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Treatment of myasthenia gravis in france: A retrospective claims database study (STAMINA)

C. Tard¹ · P. Laforet^{2,3} · G. de Pouvourville⁴ · A. Crochard⁵ · G. Chollet⁵ · C. Nevoret⁶ · S. Bouée⁶  · E. Salort-Campana⁷

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Abstract

Background This study aimed to describe treatment patterns in patients with myasthenia gravis (MG) in France.

Methods A retrospective cohort analysis was performed using the French National Health Data System (SNDS) database between 2008 and 2019. MG patients were identified using ICD-10 codes during hospitalization and/or long-term disease. We defined two adult subpopulations: a prevalent MG population of patients alive on 31/12/2019 and an incident population of newly identified patients with MG in 2012 and 2013.

Results Among the 22,079 prevalent patients, 53.1% ($n = 11,498$) received at least one chronic MG treatment in 2019. Among these treated patients, 52.5% received Acetylcholinesterase inhibitors (AChEIs) only, 10.2% were treated with corticosteroids (CS) ± AChEIs, 7.3% with non-steroidal immunosuppressive treatments (NSIST) and CS, 24.2% with NSIST w/o CS, and 5.8% received immunoglobulin and/or plasma exchange. Among the 2,661 incident patients, 84.6% received at least one chronic MG treatment over the 6-year follow-up period, and among them, 79.0% had at least one treatment category change. During the first semester of follow-up, 28.1% of patients were treated with an immunomodulator (CS, NSIST). Among patients starting treatment with immunomodulator, the proportion of those treated with CS decreased from 35.3% at initiation to 10.9% at 6 years.

Conclusion This study illustrates the complexity of MG management. Significant CS sparing was observed over time. The frequent treatment changes especially in patients with an immunomodulator treatment reflect the high variability of the disease severity. The need for personalised treatment approaches in the management of MG to reduce the burden of disease remains.

Keywords Myasthenia gravis · Management · Real-world data · Treatment

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Introduction

Myasthenia gravis (MG) is a rare, chronic neuromuscular disorder in which pathogenic autoantibodies affect the function of the neuromuscular junction. Approximately 80% of patients have antibodies against the acetylcholine receptor (AChR), 10–15% have antibodies against muscle-specific tyrosine kinase (MusK), and the remaining patients have antibodies against other receptor-related proteins or are seronegative [1–4]. MG is characterised by fluctuating motor weakness and functional disability, which has a significant impact on the lives of those affected [5].

The number of patients with MG is increasing and has more than doubled in the last 20 years, with over 700,000 people estimated to be affected worldwide [6]. MG prevalence varies significantly between countries, ranging from 15 to 179 cases/1,000,000 persons, while the annual incidence ranges from 1.7 to 21.3 per 1,000,000 persons [7]. In

a recent publication from the French STAMINA study, the prevalence (342/1,000,000) and incidence (25/1,000,000) estimates of MG in France were higher than previously reported [8].

Individual course of MG is unpredictable, although it often follows a worsening trend over the first years, and typically involves the occurrence of exacerbations, sometimes after periods of remissions [9]. This is particularly the case for MG patients with MuSK antibodies. MG may become life-threatening during myasthenic crisis defined by rapid worsening and severe weakness, mainly affecting bulbar and/or respiratory muscles, potentially leading to respiratory failure that requires intubation and/or mechanical ventilation [10].

Acetylcholinesterase inhibitors (AChEIs) are usually the first treatment to be initiated, but provide only symptomatic relief and are not sufficient in some patients with generalized MG. For patients with an inadequate response to AChEIs, the cornerstone of MG treatment has traditionally been the use of immunosuppressive therapies including non-steroidal immunosuppressive treatments (NSIST) and corticosteroids (CS) [11]. However, not all patients respond equally to these therapies; around 10–20% of patients are refractory or intolerant to conventional immunosuppressive and immunomodulatory treatments. Thymectomy is usually indicated in patients with a thymoma or in patients with AChR antibodies under 45 years of age who do not respond to immunosuppressive therapy [12]. Intravenous immunoglobulin (IVIg) and/or plasma exchange (PLEX) are indicated in case of myasthenic crisis or exacerbations as short-term interventions to rapidly improve muscle strength [13, 14]. However, the effects of IVIg and PLEX are temporary [15, 16]. Together, these factors highlight the need for individualized treatment approaches.

There has been promising development in MG treatment in recent years with particularly two novel classes of therapies: complement inhibitors and neonatal Fc receptor inhibitors [17]. These drugs specifically target some components of the immune system, offering a tailored approach to MG management.

Since the implementation of the French guidelines (“Protocole National de Diagnostic et de Soins”—PNDS) in 2015, which are to be updated [18], a few studies have been published on the real-world clinical management for patients with MG in France [7]. The present study aimed to describe treatment patterns in adult patients with MG using a comprehensive nationwide claims database with two subpopulations previously defined in the STAMINA study [8]: (1) a prevalent population in 2019 used to describe the proportions of MG treatments categories; and (2) an incident population of patients newly identified with MG in 2012 and 2013 used to describe the MG treatment patterns from the

date of identification of the condition in the database over a follow-up period of up to 6 years.

