Pegvaliase therapy for phenylketonuria: Real-world case series and clinical insights

Iris Scala [a], Lucia Brodosi [b,c,*], Daniela Gueraldi [d], Filippo Manti [e], Valentina Rovelli [f], Juri Zuvadelli [f], Giulio Agnelli [b], Chiara Cazzorla [d], Francesca Nardecchia [e], Antonina Giammanco [g], Giacomo Biasucci [h,i]

[a] Clinical Genetics Unit, Department of Maternal and Child Health, Federico II University Hospital, Naples, Italy
[b] Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy
[c] Clinical Nutrition and Metabolism Unit, IRCCS AOUBO, Bologna, Italy
[d] Division of Inherited Metabolic Diseases, Department of Women's and Children's Health, University Hospital of Padova, Padova, Italy
[e] Unit of Child Neurology and Psychiatry, Department of Human Neuroscience, University of Rome La Sapienza, Rome, Italy
[f] Clinical Department of Pediatrics, San Paolo Hospital, ASST Santi Paolo e Carlo, University of Milan, Italy
[g] Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties, University of Palermo, Palermo, Italy
[h] Pediatrics & Neonatology Unit, Guglielmo da Saliceto Hospital, Piacenza, Italy
[i] Department of Medicine and Surgery, University of Parma, Parma, Italy

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ABSTRACT

Objective: The aim of this study is to present a series of case studies on the real-life use of pegvaliase in Italy in managing patients affected by phenylketonuria (PKU) and provide practical insight and support to healthcare professionals currently approaching and facing this novel enzyme substitution therapy.

Methods: A panel of 11 PKU experts from seven leading Italian treatment centers attended online virtual meetings with the aim of reviewing their clinical and practical experiences with pegvaliase based on occurred cases. In selecting the cases, specific consideration was given to the nationwide representation of the centers involved and to the number of patients with PKU managed. Cases were thoroughly reviewed, with comprehensive discussions enabling the identification of key take-home messages regarding pegvaliase therapy.

Results: The panel discussed 18 cases, 11 males and 7 females (age range 17–43 years). At the last follow-up (up to 111 weeks after pegvaliase initiation), 11 out of 18 patients (61%) reached Phe levels below 600 μmol/l. Outcomes varied significantly across cases. All cases underscore the potential of pegvaliase in reducing Phe levels, enhancing the quality of life, and promoting social skills and independence. Additionally, the cases highlight the challenges associated with pegvaliase therapy, including managing adverse events and ensuring patient motivation and adherence.

Conclusion: This is the first report about the Italian experience of managing patients affected by PKU with pegvaliase. Given the limited real-world data on the use of pegvaliase in PKU management, this case series offers valuable insights into the practical implementation and management of pegvaliase therapy in this Country. Continued research and data collection will be crucial to confirm and progress with this treatment. Despite potential challenges, pegvaliase therapy represents a substantial promise in managing PKU in Italy. Patient education, personalized treatment approaches, and careful monitoring are important to ensure optimal patient outcomes.

1. Introduction

Phenylketonuria (PKU) was the first disorder to be identified through newborn screening (NBS) [1]. The early detection of elevated phenylalanine (Phe) by NBS allows for the prompt implementation of a lifelong, carefully monitored low-Phe diet, combined with a Phe-free protein substitute [2] to avert serious cognitive and neurological outcomes ([3,4]; [5]). However, this diet can be unpalatable and unsociable

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([6]), and compliance is often poor [7].

Even with early and effective PKU treatment, adults may experience neurocognitive problems, low self-esteem, and social disengagement ([8,9]). Furthermore, dietary therapy discontinuation and loss at follow-up indicate the need for innovative therapies.

To date, the only available pharmacological therapies for PKU are supplementation with sapropterin dihydrochloride (the synthetic form of BH4) and enzyme substitution therapy with pegvaliase (Palynziq®, BioMarin Pharmaceutical Inc., Novato, CA, USA), a PEGylated form of phenylalanine ammonia-lyase. Administered subcutaneously, pegvaliase converts phenylalanine to ammonia and trans-cinnamic acid [10], regardless of residual phenylalanine hydroxylase (PAH) enzymatic activity [5]. Another drug for PKU treatment is under development. PTC923, formerly known as CNSA-001, is an oral formulation of sepiapterin, a natural precursor of BH4, which has been shown to induce larger increases in circulating BH4 compared to sapropterin dihydrochloride [11].

