

Reproducible and Sustained Response to Prolonged-Release Fampridine in Severe GAA-FGF14 Ataxia: A Longitudinal Single-Patient Observation

Claudio Marcello Solaro

Ente Ospedaliero Ospedali Galliera

Novella Pretti

`novella.alessandra.pretti@unito.it`

Ente Ospedaliero Ospedali Galliera

Case Report

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Abstract

Background

GAA-FGF14 ataxia (SCA27B) is a late-onset hereditary cerebellar ataxia for which aminopyridines are emerging as symptomatic treatments. Evidence of treatment response is increasing, but longitudinal observations in patients with severe disability remain limited.

Case presentation:

We report a 63-year-old woman with genetically confirmed GAA-FGF14 ataxia and severe cerebellar disability, including wheelchair dependence and marked impairment of gait, stance, upper-limb coordination, and activities of daily living. Prolonged-release fampridine 10 mg twice daily was assessed using a predefined OFF–ON–OFF–ON sequence, followed by 52 weeks of continuous treatment. Outcomes included the Scale for the Assessment and Rating of Ataxia (SARA), Nine-Hole Peg Test, Box and Block Test, MAM-36, Barthel Index, and maximum walking distance.

Results

After four weeks of treatment, SARA decreased from 35 to 18, with marked improvements in upper-limb dexterity, functional status, and walking ability. Following treatment withdrawal, SARA returned to 35 and other outcomes deteriorated to approximately baseline levels. Rechallenge reproduced the initial response, with SARA again reaching 18 and parallel multidomain improvements. After 52 weeks of continuous treatment, SARA remained at 18, while upper-limb dexterity and walking distance showed further improvement.

Conclusions

This case documents a marked, reproducible, and sustained multidomain response to prolonged-release fampridine in severe GAA-FGF14 ataxia. The repeated OFF–ON–OFF–ON pattern supports a treatment-associated response and illustrates the potential value of repeated dechallenge/rechallenge and complementary functional measures for assessing individual treatment responsiveness.

Introduction

GAA-FGF14 ataxia, historically referred to as spinocerebellar ataxia type 27B (SCA27B), is caused by a heterozygous intronic GAA repeat expansion in the FGF14 gene. It is a frequent genetic cause of late-onset cerebellar ataxia, with a predominantly pancerebellar phenotype that may be accompanied by sensory deficits and other extracerebellar features. Disease progression is generally slow, although

substantial interindividual variability in clinical phenotype and functional disability has been described [1].

Aminopyridine (4-AP) is a voltage-gated potassium-channel blocker, acting predominantly on Kv1 channels, have a long history of clinical investigation in neurological disorders, including Lambert–Eaton myasthenic syndrome, in which 3,4-diaminopyridine was shown to improve motor and autonomic deficits [2]. Prolonged-release fampridine has subsequently been established as a symptomatic treatment for walking impairment in multiple sclerosis [3].

GAA-FGF14 ataxia is increasingly recognized as a potentially pharmacologically responsive hereditary ataxia and 4- AP has been investigated as a symptomatic treatment. In GAA-FGF14 ataxia, small series and single-patient studies have reported improvements in ataxia-related symptoms and gait performance, including treatment-associated changes documented using prospective ON/OFF assessments [1, 4]. Pellerin et al. investigated a large cohort of patients with idiopathic downbeat nystagmus and found that FGF14 GAA expansions were frequent in this population. Among expansion carriers, both clinician-reported and self-reported responses to 4-aminopyridine were more frequent than in patients without the expansion, providing preliminary evidence of treatment responsiveness in GAA-FGF14 disease [5]. These observations, together with evidence from multiple sclerosis, suggest that repeated ON/OFF assessment may provide a useful framework for characterizing individual treatment responsiveness to aminopyridines.

The distinction between immediate-release 4-aminopyridine and prolonged-release fampridine is relevant, as both contain the same active molecule but differ in their release characteristics and pharmacokinetic profiles. Evidence regarding aminopyridine responsiveness in GAA-FGF14 ataxia remains limited, particularly in patients with severe baseline disability. Moreover, previous reports have focused primarily on specific aspects of treatment response, such as global ataxia severity or gait performance. A predefined longitudinal design incorporating treatment exposure, withdrawal, and reintroduction, together with multidomain clinical assessment, may provide a more comprehensive approach to identifying and confirming individual treatment responsiveness.