Methods

Study design

This observational retrospective study was conducted using the SNDS national health insurance database in France. The design and methodology of the study have been described in detail previously [8].

This database includes more than 99% of the population living in France (i.e., 67.4 million people in 2019). The SNDS contains pseudonymized data on healthcare encounters (public and private), sociodemographic characteristics, diagnoses, drugs, medical devices, procedures, laboratory tests (without results), date of death, and hospitalizations with discharge summaries with main and secondary diagnoses.

Patient selection

Adult patients (≥ 18 years old) with Myasthenia Gravis (MG) were identified in the database either by:

- Long-term disease (LTD) status entitled to 100% medical coverage at any time using the ICD-10 code G70 (Myasthenia gravis and other myoneural disorders);
- At least 2 hospitalizations with the ICD-10 code G70.0 (myasthenia gravis) between January 1st, 2008, and December 31st, 2019;
- One hospitalization with the ICD-10 code G70.0 and at least one prescription of an AChEI between January 1st, 2008, and December 31st, 2019.

Patients with toxic myoneural disorders (ICD-10 code G70.1), congenital and development myasthenia (G70.2), and other specified or unspecified myoneural disorders (G70.8) were excluded from the study, as well as those who did not have any healthcare consumptions during the study period, after the identification of the disease.

Study population

We defined two subpopulations:

- An adult prevalent population identified as having an MG diagnosis before December 31st, 2019, and alive on that date, were used to describe the MG treatments dispensed during the calendar year 2019.
- An adult incident population of patients newly identified with MG between January 1st, 2012, and December 31st,

2013, without any ICD-10 code for MG in at least the preceding 4 years, was used to describe the MG treatment patterns from the first MG diagnosis over a up to 6-year follow-up period.

As we worked on a claims database which does not include the results of laboratory exams, the study does not allow differentiation between anti-AChR and anti-Musk MG.

Treatments prescribed in the prevalent population were described for the latest available year in the database at the time of extraction, i.e., 2019.

Treatments prescribed to the incident population were described during their follow-up period from identification of MG (2012–2013) until December 31st, 2019, or death, whichever came first.

Data collection and outcomes definition

Sociodemographic characteristics included age on January 1st, 2019 (prevalent population) and age at MG identification (incident population).

Exacerbations and crises were identified as defined by Harris et al. [19]:

- Exacerbations were defined as hospital stays (≥ 1 night) with either one of the following conditions:
 - with MG as a primary or secondary diagnosis, or
 - with a code for dysphagia, or
 - with an MG treatment with IVIg or with PLEX (even if they were considered as a chronic treatment).
- MG crises were defined as hospital stays for respiratory distress, respiratory failure, respiratory support, intubation, or mechanical ventilation (invasive or not), associated with a code for MG during the same hospital stay. We also considered a more stringent definition restricting the mechanical ventilation to invasive procedures, like the MGFA V class.

Thymectomies were identified through procedure codes during hospitalizations and were reported for the 6-year follow-up period in the incident population.

Outpatient treatments were identified through retail pharmacies and included AChEIs (pyridostigmine, neostigmine, ambenonium, chloride), oral CS (prednisone, prednisolone, and methylprednisolone), and non-steroidal immunosuppressive treatments (NSIST) including mycophenolic acid, azathioprine, cyclosporine, and tacrolimus. Cyclophosphamide was also usually classified as an NSIST; however, it was administered during hospital stays, and hence, was not documented specifically in the database. Nonetheless, this

treatment could be indirectly identified in the hospitalization database by referencing the Disease-Related Group (DRG) code for chemotherapy in day hospitalizations, specifically for non-cancer related indications. Drugs delivered during hospital stays could not be identified, because they did not lead to a claim, except for some expensive therapies leading to a reimbursement on top of the DRGs, such as rituximab, IVIg, and PLEX. Rituximab was considered as an NSIST and as such qualified for chronic treatment, while IVIg and PLEX could alternatively be considered as NSIST or an acute treatment, based on the number of sessions (see below).

Chronic treatment categories were defined as follows:

- AChEIs only: delivery of AChEIs and not meeting the criteria for any of the categories mentioned below;
- CS: at least 5 CS deliveries over a 6-month period with or without AChEIs and fewer than 4 sessions/year of IVIg/PLEX and no chronic NSIST delivery;
- NSIST w. CS: at least one NSIST delivery per year and at least 5 CS deliveries over a 6-month period, and fewer than 4 sessions/year of IVIg/PLEX;
- NSIST w/o CS: at least one NSIST delivery per year with fewer than 5 CS deliveries over a 6-month period and fewer than 4 sessions/year of IVIg/PLEX;
- IVIg and/or PLEX (fast-acting treatments) [20]: at least 4 sessions of treatment per year with or without AChEIs, NSIST or CS.

This classification did not differentiate 1st line of NSIST (mycophenolic acid, azathioprine) from 2nd line (cyclosporine, tacrolimus, rituximab, and cyclophosphamide).

For the sake of clarity, only changes from one treatment category to another have been described, i.e., a change from one NSIST to another was not included. Changes of treatment category were alternatively calculated over periods of 6 or 12 months.

