male, and 25 (26.0%) were recorded as having a history of malignancy (Table S2 in the supplementary material).

A clinical diagnosis of LEMS was confirmed using a VGCC antibody test for 56 (58.3%) patients and confirmatory EMG testing for 38 (39.6%) patients. The nature of confirmatory testing was not reported for two (2.1%) patients. Among the 18 patients (18.8%) who underwent baseline antibody testing at the time of enrollment in the registry (independently of any prior LEMS diagnosis), 16 (88.9%) were positive for anti-VGCC antibodies. Patients with autoimmune LEMS were younger (n = 71; 54.1 years) than patients with paraneoplastic LEMS (n = 25; 60.0 years).

At enrollment, 50 (52.1%) patients were being treated with 3,4-DAPP; 74 patients (77.1%) were exposed to 3,4-DAPP at any time during the study (Table S3 in the supplementary material). In addition, 3,4-DAP was being administered to 21 (21.9%) patients at enrollment, while 29 (30.2%) patients were exposed to 3,4-DAP at any time during the study. Other treatments were administered to 25 (26.0%) patients at enrollment. Frequently administered concomitant medications included pyridostigmine (n = 52; 54.2%), corticosteroids (n = 49; 51.0%), intravenous immunoglobulin (n = 31; 32.3%), and azathioprine (n = 26; 27.1%).

Neurophysiological Testing

Abnormal neuromuscular functioning (brief percentage increment [increase] in compound muscle action potential amplitude after a maximal voluntary contraction to the resting state, or more than 10% decrement of the 4th or 5th amplitude following 3 Hz stimulation, of the musculus abductor digiti quinti) was common. Mean (SD) percentage increment after 30 s of maximal spreading of fingers at baseline among 20 patients with data was 68.9% (138.1) and mean (SD) percentage decrement of 4th or 5th amplitude at 3 Hz stimulation at baseline among 23 patients with data was 21.6% (16.6). The low number of post-baseline values prevented analysis, but continued abnormal neuromuscular function was evident, when assessed.

Quantitative Myasthenia Gravis Score (QMG)

No differences in total QMG scores were observed at baseline between treatment groups for the 85 patients (88.5%) who had data available (Fig. 1).

Reflex Tone

Most patients had reduced reflex tone at baseline (Fig. 2). Reduced reflex tone continued to be observed throughout the course of the study across all treatment groups.

Muscle Strength

Muscle strength at baseline was generally good and maintained during follow-up. The majority of patients in all four treatment groups evaluated as a 4 (movement against partial resistance) or 5 (full strength) in 12 muscles or muscle groups. However, duration of follow-up was substantially longer for patients treated with 3,4-DAPP (up to 78 months versus 54 months for 3,4-DAP and 18 months for other treatments).

Ataxia

Ataxia line walk tests were positive for 12/47 (25.5%) patients at baseline (Fig. 3). Between 10.0% and 15.1% of patients had positive ataxia tests using other methods, including Romberg's tests, finger-to-nose test, and knee-to-heel tests (Fig. 3). Positive ataxia tests were observed in between 20.5% and 53.6% of patients during the study (Table 1). Among the 53 patients with a consistently negative Romberg's test, 20 had a positive line walking test and 10 had a positive finding for any other ataxia test. Thus, cerebellar ataxia, defined as a negative Romberg's test