Here, we describe a patient with severe GAA-FGF14 ataxia who showed a marked response to prolonged-release fampridine 10 mg twice daily. Treatment response was evaluated longitudinally across multiple clinical and functional domains using a predefined OFF–ON–OFF–ON sequence, followed by 52 weeks of continuous treatment.

Case Presentation

A 63-year-old woman was evaluated for a progressive cerebellar syndrome with onset in 2021, at 58 years of age and with a disease duration of 5 years. At the time of baseline assessment, the severity of the motor impairment had resulted in wheelchair dependence. Neurological examination demonstrated severe axial and segmental cerebellar dysfunction, with prominent bilateral postural and kinetic tremor involving the upper limbs. Impairment of deep sensory modalities was also documented. No clinically

evident ocular motor abnormalities were observed. A first-degree relative, the patient's sister, had a clinically similar disorder, supporting an autosomal dominant pattern of inheritance. Genetic testing identified a heterozygous pathogenic GAA repeat expansion in FGF14, confirming the diagnosis of GAA-FGF14 ataxia/SCA27B. The patient's clinical phenotype was characterized by severe impairment of gait, stance, upper-limb coordination, and activities of daily living. Relevant coexisting medical conditions included diabetes mellitus, cardiomyopathy.

Treatment and Longitudinal Assessment

Treatment with prolonged-release fampridine (Fampyra) was initiated at a dose of 10 mg twice daily [6].

Clinical status was assessed at predefined time points: baseline before treatment initiation (T0, OFF treatment), 4 weeks from baseline (T1, ON treatment), 6 weeks from baseline (T2, OFF treatment), 8 weeks from baseline (T3, ON treatment), and 52 weeks from baseline (T4, ON treatment) (Fig. 1).

Neurological severity was assessed using the Scale for the Assessment and Rating of Ataxia (SARA). Upper-limb dexterity was evaluated using the Nine-Hole Peg Test (9HPT) and the Box and Block Test. Functional status was assessed using the MAM-36, and Barthel Index. Maximum walking distance was also recorded.

Results

The patient showed a marked, multidomain, and reproducible clinical response to prolonged-release fampridine (Table 1; Fig. 1). Following treatment initiation, substantial improvements were observed across neurological, upper-limb dexterity, functional status, and walking outcomes. At T1 (4 weeks from baseline, ON treatment), the SARA score decreased from 35 at baseline to 18, accompanied by marked improvements in 9HPT and Box and Block performance, MAM-36 and Barthel Index scores, and maximum walking distance.

At T2 (6 weeks from baseline, OFF treatment), the clinical improvement was lost, with all outcome measures returning to or approaching baseline values (Table 1; Fig. 1).

At T3 (8 weeks from baseline, ON treatment), fampridine treatment resulted in a response closely reproducing that observed during the initial treatment phase. Neurological and functional outcomes again improved substantially across all assessed domains, supporting the reproducibility of the treatment-associated response.

At T4 (52 weeks from baseline, ON treatment), the clinical benefit was maintained. SARA remained at 18, while upper-limb dexterity and maximum walking distance showed further improvement; functional measures remained stable (Table 1; Fig. 1).

Overall, the longitudinal assessment demonstrated a marked and multidomain ON/OFF response, with loss of benefit at T2, reproducibility of the response at T3, and sustained clinical improvement at T4.

Prolonged-release fampridine was well tolerated throughout the observation period, with no clinically relevant adverse events or treatment interruptions reported.