Statistical analysis

SAS[®] V9.0.4 software program (North Carolina, USA) was used for statistical analysis. Quantitative variables were described by mean, standard deviation (SD), median, quartiles, minimum, and maximum, and qualitative variables by numbers and percentages.

Results

Patient characteristics

The prevalent population comprised a total of 22,079 adult patients in 2019, and the incident population included

2661 newly identified MG adult patients in 2012 and 2013 (Table 1).

The mean age was 60.8 (SD ± 18.6) years in the prevalent population and 60.1 (SD ± 19.0) years in the incident populations. Just over half of patients were female in both the prevalent (56.4%) and the incident population (52.5%). The mean time elapsed from the identification of MG until December 31st, 2019, was 10.6 (SD ± 9.5) years in the prevalent population. A minority of patients in the incident population (9.5%) underwent thymectomy during the 6-year follow-up.

Prevalent population (in 2019)

Chronic treatments

Out of the 22,079 adult patients from the prevalent population, 11,498 (53.1%) received at least one chronic MG treatment in 2019. Among these treated patients, more than half (n = 6036; 52.5%) received AChEIs only, 1173 patients (10.2%) were treated with CS ± AChEIs, 837 (7.3%) had NSIST w. CS, 2,787 (24.2%) had NSIST w/o CS, and 665 (5.8%) received IVIg and/or PLEX (Fig. 1).

Table 1 Description of study populations

	Prevalent population 2019 N = 22,079	Incident population 2012–2013 N = 2661
Sex, n (%)		
Male	9,630 (43.6%)	1,263 (47.5%)
Female	12,449 (56.4%)	1,398 (52.5%)
Age on December 31st 2019	on January 1st, 2019	at first identification of MG
Mean (standard deviation)	60.8 (18.6)	60,1 (19.0)
Median/Min/Max	63.0/18.0/108.0	63.0/18.0/100.0
Time since first identification of MG to December 31st 2019 (years)		
Mean (standard deviation)	10.6 (9.5)	
Median/Min/Max	8.0/0.0/65.0	
Thymectomy during the 6-year follow-up after first identification of MG. n (%)		254 (9.5%)

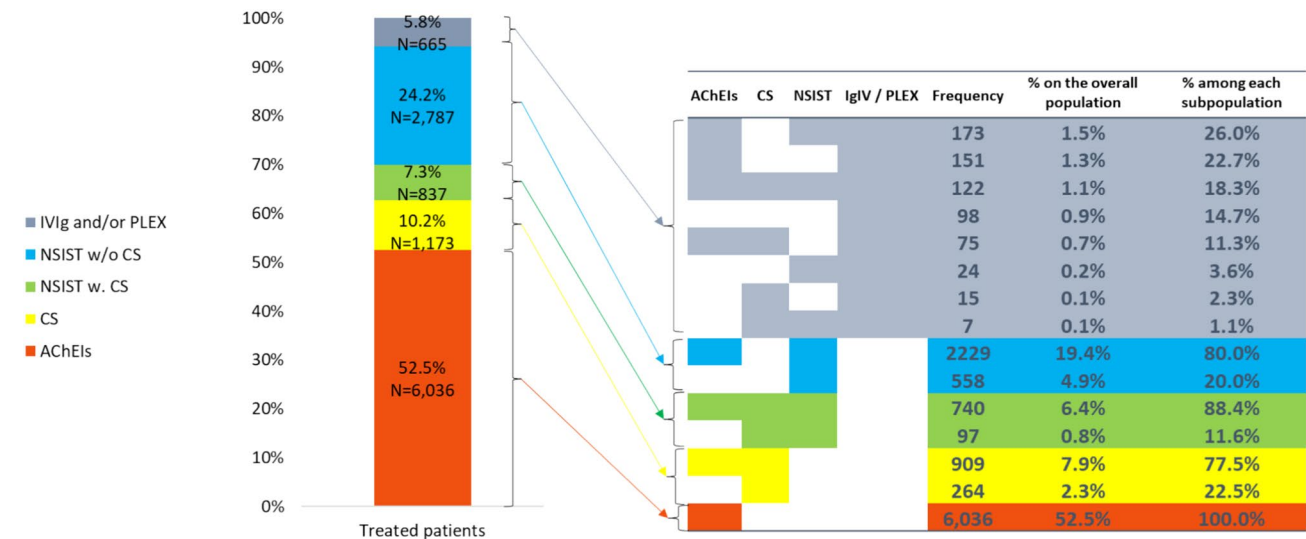


Fig. 1 Chronic treatments in 2019 for treated patients in the prevalent population (N = 11,498). The table on the right side gives the number of patients for all combinations of treatments. For example, of the 665 patients (5.8%) who were treated with ‘IVIg and/or PLEX’ (colored in grey), 173 patients were treated with IVIg/PLEX, AChEIs, and NSIST, and 151 patients were treated with IVIg/PLEX and AChEIs, etc. Definitions of chronic treatments: IVIg and/or PLEX: at least 4 sessions per year with or without AChEIs, NSIST or CS; NSIST w. CS: at least one NSIST delivery per year (mycophenolic acid, azathi-

oprine, cyclosporine, tacrolimus, rituximab, and cyclophosphamide) and at least 5 CS deliveries over a 6-month period, and fewer than 4 sessions/year of IVIg/PLEX; NSIST w/o CS: at least one NSIST delivery per year with fewer than 5 CS deliveries over a 6-month period and fewer than 4 sessions/year of IVIg/PLEX; CS: at least 5 CS deliveries over a 6-month period with or without AChEIs and fewer than 4 sessions/year of IVIg/PLEX and no chronic NSIST delivery; AChEIs only: delivery of AChEIs and not meeting the criteria for any of the aforementioned categories