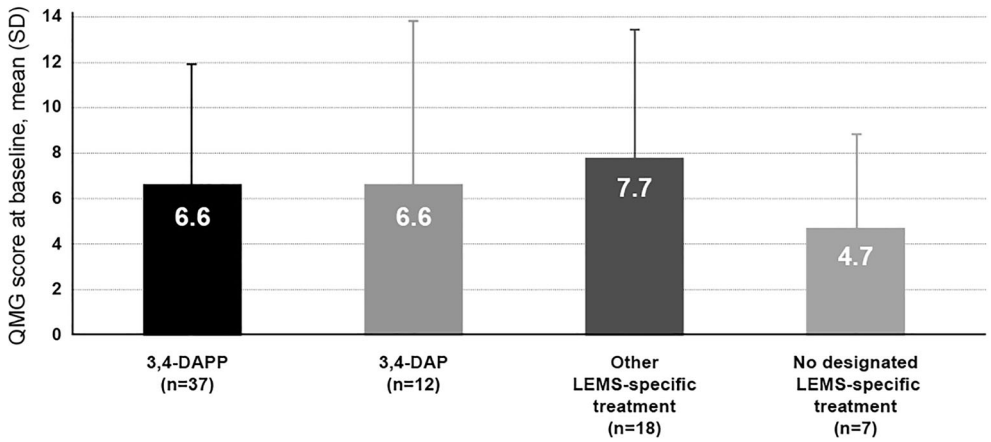

Fig. 1 QMG scores at baseline for patients enrolled in the European LEMS registry. *3,4-DAP* 3,4-diaminopyridine; *3,4-DAPP* 3,4-diaminopyridine phosphate; *LEMS* Lambert–Eaton myasthenic syndrome; *QMG* quantitative myasthenia gravis score; *SD* standard deviation

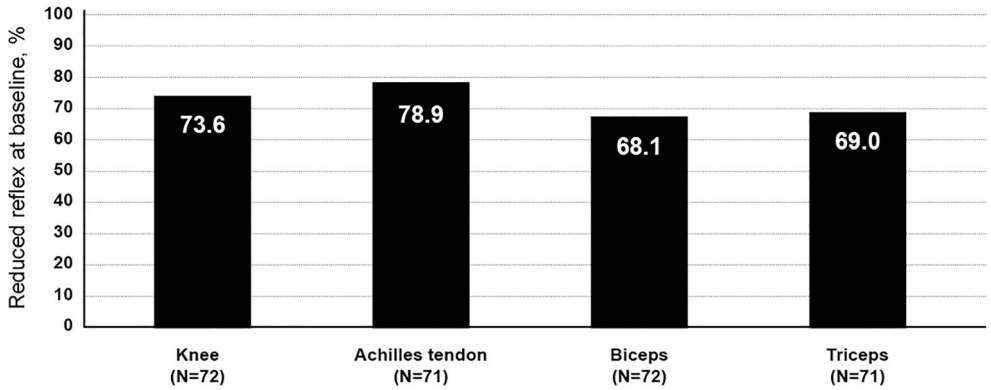

Fig. 2 Prevalence of reduced reflex tone at baseline for patients enrolled in the European LEMS registry. *LEMS* Lambert–Eaton myasthenic syndrome

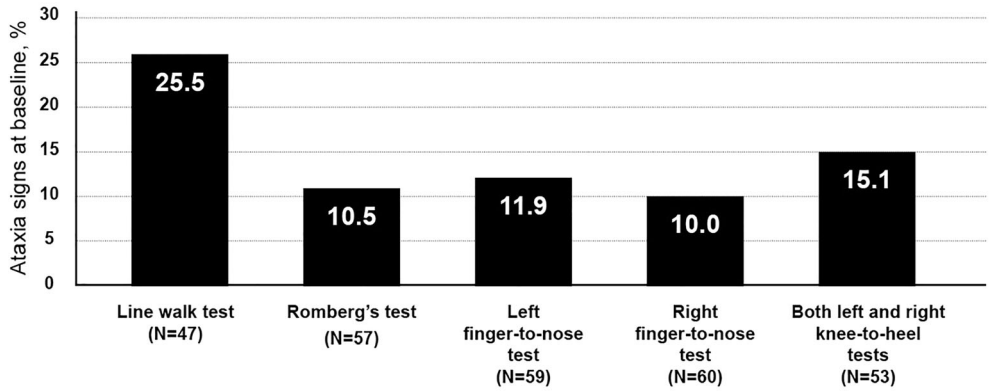

Fig. 3 Prevalence of ataxia signs at baseline for patients enrolled in the European LEMS registry. *LEMS* Lambert–Eaton myasthenic syndrome

Table 1 Ataxia test outcomes for patients enrolled in the European LEMS registry

Test	Patients (tests)	Patients with a positive test result atany time, *n* (%)
Romberg's test	75 (368)	22 (29.3)
Finger-to-nose test	78 (373)	16 (20.5)
Heel-to-knee test	72 (335)	19 (26.4)
Line walking test	69 (295)	37 (53.6)

LEMS Lambert–Eaton myasthenic syndrome

and at least one other positive ataxia test, was observed in 30 (56.6%) patients. Ataxia test performance was generally maintained during follow-up.

Autonomic Nervous System Symptoms

Dry mouth (33/61 [54.1%] patients) was the predominant ANS symptom. No notable ANS changes were observed during the study.

