Molecular Genetics and Metabolism Reports 28 (2021) 100790

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

Use of pegvaliase in the management of phenylketonuria: Case series of early experience in US clinics☆

Darius Adams [a], Hans C. Andersson [b], Heather Bausell [c], Kea Crivelly [b], Caroline Eggerding [d], Melissa Lah [e], Joshua Lilienstein [f], Kristin Lindstrom [g,*], Markey McNutt [h], Joseph W. Ray [i], Heather Saavedra [j], Stephanie Sacharow [k], Danielle Starin [l], Jennifer Tiffany-Amaro [m], Janet Thomas [n], Erika Vucko [c], Leah B. Wessenberg [o], Kaleigh Whitehall [f]

[a] Atlantic Health Morristown Medical Center, Morristown, NJ, USA
[b] Hayward Genetics Center, Tulane University Medical School, New Orleans, LA, USA
[c] Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA
[d] Cooper University Health Care, Camden, NJ, USA
[e] Indiana University School of Medicine, Indianapolis, IN, USA
[f] BioMarin Pharmaceutical Inc., Novato, CA, USA
[g] Phoenix Children's Hospital, Phoenix, AZ, USA
[h] University of Texas Southwestern Medical Center, Dallas, TX, USA
[i] University of Texas Medical Branch, Galveston, TX, USA
[j] The University of Texas Health Science Center at Houston - McGovern Medical School, Houston, TX, USA
[k] Boston Children's Hospital, Harvard Medical School, Boston, MA, USA
[l] Rare Disease Institute, Children's National, Washington, DC, USA
[m] St. Christopher's Hospital for Children, Philadelphia, PA, USA
[n] University of Colorado School of Medicine, Aurora, CO, USA
[o] OHSU Doernbecher Children's Hospital, Portland, OR, USA

ARTICLE INFO

Keywords:
Phenylketonuria
Case series
Pegvaliase
PEGylated phenylalanine ammonia lyase
PKU diet
Adverse events

ABSTRACT

Objective: To present a case series that illustrates real-world use of pegvaliase based on the initial experiences of US healthcare providers.

Methods: Sixteen healthcare providers from 14 centers across the US with substantial clinical experience in treating patients with phenylketonuria (PKU) with pegvaliase in the two-plus years since FDA approval (May 2018) provided cases that exemplified important lessons from their initial experiences treating patients with pegvaliase. Key lessons from each case and takeaway points were discussed in both live and virtual meetings.

Results: Fifteen cases of adults with PKU (eight males, seven females), representing a spectrum of age (18 to 53 years), previous PKU care, comorbidities, and socioeconomic situations were reviewed and discussed. Full extended case reports are included in the Supplement. The cases showed that treating patients with a daily injectable can be challenging due to a patient's financial problems, treatment challenges, and neuropsychological and psychiatric comorbidities, which can be identified before starting pegvaliase, but do not prohibit successful treatment. The authors agreed that patient education on adverse events (AEs), time to efficacy, dietary changes, and food preparation is an ongoing process that should start prior to initiating pegvaliase treatment. Treatment goals and planned dietary changes once efficacy is reached should be defined prior to treatment initiation and re-evaluated throughout the course of therapy. Each patient's titration schedule and dietary adjustments are unique,

Abbreviations: ACMG, American College of Medical Genetics and Genomics; AEs, adverse events; BH4, tetrahydrobiopterin; HCP, healthcare provider; I/T/M, induction, titration, and maintenance; PAH, phenylalanine hydroxylase; Phe, phenylalanine; PKU, phenylketonuria.

☆ All authors contributed equally, and are listed alphabetically.

* Corresponding author at: BioMarin Pharmaceutical Inc., 105 Digital Drive, Novato, CA 94949, USA.

