Progression and Exacerbation Timing in Myasthenia Gravis: Real World Evidence from France (RELIEF study)

Thierry Gendre [1], Didier Theis[2], Erika Guyot[3], Maeva Nolin[3], Manon Belhassen[3], Ingrid Rodriguez [4], Julia Meijer [4], Laurène Gautier[4], Julien Dupin[4], Jean-Baptiste Noury [5]

1. Département deNeurologie, APHP, CHU Henri MondorCréteil, France; 2.Départementd'information médicale, CHU de Lille, Lille, France; 3.Epimentis (PELyon), Lyon, France; 4. J&J Innovative Medicine, Issy-les-Moulineaux, France; 5. Centre deRéférence Des Maladies NeuromusculairesAOC, INSERM, LBAI, UMR1227, CHRU de Brest, Brest, France

Introduction

- Myasthenia gravis (MG) can progress to generalized (gMG) or refractory (rgMG) forms despite management strategies combining symptomatic treatments, immunosuppressive treatments (steroidal or non-steroidal), and rescue interventions (e.g., intravenous immunoglobulins (IVIg) or plasma exchange (PE)) (1).
- Although MG is often associated with progression to gMG and a substantial burden of exacerbations and crises, real-world evidence remains scarce and heterogeneous, with limited data on the timing and evolution of these events following diagnosis.
- In this context, understanding the timing of progression and acute events in myasthenia gravis (MG) is critical for optimizing care.

Objective

The objective was to estimate the time-to-progression from MG to gMG and rgMG, and to assess the time-to-first crisis or exacerbation .

Methods

- **Study design:** retrospective cohort study
- **Data source:** French health claims database - Système National des Données de Santé (SNDS) (2)
- **Analyses period:** 01/01/2014 to 12/31/2023
- **Follow-up:** at least one year (except in case of death)

Selection of populations

- Specific algorithms based on diagnosis codes and treatment dispensations were applied to identify two populations between 01/01/2014–12/31/2022: adults with a first MG diagnosis and adults with a first gMG diagnosis (see Table 1).

Outcomes

- **rgMG:** [second-line immunosuppressant (except cyclophosphamide; except rituximab dispensed as first line treatment) OR new generation therapy] OR [immunotherapy for at least 12 months AND ⩾10 mg/day of corticosteroids between the 6th and 12th month] OR [IVIg or PE after 6 months of immunosuppressive therapy OR IVIg or PE for at least 6 months]
- **Crisis:** hospitalization with an associate diagnosis of MG AND respiratory failure (main or related diagnosis), intubation, ventilation, or enteral feeding.
- **Exacerbation :** crisis, acute IVIg or PE, hospitalization for MG (main diagnosis), or hospitalization for dysphagia (main or related diagnosis) with an associate diagnosis of MG.

Statistical analysis

- Kaplan-Meier curves were drawn to describe the time to events.

Limitations

- The algorithms used to identify patients with MG, gMG and rgMG as well as crises and exacerbations were developed with the study's Scientific Committee, based on the 2015 national diagnosis and care protocol (PNDS) (1) and published literature (3-5), ensuring methodological relevance. However, the use of proxy-based identification for both populations and events, combined with the absence of external validation, may have led to false positives or false negatives.
- Because this study is a retrospective longitudinal analysis using SNDS data, it is subject to potential selection and time-related biases.

Results

Key results

Progression :

- Approximately half of patients with MG progress to gMG within 1 year of MGdiagnosis.
- About 1/5 of patients with gMG develop rgMG within 1 year of gMG diagnosis.

Exacerbations were common, affecting more than 50% of patients in the 6 months after MG diagnosis.

Crises were less frequent as 6% of patients experienced a first crisis within 1 year of MG diagnosis.

Characteristics

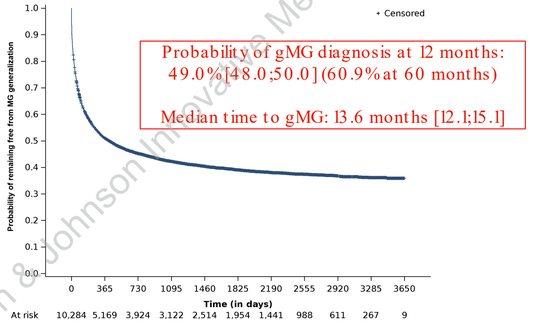
Table 1: Characteristics of adults with MG or gMG with a first diagnosis between 2014 and 2022