Daily Functioning

The majority of patients had reduced/limited functioning at baseline (Table 2). Sustained or improved functioning was observed in patients administered 3,4-DAPP during follow-up.

Inconsistent and sporadic occurrences of functional improvement and regression were observed with 3,4-DAP and other treatments. No follow-up assessments beyond baseline were performed for the unknown treatment group.

Quality of Life

Patients administered 3,4-DAPP had improvements in mean EQ-5D visual analogue scores at three consecutive follow-up assessment periods versus baseline (Fig. 4). EQ-5D assessments were limited by sample size with 3,4-DAP and other treatments, but deterioration was more common than improvement.

Safety

Overall, 55 treatment-related adverse events (AEs) were reported by 32 (33.3%) patients (Table 3). In total, 47 AEs were reported by 26 (52.0%) patients administered 3,4-DAPP, while five AEs were reported by three (14.8%) patients administered 3,4-DAP. One AE was reported by each of three (12.0%) patients administered other treatments (prednisone, azathioprine, and immunoglobulin; $n = 1$ each). Osteoporosis was reported by 5 (5.2%) patients. No other treatment-related AEs were reported by more than 3 patients.

Nine treatment-related serious AEs (SAE) were reported by eight (8.3%) patients, but multiple confounding factors were identified for each SAE, limiting interpretation of the contribution of treatment. One death (cardiorespiratory arrest) resulted from an SAE and was assessed as possibly related to a LEMS-specific medication (3,4-DAPP, pregabalin, paracetamol, and tramadol), but multiple confounding comorbidities were identified (ischemic coronaropathy, hypercholesterolemia, arterial hypertension, and Hodgkin's lymphoma). One death (*Pseudomonas* infection) resulting from an SAE was assessed as possibly related to the patient's other medications (hydrocortisone). No new safety signals were identified for any treatment, including 3,4-DAPP.

Survival Outcomes

During the study period, 13/25 (52%) patients with malignancies died (SCLC, $n = 5$; Merkel cell carcinoma, gastrointestinal malignancy, and hematologic malignancy, $n = 2$ each). Survival outcomes were similar across malignancies (Fig. 5). By comparison, there were only two deaths (2.8%) recorded among patients with autoimmune LEMS (Fig. 6).

Median survival for patients with comorbid SCLC was approximately 48 months. The median time to lung cancer diagnosis after a prior LEMS diagnosis was 31 days (range 3–84 days). The median time to a LEMS diagnosis after a patient had been diagnosed with SCLC was 50 days (range 4–750 days).

Table 2 Functional assessment outcomes at baseline for patients enrolled in the European LEMS registry

Limited/reduced function at baseline, *n*/*N* (%)	Patients with LEMS and daily functional assessment data (*N* = 59)	LEMS treatments at baseline			
		3,4-DAPP (*n* = 33)	3,4-DAP (*n* = 14)	Other (*n* = 9)	Unknown (*n* = 4)
Walk upstairs	48/59 (81.4)	30/33 (90.9)	8/13 (61.5)	6/9 (66.7)	4/4 (100)
Cycle	39/51 (76.5)	23/28 (82.1)	6/11 (54.5)	7/8 (87.5)	3/4 (75.0)
Getting up from a low chair with arm support	31/59 (52.5)	19/32 (59.4)	5/14 (35.7)	5/9 (55.6)	2/4 (50.0)
Getting up from a low chair without arm support	41/57 (71.9)	24/31 (77.4)	8/13 (61.5)	6/9 (66.7)	3/4 (75.0)
Getting up from sitting on one knee	39/51 (76.5)	23/27 (85.2)	7/12 (58.3)	7/9 (77.8)	2/3 (66.7)
Getting up from squatting	41/55 (74.5)	25/31 (80.6)	7/13 (53.8)	7/8 (87.5)	2/3 (66.7)
Climb stairs with arm support	33/58 (56.9)	18/32 (56.3)	6/13 (46.2)	6/9 (66.7)	3/4 (75.0)
Climb stairs without arm support	41/58 (70.7)	24/31 (77.4)	8/14 (57.1)	6/9 (66.7)	3/4 (75.0)
Walking on toes	28/58 (48.3)	16/33 (48.5)	5/13 (38.5)	5/8 (62.5)	2/4 (50.0)
Walking on heels	29/56 (51.8)	18/31 (58.1)	5/13 (38.5)	4/8 (50.0)	2/4 (50.0)
Getting up from a high chair with arm support	28/57 (49.1)	16/31 (51.6)	5/13 (38.5)	5/9 (55.6)	2/4 (50.0)
Getting up from a high chair without arm support	33/56 (58.9)	17/30 (56.7)	7/13 (53.8)	6/9 (66.7)	3/4 (75.0)