E-mail addresses: Darius.Adams@atlantichealth.org (D. Adams), handers@tulane.edu, kcrivell@tulane.edu (H.C. Andersson), hbausell@luriechildrens.org (H. Bausell), mspurr@iu.edu (M. Lah), joshua.lilienstein@bmrn.com (J. Lilienstein), klindstrommd@gmail.com (K. Lindstrom), markey.mcnutt@utsouthwestern.edu (M. McNutt), jwray@utmb.edu (J.W. Ray), Heather.Saavedra@uth.tmc.edu (H. Saavedra), Stephanie.Sacharow@childrens.harvard.edu (S. Sacharow), Dstarin@childrensnational.org (D. Starin), Jennifer.tiffany-amaro@towerhealth.org (J. Tiffany-Amaro), Janet.Thomas@childrenscolorado.org (J. Thomas), evucko@luriechildrens.org (E. Vucko), bjornsko@ohsu.edu (L.B. Wessenberg), Kaleigh.Whitehall@bmrn.com (K. Whitehall).

https://doi.org/10.1016/j.ymgmr.2021.100790
Received 1 July 2021; Accepted 3 August 2021

depending on occurrence of AEs and individual goals of treatment. Despite the AE profile of pegvaliase, all but two patients remained motivated to continue treatment and achieved efficacy (except one patient in whom titration was still ongoing). AEs occurring early in the treatment pathway may require prolongation of the titration phase and/or concomitant medication use, but do not seem indicative of future tolerability or eventual efficacy. Close follow-up of patients during titration and maintenance to help with dietary changes is important. *Conclusion:* This case series provides real-world experience on the use of pegvaliase. Until data from registries and independent research become available, the data presented herein can support appropriate management of patients receiving pegvaliase in clinical practice.

1. Introduction

Phenylketonuria (PKU) is a genetic disorder caused by a deficiency of the enzyme phenylalanine hydroxylase (PAH), which converts phenylalanine (Phe) to tyrosine in the liver [1]. Reduction or absence of PAH activity results in elevated levels of Phe in the blood, tissues, and the brain, which can affect brain development and function. Even individuals with early-treated PKU can develop neurologic, cognitive, developmental, psychiatric, and behavioral problems if they are poorly-adherent to treatment [2,3].

Pegvaliase (Palynziq®, BioMarin Pharmaceutical Inc., Novato, CA, USA) is a novel enzyme substitution therapy for PKU that has been approved for adults in the United States (US) [4] and for patients ≥16 years of age in Europe [5] who have uncontrolled blood Phe concentrations >600 μmol/L on existing management. Pegvaliase is a PEGylated recombinant phenylalanine ammonia lyase enzyme that is administered via subcutaneous injection [6–8]. Pegvaliase treatment is carried out using an induction, titration, and maintenance (I/T/M) dosing schedule based on individual patient tolerability; dosing starts with a low dose (2.5 mg/week) induction period for several weeks, followed by gradual titration to a maintenance dose up to 60 mg daily [7].

Pegvaliase is the first therapeutic option that has the potential to lower blood Phe levels to normal ranges irrespective of residual PAH activity, tetrahydrobiopterin responsiveness (BH4; cofactor for PAH), or genotype (including double null genotypes) [6,9]. In the phase 3 PRISM-1 (NCT01819727) and PRISM-2 (NCT01889862) trials ($N = 261$), 68%, 61%, and 51% of adult patients reached blood Phe concentrations ≤600 μmol/L (recommended level for patients aged >12 years of age in the European guidelines [10]), ≤360 μmol/L (recommended level for all patients in the American College of Medical Genetics and Genomics [ACMG] guidelines [3]), and ≤120 μmol/L (the threshold defining hyperphenylalaninemia or upper limit of normal physiological levels), respectively, within 24 months of treatment [6]. Similarly, improvements from baseline assessments of inattention and mood outcomes were observed over 24 months of treatment [6]. The most common adverse events (AEs) reported in the PRISM studies were hypersensitivity reactions, i.e. arthralgia (70.5%), injection site reaction (62.1%), injection site erythema (47.9%), and headache (47.1%), with most AEs occurring in the first 6 months of treatment [6].

Prior to the commercial approval, a steering committee with extensive pegvaliase clinical trial experience drafted recommendations for the use of pegvaliase based on the existing evidence and their experience with pegvaliase during clinical trials [8]. Pegvaliase is a novel class of therapy and the management of treated patients requires a completely new but manageable paradigm for patient selection, expectation setting, patient and caregiver education, treatment planning, drug titration, management of AEs, dietary and lifestyle modification, and long-term management. Until large-scale registry data from industry or independent researchers become available, clinicians without pegvaliase experience may seek advice and support from colleagues who have successfully managed multiple patients on pegvaliase.