AChEIs were the most frequently prescribed symptomatic chronic treatment, whatever the treatment subgroup: 77.5% in the CS subgroup; 88.4% in NSIST w. CS subgroup; 80.0% in the NSIST w/o CS subgroup; and 78.3% in the IVIg/PLEX subgroup.

Among the patients treated with IVIg and/or PLEX, 13.6% were also treated with CS and no NSIST, 29.6% with NSIST and no CS, and 19.4% were also treated with both NSIST and CS, showing a high disease severity.

In 2019, 3.8% of the patients who received NSIST w. CS, and 7.9% of the patients who received NSIST w/o CS, were treated with rituximab as a second line NSIST. This shows that twice as many patients were prescribed rituximab after a first course of NSIST w/o CS than after a first course of NSIST w. CS.

Fast-acting treatments for exacerbations and crises

A total of 5,056 episodes of exacerbations were recorded in 2019 in the prevalent population.

Among the 22,079 patients from the prevalent population, 3,165 (14.3%) had at least one exacerbation (mean 1.6 exacerbations per patient) and 1321 (6.0%) at least 2

exacerbations. Overall, 1548 (30.6%) exacerbations were treated with IVIg and/or PLEX. Of the 3165 patients with an exacerbation, 933 (29.5%) had previously been treated with a chronic NSIST.

The overall mean duration of hospital stay for exacerbation was 5.9 days (median, 3.0 days).

During hospital stays, a fast-acting treatment was delivered for 1548 exacerbations (30.6%), and IVIg was the most frequently used with more than 90% (Table 2).

Fifty-nine (1.9%) of the 3,165 patients with at least one exacerbation in 2019 were treated with rituximab in the 6 months before the exacerbation. When not treated with rituximab beforehand, 123 patients (4.0%) received a first infusion of rituximab during the month following the exacerbation.

In 2019, 467 (2.1%) out of the 22,079 patients in the prevalent population had at least one myasthenic crisis, with a total of 501 crises recorded.

The overall mean duration of hospital stay related to a crisis was 17.7 days (median, 9.0 days).

During hospital stays, a fast-acting treatment was delivered for 265 crises (52.9%), and IVIg was the most frequently used with 75% (Table 2).

Table 2 Hospitalization duration and fast-acting treatments for exacerbations or myasthenic crises in 2019 for the overall number of MG prevalent adult patients ($N=22,079$)

	Exacerbations (Harris definition ²⁰) $N=5,056$	Crises	
		Harris definition ²⁰ $N=501$	More stringent definition* $N=393$
Duration of the hospital stay (all events) days			
- Mean (standard deviation)	5.9 (11.3)	17.7 (24.4)	23.9 (29.5)
- Median/Q1/Q3	3.0/1.0/7.0	9.0/1.0/7.0	16.0/7.0/29.0
Fast-acting treatment delivered during the hospital stay of the event, n (%)			
- No	3,508 (69.4%)	236 (47.1%)	171 (43.6%)
- Yes	1548 (30.6%)	265 (52.9%)	222 (56.4%)
If yes, duration of the hospital stay (events treated with fast-acting treatments IVIg and/or PLEX), in days	$N=1,548$	$N=265$	$N=222$
- Mean (standard deviation)	7.7 (16.7)	26.1 (31.6)	30.1 (34.1)
- Median/Q1/Q3	3.0/0.0**/8.0	18.0/7.0/32.0	22.5/9.0/40.0
If yes, fast-acting treatment for the event/pts, n (%)			
- IVIg	1,406 (90.8%)	199 (75.2%)	167 (75.2%)
- PLEX	108 (7.0%)	32 (12.1%)	21 (9.5%)
- IVIg and PLEX	34 (2.2%)	34 (12.8%)	34 (15.3%)
If PLEX, number of sessions	$N=142$	$N=32$	$N=55$
o 1	114 (80.3%)	29	38
o 2	12 (8.5%)	<11	<11
o ≥ 3	16 (11.3%)	<11	<11

Patients may have had more than one exacerbation/myasthenic crisis

*Mechanical ventilation restricted to invasive procedures only

**Patients did not spend the night in the hospital

Seventy-nine (16.9%) of the 467 patients with at least one myasthenic crisis in 2019 were treated with rituximab in the 6 months before the crisis. When not treated with rituximab beforehand, 19 (4.9%) received a first infusion of rituximab during the month following the crisis.