3,4-DAP 3,4-diaminopyridine; *3,4-DAPP* 3,4-diaminopyridine phosphate; *LEMS* Lambert–Eaton myasthenic syndrome

DISCUSSION

This final analysis of the European LEMS registry provides further information on the natural history of LEMS, building on the first publication related to this registry that presented the study methodology and baseline characteristics for the first 69 patients enrolled [18]. The neurophysiologic profile of patients in this population, namely a decrement with low-frequency stimulation and increment with high-frequency stimulation, were consistent with the myographic profile of LEMS [6]. Furthermore, no notable changes in muscle strength, ataxia, reflexes, or ANS symptoms were observed with time, which was consistent with the stable disease course observed in a study of Dutch patients with LEMS [13].

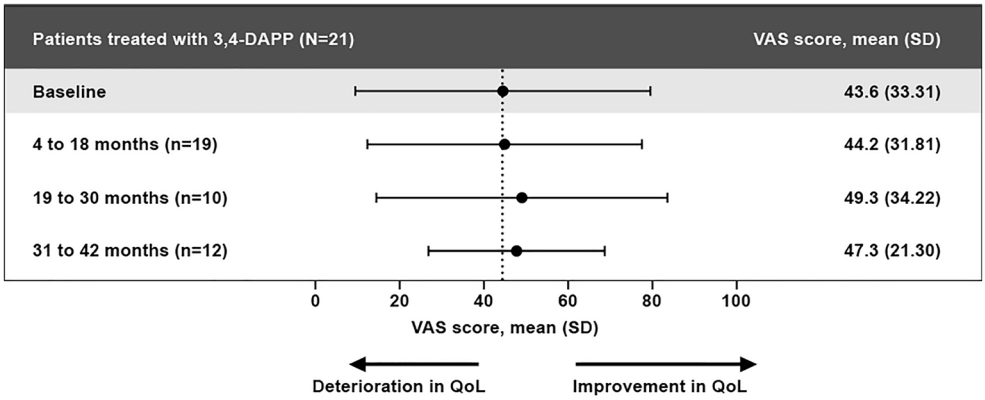

Fig. 4 Changes in quality of life measured on a 100-point VAS for patients enrolled in the European LEMS registry treated with 3,4-DAPP. *3,4-DAPP* 3,4-diaminopyridine phosphate; *LEMS* Lambert–Eaton myasthenic syndrome; *QoL* quality of life; *SD* standard deviation; *VAS* visual analog score.

Table 3 AEs reported for patients enrolled in the European LEMS registry

AEs (*N* = 96)	Events	*n* (%)
Patients with ≥ 1 AE	298	73 (76.0)
Patients with ≥ 1 LEMS-specific treatment-related AE	55	32 (33.3)
Musculoskeletal and connective tissue disorders		12 (12.5)
Gastrointestinal disorders	13	8 (8.3)
Infections and infestations	10	5 (5.2)
Nervous system disorders	6	5 (5.2)
Metabolic and nutrition disorders	5	4 (4.2)
Cardiac disorders	5	3 (3.1)
Vascular disorders	3	3 (3.1)
General disorders and administration site conditions	3	2 (2.1)
Injury, poisoning, and procedural complications	3	2 (2.1)
Patients with ≥ 1 other treatment-related AE	2	9 (9.4)

AE adverse event; *LEMS* Lambert–Eaton myasthenic syndrome

The history of malignancies among this patient population provides important additional insights into the underlying pathology of LEMS. The relationship between SCLC and LEMS is highlighted by the relatively high prevalence of a current or past history of SCLC in this registry. Notably, the interrelationship between SCLC and LEMS was evident with the rapid time to diagnosis of either condition after the first diagnosis, although the range was much longer for patients who had been first diagnosed with SCLC. In contrast, a LEMS diagnosis may prompt investigations for the presence of SCLC. The only other malignancies observed in more than one participant were prostate cancer and Merkel cell carcinoma, which are consistent with a number of case reports of comorbid LEMS in the literature