Published case reports are an important tool to share experiences with the broader medical community and generally the first type of real-world evidence available for novel therapies [11]. We present a case series that illustrates considerations for the real-world use of pegvaliase based on the initial experiences of healthcare providers (HCPs) from across the US with significant clinical experience in treating adult PKU patients with pegvaliase.

2. Materials and methods

2.1. Case selection

Sixteen HCPs, representing the 14 clinics in the US with the most substantial real-world experience treating patients with PKU with pegvaliase, provided cases that exemplified important learnings from their initial experiences, relating to the pre-initiation, induction/titration, and/or maintenance phases of treatment. Cases were presented and discussed in an in-person meeting in December 2019 in Nashville, TN, USA. Based on this meeting, key lessons from each case were drafted and shared with the authors for further discussion in a subsequent virtual platform meeting. The case summaries and final takeaway points are shared here.

Authors received consent from their respective patients to include their treatment experiences and relevant health information in this retrospective case series. No patient identification data are included.

3. Results

3.1. Patient characteristics

Fifteen cases, including two brothers (cases 1 and 2), were discussed. Patient and pre-pegvaliase baseline and treatment characteristics for all patients are summarized in and 2. The full extended case reports can be found in the Supplement (see supplementary file). In brief, the 8 male and 7 female adult PKU patients discussed represented a broad spectrum for age, previous PKU care, comorbidities, and socioeconomic situations (Table 1 and Supplement). Age at initiation of pegvaliase treatment ranged from 18 to 53 years; five patients (33%) were students, and at least four lived over 3 h away from their PKU clinic. Before initiating pegvaliase, eleven patients (73%) were following a Phe-restricted diet and were using medical foods, and five (33%) were receiving sapropterin dihydrochloride (sapropterin, Kuvan®; BioMarin Pharmaceutical Inc., Novato, CA, USA). Pre-pegvaliase baseline blood Phe concentrations ranged from 262 μmol/L to 1474 μmol/L (Table 2). Only case 5 had a Phe concentration periodically below the label-recommended value of >600 μmol/L in the last 2 years before initiating pegvaliase, though blood Phe fluctuated considerably (between 160 and 763 μmol/L) due to diet adherence challenges.

Seven patients reported one or more significant neuropsychological or psychiatric comorbidities before treatment initiation, including anxiety ($N = 4$), attention deficit hyperactivity disorder ($N = 2$), depression ($N = 2$), bipolar disorder ($N = 2$), schizophrenia ($N = 1$), hallucinations ($N = 1$), irritability ($N = 1$), and obsessive compulsive disorder ($N = 1$). The severity of symptoms varied over time in each patient and across patients. Four of 15 patients reported significant socioeconomic challenges, including economic and/or food insecurity, difficult living and/or care arrangements, and ongoing legal challenges (Supplement).

Table 1
Case overview of demographics and baseline characteristics, and details on induction/titration and maintenance. More details regarding comorbidities, pegvaliase journey, and current status are available in the Supplement (Supplementary file).