Table 1
Longitudinal clinical outcomes

Outcome measure	T0 OFF	T1 ON, 4 weeks	T2 OFF, 6 weeks	T3 ON, 8 weeks	T4 ON, 52 weeks
SARA	35	18	35	18	18
9HPT right	> 180 s	32 s	> 180 s	32 s	30 s
9HPT left	> 180 s	38 s	> 180 s	38 s	36 s
Box and Block right	2	14	2	14	16
Box and Block left	2	16	1	16	18
MAM-36	0	77	0	77	77
Barthel Index	0	65	0	65	65
Walking distance	0 m	10 m	0 m	8 m	12 m

Discussion

This longitudinal observation documents a marked, reproducible, and sustained response to prolonged-release fampridine in a patient with severe, genetically confirmed GAA-FGF14 ataxia. The response was characterized by a substantial reduction in SARA score, accompanied by improvements in upper-limb dexterity, functional status, and walking ability. Importantly, the predefined OFF–ON–OFF–ON design allowed treatment responsiveness to be assessed longitudinally within the same patient, with the initial response, loss of benefit during treatment withdrawal, and subsequent reproducibility after treatment reintroduction providing complementary evidence of a treatment-associated effect.

These findings are consistent with and extend previous observations of aminopyridine responsiveness in GAA-FGF14 ataxia. Wilke et al. reported a treatment response relevant to everyday living in six of seven treated patients and described three prospective n-of-1 treatment experiences using an ON/OFF design, in which symptomatic improvement during treatment was lost during treatment withdrawal [1]. Seemann et al. subsequently evaluated a patient receiving extended-release 4-aminopyridine 10 mg twice daily using prospective assessments before treatment, after 21 months of continuous treatment, and after a 20-hour treatment interruption. Quantitative gait measures demonstrated treatment-related ON/OFF differences, particularly during real-life walking [4]. Caneda et al. more recently documented an acute and reproducible ON/OFF response to immediate-release 4-aminopyridine, with improvement evident

approximately 40 minutes after administration and largely disappearing within 3–4 hours [7]. In a large cohort of patients with idiopathic DBN, Pellerin et al. found that FGF14 GAA expansion carriers showed more frequent clinician-reported and self-reported responses to 4-aminopyridine than non-carriers, providing preliminary evidence of treatment responsiveness in GAA-FGF14 disease [5].

In multiple sclerosis, responder-based treatment paradigms have likewise been used to identify patients showing consistent improvement during fampridine exposure compared with off-treatment assessments [3].

In light of these observations, the present case illustrates a structured approach to assessing individual treatment responsiveness in GAA-FGF14 ataxia. Rather than relying solely on a prolonged pre–post treatment comparison, the predefined OFF–ON–OFF–ON sequence incorporated an early assessment of treatment response followed by withdrawal and reintroduction. This approach may be particularly informative for symptomatic treatments with a rapid and reversible pharmacological effect, as it allows an initial indication of responsiveness to be obtained relatively early and subsequently tested within the same individual. In the present patient, clinically meaningful improvement was already evident at the first ON assessment at 4 weeks despite severe baseline disability, while the subsequent OFF and ON assessments provided an internal confirmation of the response. Importantly, this case does not establish an optimal assessment interval or demonstrate that longer observation is unnecessary; rather, it suggests that a predefined ON/OFF framework may provide a practical strategy for early identification and confirmation of individual treatment responsiveness.

The present case also adds several clinically relevant features to the existing literature. The patient had severe baseline disability, including wheelchair dependence and marked impairment of both upper- and lower-limb function, yet demonstrated a substantial response across multiple motor and functional domains. The use of complementary measures of ataxia severity, upper-limb dexterity, activities of daily living, and walking ability allowed the treatment-associated changes to be captured beyond a single outcome measure. This multidomain assessment may be particularly relevant when applying an ON/OFF design, because concordant changes across different functional domains strengthen the interpretation of an individual response. Importantly, previous n-of-1 observations have already documented responses to both immediate- and extended-release 4-aminopyridine [1, 4]. Therefore, the distinctive feature of the present case is not the prolonged-release formulation itself, but the combination of severe baseline disability, multidomain assessment, a predefined repeated OFF–ON–OFF–ON design, and long-term follow-up.

The benefit observed at T3 was maintained during 52 weeks of continuous treatment. At T4, SARA remained at 18, while upper-limb dexterity and maximum walking distance showed further improvement and functional measures remained stable. This longitudinal follow-up complements the short-term ON/OFF assessment by showing persistence of the observed symptomatic benefit during continued treatment. However, the sustained response should not be interpreted as evidence of a disease-modifying effect. The available data are more consistent with persistent symptomatic benefit during

treatment, and whether such long-term responses are representative of patients with GAA-FGF14 ataxia more broadly remains to be established.