Pegvaliase was approved for the treatment of adult patients with PKU with blood Phe levels above 600 µmol/l by the United States Food and Drug Administration (FDA) in May 2018 (https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=88195. Accessed July 20, 2023), and for the treatment of PKU patients aged ≥16 years with blood Phe >600 µmol/l by the European Medicines Agency (EMA) in May 2019 (https://www.ema.europa.eu/en/medicines/human/EPAR/palynziq. Accessed July 20, 2023). Pegvaliase is administered following an induction, titration, and maintenance (I/T/M) dosing schedule. Dosing starts with low-dose injections for 4 weeks (2.5 mg/week, induction period), followed by gradual titration to a maintenance dose of up to 60 mg daily, based on individual patient tolerability and drug efficacy [12].

Pegvaliase therapy promises to be more effective than diet alone, or diet + sapropterin combination therapy for reducing Phe levels, especially in classical PKU (Zori, Ahring et al., 2019). However, as pegylated phenylalanine ammonia-lyase is a bacterial protein, pegvaliase therapy may cause a variety of immunogenic responses (Gupta, Lau et al., 2018), mostly occurring within the first 6 months of treatment [10]. The most common AEs are arthralgia (70.5%), injection site reaction (62.1%), injection site erythema (47.9%), and headache (47.1%). Acute systemic hypersensitivity events (including anaphylaxis) may also occur, albeit rarely [10]. To reduce the occurrence of severe AEs, pegvaliase therapy is initiated and titrated slowly and requires premedication with H1 and H2 antagonists as well as antipyretics before each pegvaliase dose during the induction and titration phases from the day before the first administration [13]. Patients are also required to carry autoinjectable epinephrine [14]. During maintenance, premedication is administered based on patient tolerability [13].

Clinicians with proven experience in managing PKU patients with enzyme substitution therapy have drafted a consensus statement with recommendations on the use of pegvaliase [14].

In Italy, there are specific guidelines for using pegvaliase to manage PKU [13]. However, there are differences between the summary of pegvaliase product characteristics drafted by the Italian medicine Agency (AIFA) and that of other countries for certain aspects. For example, in Italy it is mandatory for patients undergoing pegvaliase treatment to be assisted by a caregiver/observer. The caregiver must be trained to recognize the signs and symptoms of acute systemic hypersensitivity reactions, use adrenaline injection devices correctly in emergencies, and understand the importance of seeking immediate medical assistance.

Despite the availability of guidelines and recommendations, real-world data regarding pegvaliase use are limited. There are currently no reports on the Italian experience with pegvaliase in clinical practice. To address this gap and considering the importance of case reports in describing the outcomes of novel therapies ([15], we present a case series on the use of pegvaliase in the management of patients with PKU in Italy. The objective of this manuscript is to support colleagues who

aim to manage PKU with pegvaliase, based on the clinical experience of Italian healthcare providers with this novel enzyme substitution therapy.

2. Materials and methods

In October 2022, a panel of 11 PKU experts from seven specialized Italian centers with extensive experience in treating PKU patients attended a virtual clinical practice review meeting. The meeting was held in collaboration with BioMarin Pharmaceutical Inc. and the independent consulting agency Poliste (Cagliari, Italy). The panel included three pediatricians (GB, IS, VR), two nutrition science clinicians (LB, GA), one dietitian (JZ), three child neuropsychiatrists (FM, FN, DG), one psychologist (CC), and an internal medicine clinician (AG).

During the meeting, the PKU experts discussed key aspects of enzymatic therapy in PKU patients by presenting several clinical cases drawn from their own experience. In selecting the cases, specific consideration was given to the nationwide representation of the centers involved and to the number of patients with PKU they managed. Informed consent was obtained during data collection and all data were anonymized. Data collection and presentation were conducted in accordance with ethical standards. This manuscript provides case summaries and key learnings from each case.

3. Results

3.1. Patient characteristics

The panel discussed a total of 18 cases, including 11 males and 7 females (age range 17 to 43 years). Among the patients, two were brothers (cases 5 and 6). Genetic information was available from 12 patients. All patients treated with pegvaliase had pre-treatment Phe levels exceeding 600 µmol/l and were older than 16 years old, as per label requirements.