Case	1[a]	2[a]	3	4	5	6	7	8	9	10	11	12	13	14	15
Demographics and baseline characteristics															
Age, years	27	29	19	21	21	18	39	26	33	40	43	19	53	23	35
Sex	M	M	M	M	M	F	F	F	M	F	F	M	M	F	F
Height, m	1.64	1.64	1.91	1.72	1.67	1.66	1.61	1.60	1.68	1.60	1.58	1.72	1.73	1.65	1.62
Weight, kg	59	68	119	62	57	56	79	64	74	65	64	71	106	78	111
BMI	22.0	25.5	32.6	20.8	20.6	20.5	30.6	25.2	26.1	25.5	25.6	24.2	35.5	28.8	42.4
Phe-restricted diet[b]	No	No	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Sapropterin dihydrochloride at baseline[c]	Former	Former	No	No	No	Yes	Yes	No	No	Yes	No	No	No	No	No
Induction/titration															
Premedication[d]	H1/H2	H1/H2	H1/ H2	H1/H2	H1/H2	H1/H2	H1/ H2	H1/ H2	H1/H2	H1/H2	H1/ H2	H1/ H2	H1/ H2	H1/ H2	H1/ H2
Temporary dose interruption	No	No	No	No	Yes	Yes	No	No	Yes	No	No	No	No	No	No
Reason for interruption					Possible anaphylaxis/ anxiety	Recurrent hives			Anaphylaxis						
Discontinuation	No	No	No	No	Yes	Yes	No	No	No	No	No	No	No	No	No
Reason for discontinuation					Possible anaphylaxis/ anxiety	Recurrent hives/ patient decision									
Maintenance															
Achieved efficacy[e]	Yes	Yes	No[f]	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Time to efficacy, weeks	12	8	NA[f]	5			13	10	17	20	9	50	68	11	22
Dose at efficacy, mg	20/ day	10 4×/ wk	NA[f]	2.5 2×/ wk			20/ day	20/ day	10/day	10 4× & 20 3×/ wk	10/ day	40/ day	60/ day	20/ day	20/ day
Discontinuation	No	No	No	No			No	No	No	No	No	No	No	No	No
Last follow-up															
Pegvaliase treatment status	Maint.	Maint.	Titr.	Maint.	Discont.	Discont.	Maint.	Maint.	Maint.	Maint.	Maint.	Maint.	Maint.	Maint.	Maint.
Pegvaliase dose, mg	10/ day	10/day	10/ day	10 5×/ wk			20/wk	20/ day	20/day	10/day	10/ day	40/ day	60/ day	20/ day	40/ day

BMI: body mass index; F: female; M: male; NA: not available.
[a] Cases 1 and 2 are siblings.
[b] >75% of protein from medical food.
[c] Sapropterin dihydrochloride was discontinued after achieving efficacy; patients not receiving sapropterin dihydrochloride were either non-responders or never tried this therapy (see Supplement for further details).
[d] See Supplement for dosing and duration, if available.
[e] Efficacy was defined by clinic.
[f] Titration ongoing.

3.2. Pre-initiation

Patients had different motivations and personal goals for treatment including a desire to eat a normal diet, to increase food choices, or to experience fewer symptoms that they associated with uncontrolled blood Phe levels (Supplement).

Table 1 and the Supplement provide information on premedications used by the patients. No data are available to inform an optimal premedication regimen. The clinical trial study instruction was to use the highest dose of each premedication per their respective labels, as tolerated.

3.3. Induction/titration

While for the majority of patients the prescribed standard induction and titration schedule in the label was sufficient, the schedule was revised in three cases (cases 6, 9, and 10) due to AEs. Case 13 had a slower induction regimen due to early AEs. Fourteen patients experienced AEs, including injection site reactions, arthralgia/joint pain, rash/erythema/hives, acute systemic hypersensitivity/anaphylaxis, upper respiratory tract/ear infections, prolonged cough, pedal edema with skin breakdown, chest pain, and leukocytosis (Supplement). Three patients had a temporary dose interruption. One interruption was due to possible non-life-threatening anaphylaxis/anxiety (case 5), one to recurrent hives (case 6), and one to acute systemic hypersensitivity/anaphylaxis (case 9) (Table 1). Eight patients (cases 1, 2, 7, 8, 10, 11, 14, and 15) experienced blood Phe levels below 30 μmol/L upon reaching efficacy (in the titration or maintenance phase) for several weeks, indicated by all sequential blood Phe measurements below this level. Blood Phe increased after protein intake was increased (cases 7 and 10) or after reducing the pegvaliase dose (case 14). Levels were still below 30 μmol/L at last follow-up in cases 1, 2, 8, 11, and 15, but without causing any adverse effects.

Mean time to efficacy, as defined by each clinic separately (e.g. blood Phe in the range of 120–360 μmol/L for more than two consecutive levels; blood Phe <360 μmol/L for two consecutive levels; blood Phe <360 μmol/L while on normal diet and off medical food, formula, or sapropterin), was 20.4 weeks (median: 12.5 weeks; range: 5 to 68 weeks) for those who had achieved efficacy. In case 3, titration was still ongoing at 14 weeks after treatment initiation. Two patients discontinued pegvaliase early (case 5 after 18 weeks and case 6 after 33 weeks of treatment) due to AEs (recurrent hives and possible non-life-threatening anaphylaxis/anxiety) (Table 1 and Supplement).