When using the more stringent definition of myasthenic crises requiring mechanical ventilation to be invasive, overall, 318 patients (1.4%) had at least one crisis in 2019, with a total of 393 crises. Of these 393 crises, more than half ($n = 222$) were treated with a fast-acting treatment: 167 (75.2%) were treated with IVIg, 21 (9.5%) were treated with PLEX, and 34 (15.3%) were treated with both (Table 2).

Incident population (6-year follow-up)

Whole population

Overall, 2,661 adult patients were first identified with MG in 2012 or 2013. At least one chronic MG treatment was prescribed to 2,250 of these patients (84.6%) during the up to 6-year follow-up period.

Among those 2,250 patients, 1,777 (79.0%) changed treatment category at least once by the end of the follow-up (Fig. 2). Most of them received AChEIs ($n = 286$; 60.5%). Changes of patients' treatment category over the 6-year follow-up period are illustrated as a Sunburst diagram showing the variety of treatment pathways (Fig. 2). During the

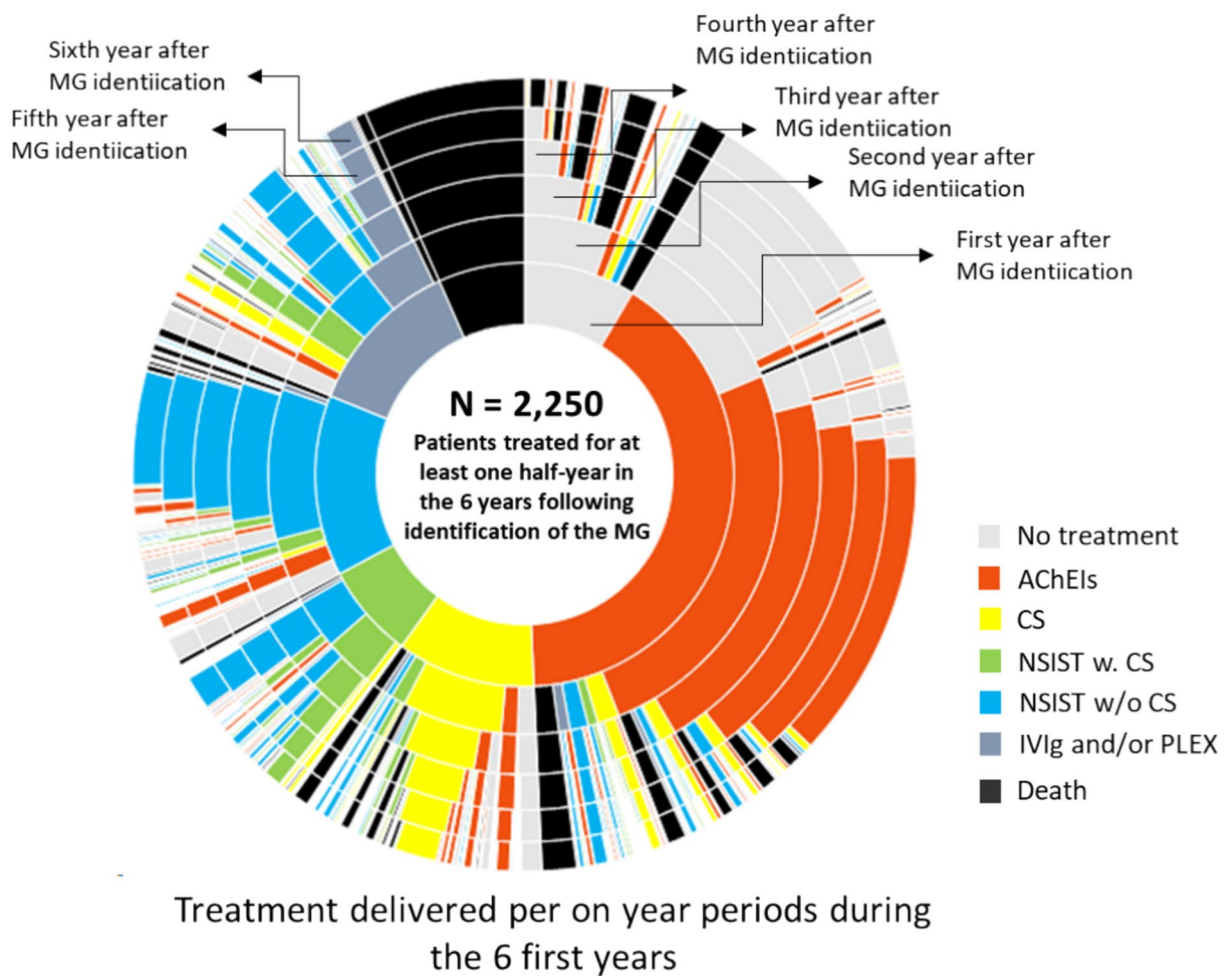


Fig. 2 Sunburst diagram depicting 1-year treatment sequences over the first 6 years following MG identification (each ‘spoke’ follows a patient over time: successive treatments for the same patients are visualized through each circle, chronologically from the centre to the periphery). IVIg and/or PLEX: at least 4 sessions per year with or without AChEIs, NSIST, or CS; NSIST w. CS: at least one NSIST delivery per year (mycophenolic acid, azathioprine, cyclosporine, tacrolimus, rituximab, and cyclophosphamide) and at least 5 CS deliver-

ies over a 6-month period, and fewer than 4 sessions/year of IVIg/PLEX; NSIST w/o CS: at least one NSIST delivery per year with fewer than 5 CS deliveries over a 6-month period and fewer than 4 sessions/year of IVIg/PLEX; CS: at least 5 CS deliveries over a 6-month period with or without AChEIs and fewer than 4 sessions/year of IVIg/PLEX and no chronic NSIST delivery; AChEIs only: delivery of AChEIs and not meeting the criteria for any of the aforementioned categories

follow-up period, the mean number of treatment category modifications was 2.89 (median 1).