The severity of the baseline phenotype should also be considered when interpreting the findings. GAA-FGF14 ataxia is generally characterized by slow progression, and the cohort reported by Wilke et al. showed a mean annual increase in SARA of approximately 0.29 points, with no patient exceeding a SARA score of 18 [1]. In the present patient, diabetes mellitus and cardiomyopathy may have contributed to the marked baseline functional impairment. Nevertheless, the magnitude and reversibility of the changes observed across multiple outcome measures, together with their reproducibility after treatment reintroduction, are difficult to attribute to the natural history of the underlying disorder alone.

This interpretation should be tempered by the inherent limitations of a single-patient observation. There was no blinded placebo-controlled phase, and learning effects, motivation, rehabilitation, or changes in general condition may have influenced clinical assessments. Accordingly, the present findings should be interpreted as supportive evidence of individual treatment responsiveness rather than proof of efficacy. Nevertheless, the predefined OFF–ON–OFF–ON sequence, the concordance of changes across multiple outcome measures, and the subsequent 52-week follow-up provide a coherent longitudinal framework for characterizing treatment response in this patient.

Conclusion

This longitudinal single-patient observation documents a marked, reproducible, and sustained response to prolonged-release fampridine in severe GAA-FGF14 ataxia. The predefined OFF–ON–OFF–ON design may represent a potential approach for the early identification and confirmation of individual treatment response, warranting further evaluation in larger prospective cohorts.

Declarations

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Ethics. Ethical approval was granted by the Local Ethical Committee of Regione Liguria.

Consent to participate. Informed consent was obtained from the participant described in this case report.

Consent to publish. Patient signed informed consent regarding publishing their data.

Data. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contribution. Conceptualization, methodology, investigation: Claudio Solaro; Writing - original draft preparation: Novella Pretti. Both authors have revised and agreed to the published version of the manuscript.

References

1. Wilke C, Pellerin D, Mengel D, Traschütz A, Danzi MC, Dicaire MJ, Neumann M, Lerche H, Bender B, Houlden H, RFC1 study group, Züchner S, Schöls L, Brais B, Synofzik M. GAA-FGF14 ataxia (SCA27B): phenotypic profile, natural history progression and 4-aminopyridine treatment response. *Brain*. 2023;146(10):4144–57. 10.1093/brain/awad157.
2. 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(23):1567–71. 10.1056/NEJM198912073212303.
3. Goodman AD, Brown TR, Krupp LB, Schapiro RT, Schwid SR, Cohen R, Marinucci LN, Blight AR, Fampridine. MS-F203 Investigators. Sustained-release oral fampridine in multiple sclerosis: a randomised, double-blind, controlled trial. *Lancet*. 2009;373(9665):732–8. 10.1016/S0140-6736(09)60442-6.
4. Seemann J, Traschütz A, Ilg W, Synofzik M. 4-Aminopyridine improves real-life gait performance in SCA27B on a single-subject level: a prospective n-of-1 treatment experience. *J Neurol*. 2023;270(11):5629–34. 10.1007/s00415-023-11868-y.
5. Pellerin D, Heindl F, Wilke C, Danzi MC, Traschütz A, Ashton C, Dicaire MJ, Cuillerier A, Del Gobbo G, Boycott KM, Claassen J, Rujescu D, Hartmann AM, Zuchner S, Brais B, Strupp M, Synofzik M. GAA-FGF14 disease: defining its frequency, molecular basis, and 4-aminopyridine response in a large downbeat nystagmus cohort. *EBioMedicine*. 2024;102:105076. 10.1016/j.ebiom.2024.105076.
6. European Medicines Agency. Fampyra (fampridine) – product information. <https://www.ema.europa.eu/en/medicines/human/EPAR/fampyra>
7. Caneda C, Bertoncello E, Peghin A, Satolli S, Santorelli FM, Tinazzi M, Di Vico IA. (2026), ON/OFF Phenomenon in 4-Aminopyridine Therapy in Spinocerebellar Ataxia 27B: Therapeutic and Diagnostic Insights. *Mov Disord Clin Pract*. <https://doi.org/10.1002/mdc3.70692>