3.4. Maintenance

Cases are summarized as of the end of the virtual advisory board. After induction and titration, the 12 patients achieving efficacy were kept on a maintenance dose ranging from 20 mg weekly to 60 mg daily (Table 1). Blood Phe concentration in these patients ranged from 0 to 321 μmol/L (mean 72 μmol/L) (Table 2). Seven patients had required pegvaliase dose adjustments after achieving efficacy (cases 1, 2, 4, 7, 9, 10, and 15). Change from baseline in natural protein intake in those achieving efficacy ranged from 0 to +73 g/day (mean increase 46.7 g/day). At last follow-up, natural protein intake in these patients ranged from 20 to 100 g/day (mean 69.8 g/day), and total protein intake ranged from 55 to 100 g/day (mean 76.2 g/day) (Table 2). Some patients experienced difficulty adjusting to a new diet with higher protein intake (cases 1, 2, 8, 10, 14, and 15); however, 11 of the 12 patients reaching efficacy were no longer on medical food supplementation (Supplement).

4. Discussion: Key learnings of the case series (Table 3)

4.1. Pre-initiation

4.1.1. Patient education

Education of patients receiving pegvaliase is an ongoing process that starts before initiation of pegvaliase treatment. No assumptions should be made about patients' understanding of expected AEs with pegvaliase treatment, use of premedications, time to efficacy, proper injection technique, dietary changes, or ability to prepare food. All providers and patients must be enrolled in the Palynziq REMS program (www.palynziqrems.com), designed to mitigate the risk of acute systemic hypersensitivity/anaphylaxis, and follow the prescribing and counseling steps outlined in the program, including reinforcing the importance of the presence of a trained observer and discussing the similarity in symptoms between anxiety and anaphylaxis. Patients should be aware that adverse reactions may result in changes to pegvaliase dosing, and that this can considerably prolong the titration process and time to efficacy. In addition, it is important to begin diet education before the initiation of pegvaliase and throughout treatment (i.e. what constitutes a healthy diet; reviewing options for higher protein foods if/when diet changes are warranted). Assessment of a patient's dietary intake and eating behaviors during follow-up visits is essential.

Table 2
Case overview of blood phenylalanine (Phe) and protein intake at pre-pegvaliase baseline and last follow-up.

Case	1	2	3	4	5[a]	6[a]	7	8	9	10	11	12	13	14	15
Blood Phe, μmol/L															
Pre-pegvaliase baseline	1354	1474	757	987	262	611	1174	923	1437	854	1283	884	789	799	1223
Last follow-up[b]	18	6	889[d]	321			72	23	133	61	0	103	69	36	18
Change from baseline	−1336	−1468	+132[d]	−666			−1102	−900	−1304	−793	−1283	−781	−720	−763	−1205
Natural protein intake, g/day[c]															
Pre-pegvaliase baseline	16	40	10	7	12	14	75	14	NA	22	15	20	15	10	20
Last follow-up	73	100	10[d]	55			75–100	77		95	65	73	65	70	20
Change from baseline	57	60	0[d]	48			0	63		73	50	53	50	60	0
Medical food protein, g/day															
Pre-pegvaliase baseline	0	0	60	70	100	40	0	31	0	100	50	75	45	92	60
Last follow-up	0	0	60[d]	0			0	0	0	0	0	0	0	0	60
Total protein intake, g/day															
Pre-pegvaliase baseline	16	40	70	77	112	54	75	45	29	122	65	NA	60	102	80
Last follow-up	73	100	70[d]	55			75–100	77		95	65	73	NA	70	79
Change from baseline	57	60	0[d]	−22			0	32		−27	0	NA	NA	−32	−1

NA: not available.
[a] Data at last follow-up are not reported for cases 5 and 6 who discontinued treatment.
[b] If range was reported, upper limit was included.
[c] If range of natural protein intake was reported, average values are included; if the actual consumption was unavailable, prescription is included.
[d] Titration ongoing.