Patients were already experiencing a wide range of comorbidities at the start of the pegvaliase intervention, including neuropsychological and psychopathological comorbidities such as mild-to-moderate cognitive disability (3/18), concentration/problem-solving deficits (2/18), and anxiety (4/18). Of the patients, 12 were on a restricted diet. Among these individuals, the majority (10 out of 12) reported difficulties in maintaining their dietary regimen. The patients' BMIs ranged from 17.3 to 36.4 kg/m^2.

Patients initiated pegvaliase treatment for various reasons, including feelings of guilt for the lack of Phe control, dissatisfaction with previous treatment outcomes, difficulty in controlling Phe levels, a desire for dietary freedom and improved metabolic control, and social factors such as the desire to get married or participate normally in social interactions around food. While none of the patients were being treated with sapropterin dihydrochloride when pegvaliase treatment was initiated, some may have had a sapropterin challenge in the past.

Most of the patients (17/18) received premedication with a combination of H1 (cetirizine or fexofenadine) and H2 receptor antagonists (famotidine), while one patient received only H1 antagonists. Additionally, 17 out of 18 patients received antipyretics (acetaminophen). Out of the 18 patients, six required topical steroids to manage AEs at the injection site, such as erythema and swelling. Among these six patients, two also received steroids for the treatment of arthralgia. Detailed information on premedication is presented in Supplementary Table 1 and in the Supplement.

Before treatment, the patients' blood Phe levels ranged from 685 µmol/l to 1772 µmol/l, with an average of 1084 µmol/l. At the last follow-up, their blood Phe levels ranged from 28 µmol/l to 1562 µmol/l (average: 617 µmol/l). The patients' natural protein intake increased slightly from an average of 45 g/day (range 6–120 g/day) before treatment to an average of 61 g/day at the last follow-up.

Their medical food protein intake decreased from an average of 35 g/

day before treatment (range:0–90 g/day) to an average of 14 g/day (range: 0–90 g/day) at the last follow-up. The patients' total protein intake remained relatively stable, with an average of 75 g/day (range: 32–120 g/day) before treatment and 76 g/day (range: 32–120 g/day) at the last follow-up.

The patients' baseline and treatment characteristics are summarized in Supplementary Table 1 and their extended case reports are provided in the supplementary file.

3.2. Induction/titration

The initial plasma Phe levels varied between 685 μmol/l and 1772 μmol/l. For patients for whom information about phenylalanine tolerance was available, the range was 340 mg/day to 1178 mg/day. All patients followed the standard I/T/M protocol described in the pegvaliase summary of product characteristics (available at https://www.ema.europa.eu/en/documents/product-information/palynziq-epar-product-information_en.pdf. Accessed July 20, 2023). One patient (case 11) experienced dose interruption after 7 weeks of treatment due to AEs. After one month, treatment was re-initiated with a modified protocol (extended induction/titration).

Twelve out of 18 patients experienced AEs, including injection site reactions, erythema, swelling, and arthralgia. However, only one patient required a temporary dose interruption due to recurrent AEs.

3.3. Maintenance

At the time of this paper's preparation, 11 out of 18 patients (61%) had achieved stable Phe levels within the therapeutic range. This was accomplished within 11 to 48 weeks, with effective doses ranging from 20 to 40 mg.

Three patients experienced a 'transitory' response, with Phe levels not yet stabilized within the therapeutic range. Three patients have not yet responded to the treatment, and one discontinued before reaching the maintenance dose.

Patients were maintained on doses between 20 and 40 mg/day. At the last follow-up, most were in the maintenance phase of treatment, with blood Phe levels between 61 and 1425 μmol/l and total protein intake from 32 to 140 g/day (Table 1).

4. Discussion

4.1. Educating patients and managing therapy with pegvaliase

Pegvaliase enzyme substitution therapy can be prescribed to patients with PKU aged 16 years and older who are unable to maintain blood Phe levels below 600 μmol/l despite dietary treatment and other available medications. However, pegvaliase therapy is reported to be associated with commonly occurring AEs, such as injection site reactions, arthralgia, and occasionally, type III hypersensitivity [10]. Hypersensitivity AEs usually spike during the induction/titration phase before subsiding during the maintenance phase [16].