Focus on patients initiating treatment with CS and/or NSIST

Among the 2,250 patients treated during at least one semester over the 6-year follow-up, 632 (28.1%) patients received an immunomodulator (CS, NSIST) treatment on the first semester (Fig. 3). The initiated immunomodulator treatment was CS for 35.3%, NSIST w. CS for 28.2% and NSIST w/o CS for the remaining 36.6%. During the last semester, among the patients who remained on treatment and after excluding death ($n = 119$), these proportions were 10.9%, 12.5%, and 35.3%, respectively, showing a decrease of patients treated with CS and NSIST w. CS.

Over the 6 years of follow-up, 78.0% of the 632 patients who initiated treatment with an immunomodulator during the first semester switched treatment category. This proportion was even higher in the CS and NSIST w. CS subgroups with, respectively, 81.2% and 86.0% having at least one treatment category modification (vs. 68.8% in the NSIST w/o CS subgroup). In the CS and NSIST w. CS subgroups,

respectively, 52.0% and 55.6% had two or more treatment category modifications.

Impact of age at first identification of MG on chronic treatment pattern

Distribution of chronic treatment categories was almost similar across the different age groups (< 50, 50–64, 64–79 years, and ≥ 80 years) at first identification of MG (Supplementary, Fig. 1). However, when comparing treatment in the last 6 months of the 6-year follow-up, the increase in the proportion of patients receiving no treatment and the decrease in the proportion of patients receiving NSIST w/o CS were both higher in patients under 50 years of age than in older patients.

Impact of calendar year of first MG identification on chronic treatment pattern

No significant difference was seen in the distribution of chronic treatment categories over the first year after MG