	MG (N = 10,284)	gMG (N = 6,905)
Identification principle in the SNDS	Long-term disease for MG OR at least two hospitalizations for MG OR at least one hospitalizations for MG and two dispensing of acetylcholinesterase inhibitor	Immunosuppressive therapy OR second-line immunosuppressant [a] OR IVIg OR PE OR new generation therapy OR thymectomy
Male, n (%)	5,074 (49.3%)	3,445 (49.9%)
Age at diagnosis, mean (SD), (in years)	61.3 (18.2)	62.4 (18.1)
Comorbidities, n (%)*		
Type 1and type 2 diabetes	1,030 (10.0%)	890 (12.9%)
Thymoma	174 (1.7%)	489 (7.1%)
Depressive episode	363 (3.5%)	304 (4.4%)
Follow-up duration, mean (SD), (in years)	4.8 (2.6)	4.7 (2.7)

*Abbreviations: gMG : generalized myasthenia gravis;IVIg: intravenous immunoglobulins;MG : myasthenia gravis; PE: plasma exchange; SD: standard deviation. *Comorbidities were identified during the year preceding the first recorded diagnosis of MG or gMG, based on ICD10-coded diagnoses from MCO hospital stays or LTD status.*

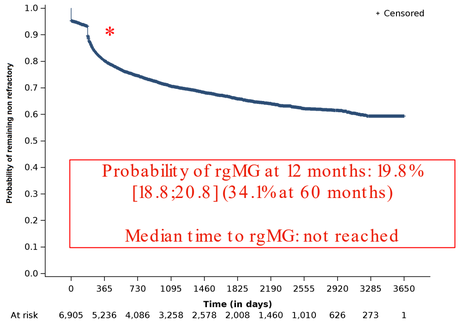
Progression

Figure 1: Kaplan Meier curve for the progression to gMG in MG adults



Among the 6102 patients who progressed to gMG, median time to generalization was 66 days, with 4251 events (70%) occurring within the first 6 months.

Figure 2: Kaplan Meier curve for the progression to rgMG in gMG adults



**The observed inflection in the curve likely reflects the use of identification criteria based on a 6-month evaluation window to assess treatment chronicity or the inability to reduce therapy, as well as partial overlap between some gMG and rgMG criteria (e.g. dispensing of new-generation therapies). Consequently, this pattern should not be interpreted as clinically meaningful, as it primarily reflects methodological constraints rather than true changes in patient status.*

First crisis or exacerbation

Figure 3: Kaplan Meier curve for the occurrence of first crisis in MG adults

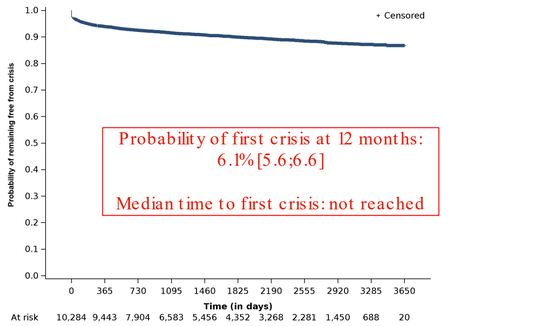
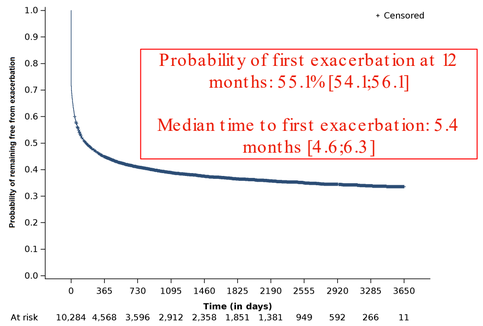


Figure 4: Kaplan Meier curve for the occurrence of first exacerbation in MG adults



Conclusion

- These real-world findings show rapid progression to gMG in most patients, followed by a slower but continued disease evolution, with a significant proportion ultimately developing refractory disease.
- Most of the patients also experience first exacerbation (including crisis, which represent severe events requiring intensive care) within one year of diagnosis, underscoring the need for early and sustained disease control.

Conflicts of Interest

Thierry Gendre: consulting fees from J&J, UCB, and Amgen; paid oral presentations from Argenx and CSL Behring; conference expenses from Alexion. Didier Theis and Jean-Baptiste Noury: consulting fees from J&J. Erika Guyot, Maeva Nolin, Manon Belhassen employees of Epimentis (PELyon) Ingrid Rodriguez, Julia Meijer, Laurène Gautier and Julien Dupin: employees of J&J. The study is sponsored by J&J.

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