The associated risks of this treatment require comprehensive patient education. Patients need to be fully informed about the benefits, potential risks, and administration of the therapy, including the rare but serious risk of anaphylaxis [14]. As illustrated in Case 1, it is important to bridge the gap in understanding between patients and healthcare providers. A comprehensive education aids in the effective management of both the benefits and dangers of pegvaliase treatment and can be achieved through preliminary meetings with the patient and their caregivers/observers, supplemented by appropriate educational materials [14]. It is worth remembering that the Italian Medicine Agency (AIFA) requires pegvaliase patients to be supported by a caregiver/observer who must be trained to recognize signs and symptoms of an acute systemic hypersensitivity reaction and to act accordingly.

4.2. Administration of pegvaliase and management of adverse events

Administering pegvaliase requires thoughtful consideration of patient-specific needs. Usually, treatment starts with the administration of a 2.5 mg dose weekly for 4 weeks during the induction phase. Then a gradual dose increase occurs in the titration phase (2.5 mg twice a week for one week, then 10 mg once weekly for a week, followed by 10 mg twice weekly for a week, then 10 mg four times a week for a week, and finally, 10 mg/day for a week). On completion of the titration phase, the daily dose increases to 20 mg for the maintenance phase, as per the pegvaliase summary of product characteristics (SmPC). In our case series, the time required to reach a maintenance dose of 20 mg varied. For instance, cases 5, 8, 9, 12, 14, and 15 needed >9 weeks to reach the 20 mg dose.

An extended induction/titration phase has already been described by other authors [17], who attributed the extension to AEs occurring during these phases. AEs were mitigated by extending the induction and titration protocols. Our observations support this hypothesis and further

Table 1
Blood phenylalanine (Phe) and protein intake at pre-pegvaliase baseline and last follow-up.

Case	Blood Phe, μmol/l		Natural protein intake, g/day		Medical food protein, g/day		Total protein intake, g/day	
	Pre-pegvaliase baseline	Last follow-up	Pre-pegvaliase baseline	Last follow-up	Pre-pegvaliase baseline	Last follow-up	Pre-pegvaliase baseline	Last follow-up
1	685	82	9	65	60	0	69	65
2	1008	72	55	65	0	0	55	65
3	1149	845	6	74	32	0	48	74
4	752	323	20–35	82	70	0	90–105	82
5	878	162	75–100	75–100	0	0	75–100	75–100
6	1320	1024	100	100	0	0	100	100
7	1772	692	100–120	100–120	0	0	100–120	100–120
8	1236	1425	66–140	66–140	0	0	66–140	66–140
9	768	583	15–41	15–41	50	50	65–91	65–91
10	1510	61	55	55	45	45	100	100
11	1342	1562	23–29	23–29	90	90	113–119	113–119
12	1126	62	16–20	60–70	45	0	61–65	60–70
13	987	455	25–30	25–30	60	60	85–90	85–90
14	1256	1193	55–60	55–60	0	0	55–60	55–60
15	1302	1128	14–26	14–26	18	18	32–44	32–44
16	1161	257	9	9	65	65	74	74
17	1546	69	31	70	55	0	86	70
18	731	949	15.8	74	50	0	65.8	74

suggest the need for a personalized approach to each patient. Each case may highlight the need for strict follow-up to avoid potential risks of serious adverse events (SAEs) and to adjust dosages accordingly, such as by introducing steroids when necessary.

Therefore, the I/T/M dosing regimen could be adjusted based on a patient's response to pegvaliase and dietary protein intake. With our cases, the maximum pegvaliase doses varied, with 40 mg in cases 1, 2, 3, 5, 6, 7, 8, 9, 13, and 60 mg in case 18. It is important to mention that aside from case 13 (where the maximum dose was reached after 42 weeks), the time to maximum daily dose was achieved between 22 and 29 weeks from the start of therapy - a time shorter than what has been reported by other authors [18] and also shorter than the 33 weeks specified in the prescribing label.

AEs were common and sometimes required adjustments in the induction schedule, as seen in cases 5, 8, and 9, or led to temporary interruptions in therapy. For instance, case 11 required a suspension in therapy and an extension of the induction/titration phase.