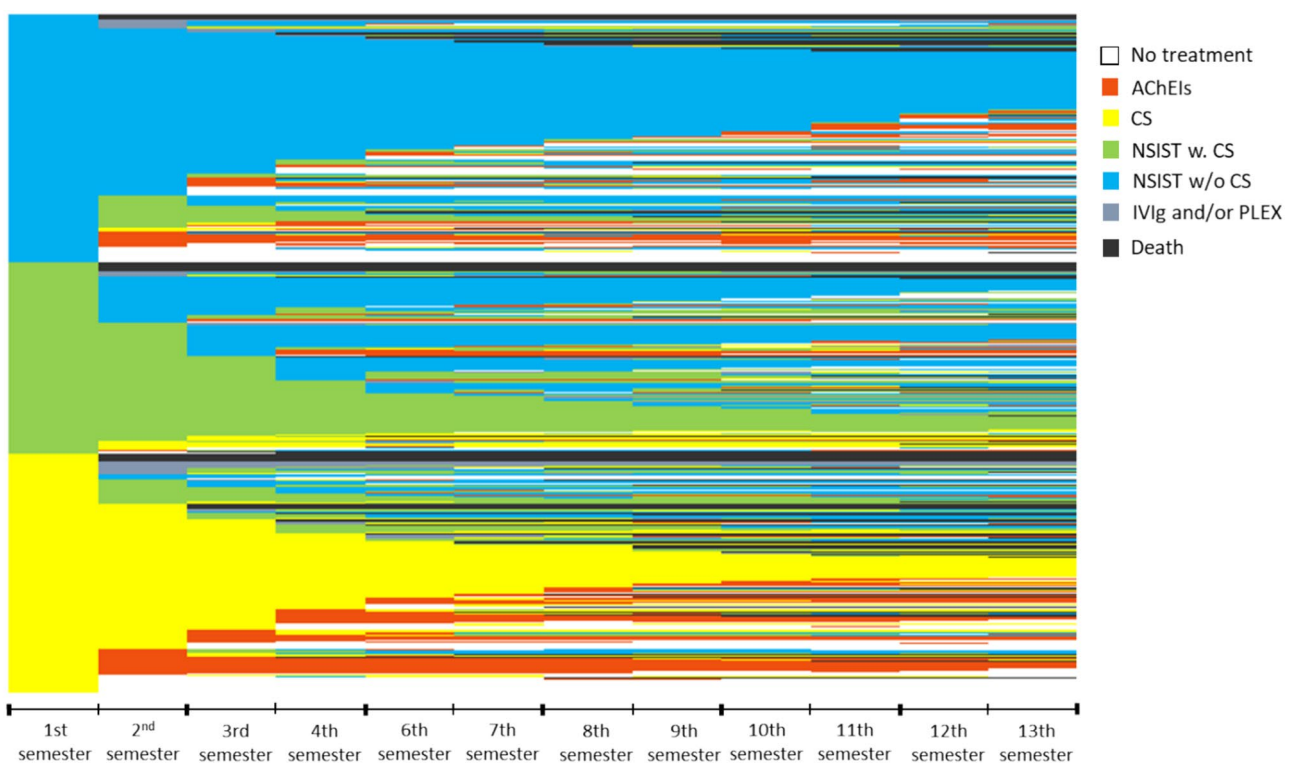


Fig. 3 Modifications of treatment for the 2012–2013 incident patients treated with CS and/or NSIST in the first 6 months ($N = 632$ patients). IVIg and/or PLEX: at least 4 sessions per year with or without AChEIs, NSIST or CS; NSIST w. CS: at least one NSIST delivery per year (mycophenolic acid, azathioprine, cyclosporine, tacrolimus, rituximab, and cyclophosphamide) and at least 5 CS deliveries over a 6-month period, and fewer than 4 sessions/year of IVIg/PLEX;

NSIST w/o CS: at least one NSIST delivery per year with fewer than 5 CS deliveries over a 6-month period and fewer than 4 sessions/year of IVIg/PLEX; CS: at least 5 CS deliveries over a 6-month period with or without AChEIs and fewer than 4 sessions/year of IVIg/PLEX and no chronic NSIST delivery; AChEIs only: delivery of AChEIs and not meeting the criteria for any of the aforementioned categories

identification, regardless of the year of MG identification (2012–2019) (Supplementary, Fig. 2).

Discussion

Main findings

This retrospective study sheds light on the treatment landscape for MG in France using a comprehensive claims and hospitalization database (SNDS) that covers more than 99% of the total population living in France.

Our study revealed that monotherapy with AChEIs was the most common chronic therapy for MG. This finding applied in both the prevalent population in 2019, and the incident population over the first year after MG identification in 2012–2013 with 52.5% and 47.3% of patients being prescribed AChEIs, respectively. After AChEIs, the most frequent chronic treatments in the prevalent and incident populations, respectively, were NSIST w/o CS (24.2% and 10.7%), CS (10.2% and 10.3%), and NSIST w. CS (7.3% and 8.2%). During crises and exacerbations,IVIg were by far the most widely used fast-acting treatment. Interestingly, we found a significant proportion of untreated patients, which was also the case in a recent German study ([21]). This may be partly explained by ocular MG cases, which present with mild symptoms that may not require treatment and by remissions during the course of the disease.

Over a 6-year follow-up period, the mean number of treatment category modifications was 2.89 per patient, with 79.0% of patients changing treatment category at least once, possibly showing an active disease. The multiplicity of treatment patterns between patients and over time reflects the variability of MG disease activity but could also be explained by different physician practices. These results highlighted the inadequate response to available therapies in managing patients with MG and the importance of regularly reassessing and possibly adapting treatment strategies in MG to ensure disease control and patient well-being.

Considering all NSISTs without differentiation, the proportion of incident patients receiving NSIST w/o CS was the highest during the last year of follow-up, indicating the need to readjust chronic treatment over time. A sustained control by immunomodulation was most often observed with NSIST (first or second treatment line).

During the 6-year follow-up, there was a marked reduction in the percentage of patients receiving CS. The design of the study, based on the SNDS, did not allow the reason for CS removal to be recorded (lack of efficacy, adverse event, better control of the disease, etc), neither the CS dose tapering. However, CS sparing was almost systematic and clearly shown in incident patients initially receiving CS with or without NSIST.

These findings were aligned with the recommendations outlined in the PNDS guidelines [18] which endorse the use of AChEIs as symptomatic therapeutic approach in the MG management followed by immune suppressive agents including CS and NSIST, with the recommendation over time to taper CS dose and/or stop CS use.

Comparison with similar studies

The comparison of the STAMINA study with a similar study conducted by Wartmann et al. [22], over 10 years in Germany, offers insights into regional variations in MG treatment patterns. The STAMINA study found monotherapy with AChEIs to be the predominant therapy (52.5%), whereas in the study by Wartmann et al., AChEIs combined with CS/ NSIST were the most prescribed base therapy (43.6% in 2020). These discrepancies may be explained as the authors only included patients treated with one of these drugs.

However, our results align closely with those by Mahic et al. [23], who conducted a retrospective study in five European countries (France, Germany, Italy, Spain, and the United Kingdom) through the Adelphi Real-World Disease Specific Program in MG, a point-in-time survey of healthcare providers and MG patients. Their findings corroborated our observation of AChEIs being the most frequently prescribed chronic treatment for MG patients, followed by CS and azathioprine.

If these therapies fail to control MG, the PNDS guidelines recommended the use of rituximab [9]. Although rituximab was not commonly prescribed in our study (3.8% of those treated with NSIST w. CS and 7.9% of those treated by NSIST w/o CS), its usage was higher than the 0.6% to 2.2% reported in Germany [18]. Of note, we found that while most patients did not use rituximab, 4% to 5% initiated a rituximab treatment shortly after experiencing an exacerbation or a crisis. This highlighted the option of rituximab for MG patients (especially for patients with MuSK antibodies) with uncontrolled disease despite not being approved in this indication in France.