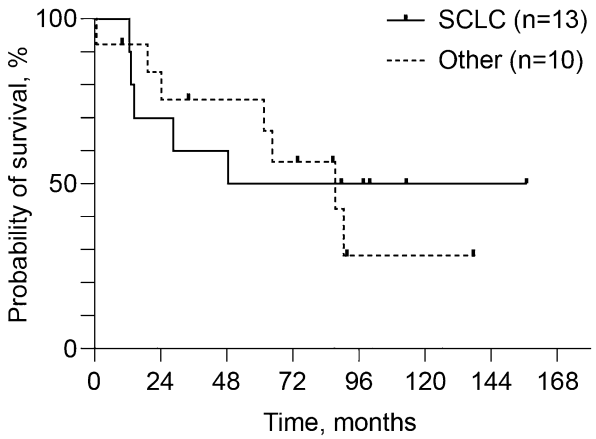

Fig. 5 Survival of patients with LEMS with SCLC versus other malignancies. Two patients with other malignancies are excluded from this analysis because the date of diagnosis was not available. One patient with colon cancer died and one patient with malignant thymoma remained alive at the end of follow-up. *LEMS* Lambert–Eaton myasthenic syndrome, *SCLC* small cell lung cancer

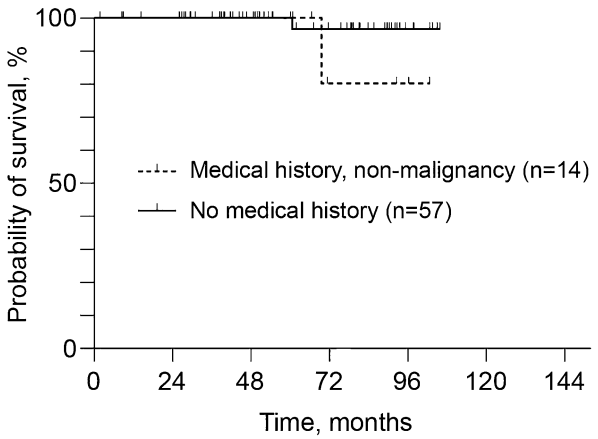

Fig. 6 Survival of patients with LEMS and no history of malignancy. *LEMS* Lambert–Eaton myasthenic syndrome

[2, 19]. In addition, the prognosis for a patient with idiopathic LEMS is similar to a patient without LEMS, although the prognosis for patients with paraneoplastic LEMS is determined by the associated neoplasm [3, 13].

The low prevalence of Merkel cell carcinoma, rarity of LEMS, and case reports of surgery for Merkel cell carcinoma resulting in the symptoms of LEMS diminishing provide additional evidence supporting a potential link between these conditions [20], although the low prevalence makes it less obvious than with SCLC. In particular, Merkel cell carcinoma is nearly indistinguishable from SCLC histologically [19]. Therefore, it has been recommended that Merkel cell carcinoma should be considered as a potential underlying pathology in patients with LEMS because it can present as occult lymph node involvement with primary cutaneous findings absent [19].

The presence of LEMS in patients with prostate cancer is also consistent with several case reports, as is the presence of thymoma [2]. A potential correlation between lymphoproliferative disorders and LEMS has also been noted in the past [2], but no active cases were reported among participants with a history of these disorders at the time of enrollment. Furthermore, a paraneoplastic origin of LEMS among patients with malignancies other than SCLC in this study cannot be ruled out. Extrapulmonary small cell carcinomas are known to present in the prostate, cervix, gastrointestinal system, and head and neck region [20]; these are all sites of reported malignancies in this patient population.

Beyond the management of any underlying pathologies, such as a malignancy, effective and well-tolerated symptomatic treatment is an important first-line treatment option for patients with LEMS. Patients with LEMS have lower health-related quality of life than the general population, which is largely related to physical limitations [13].

The European LEMS registry provides additional support for the risk–benefit balance previously determined for 3,4-DAPP in the symptomatic treatment of patients with LEMS. Short-term outcomes data from phase 3 clinical trials have previously indicated that patients with LEMS treated with 3,4-DAPP achieve improved outcomes compared with placebo [16, 17]. 3,4-DAPP appeared to be associated with sustained or improved functioning and improved patient quality of life during follow-up in this real-world population, which is consistent with previous observations.

Patients with LEMS often have a poor or very poor health status and impaired quality of life, with 75% of patients reporting activities of daily

living always or often being affected by LEMS [7].