Best practices and strategies to mitigate AEs have been discussed elsewhere [16,14]. As per the prescribing label, most patients in this report were premedicated with H1 + H2-receptor antagonists (cetirizine 10 mg/day, or fexofenadine 120 mg/day, or fexofenadine 120 mg twice a day and famotidine 40 mg/day), and antipyretic drugs. However, patient 16 was premedicated with only an H1 antagonist (cetirizine 10 mg/day). This deviation from the prescribing label is justified by real-world evidence showing that H1 antagonists are likely the most effective in reducing AEs [16]. Therefore, the use of H2 antagonists is not strictly recommended and various centers prescribe only one H1 receptor antagonist [19].

Premedication may be discontinued upon reaching the maintenance phase or when the patient experiences no AEs. Hypersensitivity reactions may be managed by prescribing steroids over a short period, as done in cases 5, 9, 12 and 15.

4.3. Psychological features and patient well-being

Psychological well-being is a crucial consideration when initiating pegvaliase treatment. Some patients may experience acute anxiety with somatic symptoms, which can be challenging to distinguish from hypersensitivity reactions such as throat and chest tightness, dyspnea, and cardiac symptoms. More vulnerable individuals may grapple with anxiety and other psychological issues, potentially impeding their engagement in therapy or even posing a barrier to treatment [20].

A multidisciplinary management approach can offer the necessary support to help patients overcome these challenges and maintain motivation. For example, patient 4 benefited from nutritional counseling and lost weight; patient 16 experienced a significant improvement in anxiety symptoms and attentional functions; and patients 17 and 18 achieved better social and relational outcomes, improving their overall quality of life.

A specific educational and psychological program can enable patients to successfully participate in therapy and achieve positive outcomes. For instance, patient 3 improved his attention and school performance and now participates in social events with friends. By addressing the psychological needs of patients, we can ensure they have the best possible experience with this new therapeutic option. Even when Phe levels normalize, it remains important to focus on patients' emotional aspects [13]. This approach is also vital for supporting patients in adhering to long-term therapy, which could potentially impact therapy engagement and outcomes. Therefore, it is critical to proceed cautiously during dose escalation and the maintenance period monitoring any emerging psychological factors [14].

4.4. PKU treatment and dietary considerations

The goal of PKU treatment is to strictly control blood Phe levels. The U.S. National Institute of Health (NIH) guidelines recommend a target range of 120–360 μmol/l for patients of all ages [20]. Meanwhile, European guidelines suggest a target of 120–360 μmol/l for patients younger than 12 years and 120–600 μmol/l for patients aged 12 years and older, to prevent neurodevelopmental derangement and impairment of neurocognitive function [1]. Pegvaliase treatment aims to reach these target levels through personalized dosing, which considers the patient's needs and response (cases 12 and 17), particularly in patients experiencing AEs, to prevent permanent discontinuation (case 11).

The wide array of individual responses and clinical courses presented here suggest that: (a) therapy outcomes should be evaluated considering biochemical parameters as well as the patient's quality of life and emotional and behavior symptoms, (b) given that patients treated with pegvaliase can achieve physiological levels of blood Phe, the normalization of blood Phe levels may be considered a therapeutic target; and (c) the long-term monitoring of anthropometric parameters and adequate body composition should be considered as a secondary objective, following diet liberalization.

Dietary management remains fundamental to PKU treatment, but adherence to a restrictive diet can be challenging [21,13,22]. On the other hand, successfully reducing Phe levels and liberalizing the diet can significantly enhance a patient's quality of life, enabling them to participate more freely in social activities, as demonstrated in case 3. Hence, achieving therapeutic efficacy with pegvaliase should go together with dietary adjustments, such as increasing natural protein intake and discontinuing the intake of hypoproteic food and medical formulas, as demonstrated in case 10. In patients on an almost unrestricted diet (case 17), blood Phe levels may drop suddenly, while in others, like case 6, levels may fluctuate if the diet remains unchanged. Therefore, frequent monitoring of Phe levels and diet is advisable. Case 18 highlights the psychological challenges of transitioning from a protein-restricted to a liberalized diet. As the patient's Phe levels decreased, they autonomously decided to liberalize their diet, but later struggled with diet management. This could have stemmed from the patient realizing the therapy's efficacy, making it difficult for them to continue bearing the burden of their disease.