Our definitions of exacerbations and myasthenic crises were based on those used by Harris et al. [20]. However, given that only 30.6% of exacerbations and 52.9% of crises were treated with IVIg and/or PLEX during the hospital stay, these selection criteria may be questioned. Therefore, we alternatively considered a more stringent definition for crises, restricted to invasive mechanical ventilation (like the MGFA V class). The treatment rate slightly increased to 56.4%. Nonetheless, patients identified as untreated may have received other treatment during their hospitalizations that could not be captured in the SNDS database, such as CS. In the STAMINA study, a notable proportion (29.5%) of MG

patients experiencing exacerbation had previously received chronic NSIST.

In our study, the mean duration of hospital stays for patients experiencing a myasthenic crisis (according to the Harris definition) was 17.7 days, while for those with an exacerbation, it averaged 5.9 days. Mahic et al. [24] reported a mean length of stay of 6 days (4.7 days for France). Among these, the most common reason for admission was IVIg treatment administration (31.5%) followed by treating a complication (24.7%). Of note, our study reveals that France had the highest hospitalization rate in the past 12 months compared with the other European countries, with one in three patients hospitalized. This may be explained by the French management organization in expert centres for patients presenting with rare diseases. Another explanation may be that we included day hospitalization (without overnight), which could be considered as outpatient care and excluded in the other countries.

We found that 9.5% of incident patients in France underwent thymectomy over the 6-year follow-up period, whereas this proportion was 4.4% in Germany but on a 2-year period after the onset of the disease [22] and 2.9% in UK on a 1- to 6-year follow-up period [24]. In France, thymectomy is recommended only in case of a thymoma and for MG patients below 45 years old [18], whereas half of the patients in STAMINA were above 63 years at first MG identification.

Strengths and limitations

The main strength of our study is the use of the nationwide claims database that covers more than 99% of the French population, and, therefore, provides a robust representation of MG patients in France.

We acknowledge several limitations in our analysis. First, our data lacked clinical details, such as antibody status (e.g., anti-AChR or anti-MuSK antibodies), differentiation between ocular and generalized MG, and symptom severity. Consequently, we could not assess specific treatment patterns in the context of these parameters. Second, it was unclear whether certain medications, such as CS and NSIST, were specifically prescribed for MG or for the management of concurrent conditions including other autoimmune diseases. Our definition of a chronic treatment with CS was based on at least 5 CS deliveries over a 6-month period. Some patients treated for MG with CS could have a smaller number of deliveries. This bias may lead to an underestimation of patients treated with CS. The description of treatment for incident patients is based on a cohort identified in 2012 and 2013. Although the management of MG did not change between 2012 and 2019 (Fig. 2 in additional material), it may be different beyond 2019 with the availability of rituximab.

Finally, we may have missed drugs delivered during hospitalizations, like corticosteroids, because they did not lead to a reimbursement claim, possibly leading to an underestimation of the use of some treatments. Moreover, there may be an overestimation of the crisis and exacerbations due to the algorithm we used (MG patients may have been hospitalized for another reason, fast-acting treatments may have been used before a surgical procedure...). This may explain the absence of identified treatment in some patients experiencing crises and exacerbations.

Our findings underscored the challenges associated with effectively managing patients with MG and emphasized the potential benefits of personalized treatment strategies to enhance patient outcomes and alleviate the burden on patients.

Conclusion

This study contributes to the understanding of real-world MG treatment patterns and highlights the challenges faced by healthcare providers in managing patients presenting with MG in France. Significant CS sparing was observed over time. The frequent treatment changes especially in patients with an immunomodulator chronic treatment may reflect the continuous need for adaptation. There remains a need for ongoing assessment and personalised treatment approaches in the management of MG to reduce the burden of disease and improve patient outcomes.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00415-024-12714-5>.

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Author contributions SCE, LP, DePG, TC, CA, CG, NC, EC, and BS participated in the study design and the interpretation of the study results. NC, EC, and BS performed the statistical analysis. SCE, LP, DePG, TC, CA, CG, NC, EC, and BS participated in the writing of the manuscript.

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Data availability Data from non-interventional studies are outside of UCB's data sharing policy and are unavailable for sharing. The data in this study were obtained from the French nationwide claims and hospitalization database, the Système National des Données de Santé (SNDS). According to French law, a specific process needs to be followed to access the SNDS.

Declarations

Conflicts of interest SCE, LP, DePG, and TC received fees (advisory boards, consultation, education, presentations) from UCB. CA and

CG are employees of UCB, which supported this study. NC, and BS are CEMKA employees, who received fees from UCB to conduct this analysis.

Ethical approval The study protocol was approved by the HDH (Health Data Hub), the National Data Protection Authority CNIL (Commission Nationale de l'Informatique et des Libertés) (date of acceptance: 09/23/2021, reference MLD/MFI/AR2110968), and the National Medical Council (Conseil National de l'Ordre des Médecins—CNOM).

Patient consent According to HDH and CNIL, no written informed consent was required for the study. The research complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

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