Figures

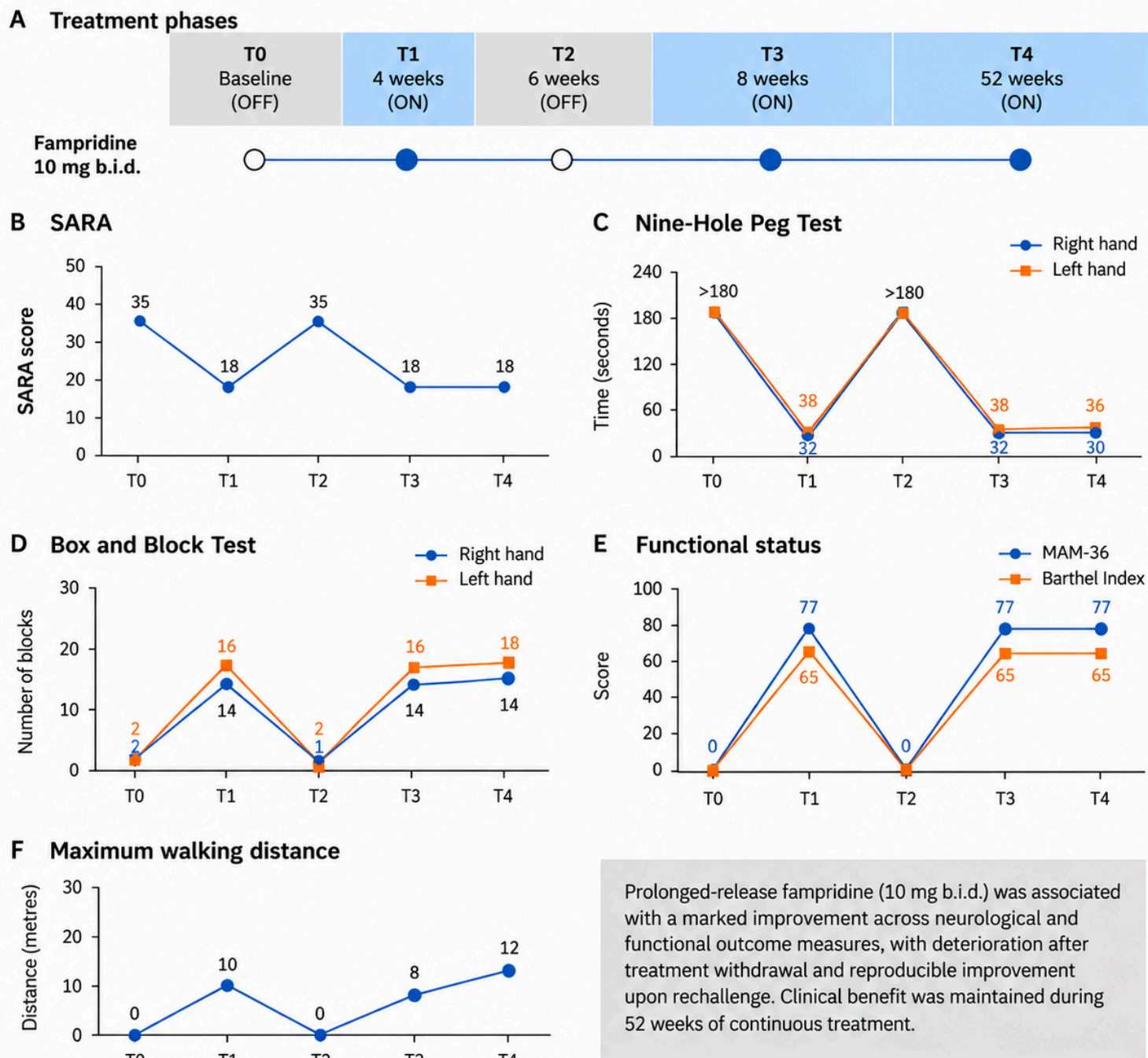


Figure 1

Longitudinal ON/OFF response to prolonged-release fampridine.

A: Treatment phases; **B:** Scale for the Assessment and Rating of Ataxia (SARA); **C:** Nine-Hole Peg Test (9HPT); **D:** Box and Block Test; **E:** Functional status (MAM-36 and Barthel Index); **F:** Maximum walking distance.