4.5. Patient response time and expectation management

Interpreting the efficacy of pegvaliase treatment requires a nuanced understanding of the patient response. While it is true that at the time of writing this paper, only 11 out of 18 patients (61%) achieved efficacy, this does not fully capture the complexity of the treatment response. Many of the six patients who had not yet reached efficacy, with blood Phe levels still above 600 μmol/l, had already experienced a significant decrease from baseline. At least one patient's Phe levels dropped below 600 μmol/l before liberalizing their diet. None of the patients had been increased to the maximal possible dose of 60 mg/day, and one patient was still in the induction phase, making it premature to include them in the efficacy calculation. Only three patients (Cases 8, 14 and 15) had failed to respond to the pegvaliase treatment, but they had only been treated with a 20 mg per day dose.

Furthermore, the patients who had not yet reached efficacy were likely still adjusting to the optimal dose. These patients had been on the maintenance dose of 20 mg for a shorter period, necessitating longer-term follow-up and evaluation.

Enzymatic therapy can successfully reduce and normalize Phe levels in patients, leading to improvements in social skills and independence (case 7). However, treatment response can be unpredictable and may take a significant amount of time. In some instances, reaching the desired therapeutic target may take over 8 months (cases 5, 6, and 16). The scientific literature suggests that it may take up to 48 months of treatment before a response is observed. In our clinical experience, we emphasize the critical importance of patients, their families, and caregivers maintaining a clear understanding of the treatment timeline. This understanding is essential for managing expectations, sustaining motivation, and establishing a solid foundation for the effective management

of this shared medical journey. Addressing any feelings of frustration or disappointment that may arise during the course of treatment is pivotal for its ultimate success.

Pegvaliase treatment requires consistent monitoring and follow-up, from pre-treatment education to the maintenance phase. Therefore, it is essential to identify *a priori* patients who are psychologically prepared to adhere to this enzyme substitution therapy. A robust patient support program (case 2) could prove beneficial. In Italy, the figure of the caregiver/observer is mandatory for patients undergoing pegvaliase treatment. Patients with challenging behaviors and/or intellectual disabilities who are unable to self-administer the therapy will require the supervision of adequately chosen and trained caregivers/observers to provide the necessary support, as demonstrated in case 6.

Lastly, the clinical cases presented in this document represent a small sample of potential clinical scenarios and challenges associated with pegvaliase therapy. They do not fully generalize to larger patient populations or diverse clinical settings and should be interpreted as complementary to the results of clinical trials published to date.

5. Conclusion

Real-world data on the management of PKU patients with pegvaliase are still limited, and continued research and data collection are essential to further improve patient outcomes and the management of this challenging disorder. The cases presented here are drawn from the extensive clinical experience of Italian healthcare providers with pegvaliase and are intended to support colleagues aiming to manage PKU with this novel enzymatic therapy. Pegvaliase therapy is challenging due to its AE profile, the I/T/M schedule, and the delay in drug efficacy. However, it is also effective in reaching the therapeutic goal. At the last follow-up, 10 out of the 18 patients described in this study achieved blood Phe levels lower than 600 μmol/l.

The achievement of therapeutic efficacy is based on a patient's tolerability to pegvaliase and dietary protein intake and may require tailored therapy.

The effectiveness of enzymatic therapy can be unpredictable and may require a significant amount of time. Therefore, it is crucial to educate patients and their caregivers about pegvaliase treatment, its administration, and the potential risks of severe AEs. Patients should also be supported in learning more about their personal experiences in relation to the therapy, to help them implement new and more effective strategies. By providing patients with the necessary information and support, they can better manage their treatment and achieve positive outcomes.

Anxiety and other psychological factors may act as a barrier to the engagement of patients with therapy and to its success. The transition from a Phe-restricted diet to a normal diet is psychologically challenging, so patients may benefit from nutritional education and counseling. A multidisciplinary management approach and a specific educational and psychological program can enable patients to successfully participate in therapy and achieve the best possible outcomes with this new therapeutic option.

Author contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas, took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Declaration of competing interest

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgme.2024.108151.

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