The observations made in this study are consistent with an earlier case series that reported improved daily function over 5 years of treatment with 3,4-DAPP [21]. However, improved ANS symptoms were not observed in this study, which may be a function of many patients in the LEMS registry being co-administered anticholinesterase therapy, whereas 3,4-DAPP was only administered in combination with corticosteroid or immunosuppressant therapy in this case series [21]. Tests for ANS symptoms, such as salivation, may also lack sensitivity in patients with LEMS [6].

Furthermore, in both studies no difference in QMG outcomes was observed with 3,4-DAPP treatment, but mean QMG score was notably higher in this study (6.6) than the case series (2.86), with no patient in the case series registering a value greater than 6 at any time [21]. Early studies of 3,4-DAP also indicated that treatment efficacy is maintained after a minimum of 15 months follow-up, suggesting no clinically relevant receptor desensitization or downregulation in response to treatment [22].

Data on the long-term safety of 3,4-DAP and 3,4-DAPP is limited, despite preclinical studies identifying the potential for 3,4-DAP to affect the cardiovascular, nervous, and gastrointestinal systems, and induce salivation and miosis [6]. AEs associated with 3,4-DAP therapy are generally mild and include perioral and extremity paresthesias, nausea, vomiting, and elevated liver enzymes [3], and 3,4-DAPP was well tolerated by patients in this registry with no new safety signals observed. Paresthesias were reported by 10 out of 12 patients in the initial study of 3,4-DAP in patients with LEMS [22], but were not observed in any patients in the European LEMS registry.

Seizures have been reported in patients administered 3,4-DAP, but are rare because of the low penetration of 3,4-DAP into the central nervous system. Therefore, seizures are generally associated with doses well above the recommended daily intake [3]. Earlier studies have also demonstrated no significant pharmacokinetic interaction between 3,4-DAP and co-administered pyridostigmine [9].

3,4-DAPP offers key advantages over 3,4-DAP, including a shorter time to peak concentration and is associated with higher plasma drug concentrations [6]. The standardized preparation of 3,4-DAPP in tablet form also avoids the variability associated with 3,4-DAP compounding [14].

Immunosuppressant therapies may also be efficacious in patients with LEMS, but are associated with an increased risk of AEs compared with aminopyridines or anticholinesterase therapy. However, immunosuppressant therapy may not be appropriate for the approximately 50–60% of patients with LEMS who also present with SCLC, who may be undergoing chemotherapy [6, 8]. Long-term follow-up of patients with LEMS has also found that a higher proportion reported independent self-care after initiating treatment with 3,4-DAP or pyridostigmine [13].

This study is limited by its non-interventional, observational registry design, which meant that treatments and assessments were at the discretion of the treating physician and often varied across time and between patients. Furthermore, many patients were lost to follow-up and the non-standard approach to LEMS-related testing across participating centers limited sample sizes. The rarity of LEMS also limits the ability to perform any statistical analyses or correlate any underlying pathologies with the presence of LEMS. Patients with paraneoplastic LEMS may also have been referred for antineoplastic therapy and not enrolled in the registry.

CONCLUSIONS

LEMS negatively affects quality of life, but is associated with a stable disease course that can be managed with symptomatic treatment. No new safety signals were observed following long-term symptomatic management of LEMS with 3,4-DAPP.

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Compliance with Ethics Guidelines. Compliance with Ethics Guidelines All registry procedures were conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Declaration of Helsinki 1964, as revised in 2013. Informed consent was obtained from all patients included in the study. The LEMS registry protocol, patient information sheet, and informed consent form have been submitted to and approved by an ethics committee (EC), subject to applicable local laws at each center where the registry is being conducted. In countries participating in the LEMS registry where approvals other than an EC approval were required, all applicable requirements were met and approved. Applicable approvals were completed and in place prior to site initiation and patient enrollment. All documents are on file at SERB SA (Brussels, Belgium).

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. Abenroth DC, Smith AG, Greenlee JE, Austin SD, Clardy SL. Lambert–Eaton myasthenic syndrome: epidemiology and therapeutic response in the national veterans affairs population. Muscle Nerve. 2017;56:421–6.

2. Titulaer MJ, Lang B, Verschuuren JJGM. Lambert–Eaton myasthenic syndrome: from clinical characteristics to therapeutic strategies. Lancet Neurol. 2011;10:1098–107.

3. Anwar A, Saleem S, Ahmed MF, Ashraf S, Ashraf S. Recent advances and therapeutic options in Lambert–Eaton myasthenic syndrome. Cureus. 2019;11:e5450.

4. Gilhus NE. Lambert–Eaton myasthenic syndrome; pathogenesis, diagnosis, and therapy. Autoimmune Dis. 2011;2011:973808.

5. Ivanovski T, Miralles F. Lambert–Eaton myasthenic syndrome: early diagnosis is key. Degener Neurol Neuromuscul Dis. 2019;9:27–37.

6. Lindquist S, Stangel M. Update on treatment options for Lambert–Eaton myasthenic syndrome: focus on use of amifampridine. Neuropsychiatr Dis Treat. 2011;7:341–9.

7. Harms L, Sieb JP, Williams AE, et al. Long-term disease history, clinical symptoms, health status, and healthcare utilization in patients suffering from Lambert Eaton myasthenic syndrome: results of a patient interview survey in Germany. J Med Econ. 2012;15:521–30.

8. Skeie GO, Apostolski S, Evoli A, et al. Guidelines for treatment of autoimmune neuromuscular transmission disorders. Eur J Neurol. 2010;17:893–902.

9. Wirtz PW, Verschuuren JJ, van Dijk JG, et al. Efficacy of 3,4-diaminopyridine and pyridostigmine in the treatment of Lambert–Eaton myasthenic syndrome: a randomized, double-blind, placebo-controlled, crossover study. Clin Pharmacol Ther. 2009;86:44–8.

10. Sanders DB, Juel VC, Harati Y, et al. 3,4-Diaminopyridine base effectively treats the weakness of Lambert–Eaton myasthenia. Muscle Nerve. 2018;57:561–8.

11. Keogh M, Sedehizadeh S, Maddison P. Treatment for Lambert–Eaton myasthenic syndrome. Cochrane Database Syst Rev. 2011;2011:CD003279.

12. Zhang N, Hong D, Ouyang T, et al. 3,4-Diaminopyridine treatment for Lambert–Eaton myasthenic syndrome in adults: a meta-analysis of randomized controlled trials. BMC Neurol. 2021;21:371.

13. Lipka AF, Boldingh MI, van Zwet EW, et al. Long-term follow-up, quality of life, and survival of patients with Lambert–Eaton myasthenic syndrome. Neurology. 2020;94:e511–20.

14. Green DM, Jones AC, Brain KR. Content variability of active drug substance in compounded oral 3,4-diaminopyridine products. J Clin Pharm Ther. 2012;37:53–7.

15. Raust JA, Goulay-Dufaÿ S, Le Hoang MD, Pradeau D, Guyon F, Do B. Stability studies of ionised and non-ionised 3,4-diaminopyridine: hypothesis of degradation pathways and chemical structure of degradation products. J Pharm Biomed Anal. 2007;43:83–8.

16. Oh SJ, Shcherbakova N, Kostera-Pruszczyk A, et al. Amifampridine phosphate (Firdapse®) is effective and safe in a phase 3 clinical trial in LEMS. Muscle Nerve. 2016;53:717–25.

17. Shieh P, Sharma K, Kohrman B, Oh SJ. Amifampridine phosphate (Firdapse) is effective in a confirmatory phase 3 clinical trial in LEMS. J Clin Neuromuscul Dis. 2019;20:111–9.

18. Mantegazza R, Meisel A, Sieb JP, Le Masson G, Desnuelle C, Essing M. The European LEMS registry: baseline demographics and treatment approaches. Neurol Ther. 2015;4:105–24. https://link.springer.com/content/pdf/10.1007/s40120-015-0034-0.pdf.

19. Nguyen ND, Simmons DB, Bersabe AR, et al. Lambert–Eaton myasthenic syndrome and Merkel cell carcinoma. Cutis. 2019;103:E19-23.

20. Siau RT, Morris A, Karoo RO. Surgery results in complete cure of Lambert–Eaton myasthenic syndrome in a patient with metastatic Merkel cell carcinoma. J Plast Reconstr Aesthet Surg. 2014;67:e162–4.

21. Portaro S, Brizzi T, Sinicropi S, et al. Five years experience on 3,4-diaminopyridine phosphate in Lambert–Eaton syndrome: case reports. Medicine (Baltimore). 2017;96:e7839.

22. McEvoy KM, Windebank AJ, Daube JR, Low PA. 3,4-Diaminopyridine in the treatment of Lambert–Eaton myasthenic syndrome. N Engl J Med. 1989;321:1567–71.