Table 3
Key lessons from the case series.

Pre-initiation
• Patient education is an ongoing process that starts during pre-initiation. No assumptions should be made about patients' understanding of AEs, time to efficacy, diet changes, or ability to prepare food. • Patient-specific factors that may interfere with treatment success, such as socioeconomic challenges, comorbidities, or prior non-adherence to diet and/or pharmacotherapy, should be identified and addressed before starting pegvaliase, but these factors do not in themselves prohibit success with pegvaliase. • Socioeconomic barriers and other challenges such as irregular dietary habits and food insecurity that may prevent lifestyle changes should be discussed before initiating pegvaliase. • Treatment initiation should be planned with the patient's upcoming life events in mind. • Treatment goals, patient expectations, and planned changes once efficacy is reached should be clearly defined upfront.
Induction/titration
• Initiation of pegvaliase can be challenging in patients living in geographically remote areas. For these patients, it may be difficult to identify an appropriate location and to find and educate local health care providers for the first injection. • Each patient's titration and diet adjustments are unique; a flexible titration schedule that allows for adjustments when patients experience AEs can help avoid discontinuations. • While some patients show a reduction in blood Phe level very quickly after treatment initiation with few or no AEs, others require more than a year for an effect to become apparent. • Patients that experience hypersensitivity reactions early on can still achieve efficacy, but this may require prolonging the titration phase and/or concomitant medication use. • Patients and caregivers may have a difficult time distinguishing between acute systemic hypersensitivity/anaphylaxis and anxiety. From a safety point of view, it is best to react as if the patient has anaphylaxis.
Maintenance
• To prevent issues with dietary changes, providers should keep in close communication with their patients, make any changes to diet slowly with specific recommendations of how to increase protein, and avoid making assumptions about patients' understanding or goals for their new diet. • Providers should continue to discuss injection site rotation with patients and have continued discussion around life events that might impact pegvaliase use during maintenance.

AEs: adverse events.

4.1.2. Evaluation of patient-specific factors

In this case series, treatment success was seen in patients across different ages, previous PKU care, comorbidities, and socioeconomic challenges, suggesting that these factors do not prohibit treatment with pegvaliase. However, patients with socioeconomic difficulties, historical non-adherence with treatment/diet, or significant psychiatric comorbidities must be individually assessed for willingness and appropriateness before initiating treatment.

Psychological factors such as anxiety that may interfere with treatment success should be identified, discussed with the patient, and in some cases prophylactically treated before starting pegvaliase. Baseline neuropsychological testing may be performed in the hour-long observational period directly following the first injection. Follow-up visits are an opportunity to reassess patients' psychosocial health comprehensively. For patients with neurocognitive or psychiatric issues, it may be important to develop a “contract” with families, especially during the titration period to optimize treatment success (case 4).

Additional factors that should be evaluated and discussed before initiating pegvaliase are socioeconomic barriers and other dietary challenges, such as irregular dietary habits and food insecurity, that may hinder lifestyle changes (such as in cases 1, 2, 14, 15).

In addition, case 6 illustrates that treatment initiation should be planned with the patient's life events in mind. This patient discontinued pegvaliase when she started college as she feared significant side effects while away from home. To avoid similar situations, HCPs should proactively discuss the duration, expectations, and requirements of the induction and titration period, as well as potential AEs, and how these may interfere with the patient's plans during the titration period.

Finally, treatment goals, patient expectations, and planned changes once efficacy is reached (e.g. discontinuation of sapropterin) should be clearly defined during the pre-initiation period. Primary motivations for pegvaliase treatment vary between patients. Some may be motivated by the ability to eat a more normal diet, while others may want to be able to think more clearly (resulting from improved Phe levels). It is recommended to discuss the patient's dietary goals (e.g. decrease medical food/formula, increase natural protein intake) before treatment is initiated. Some patients may not wish to totally normalize diet or may be hesitant to administer two injections a day (case 15). It can be helpful to re-evaluate goals through the course of therapy, since goals can change as experience evolves.

4.2. Induction and titration

4.2.1. Premedication

Premedication regimes have changed considerably over time and vary from clinic to clinic. Some providers prescribe daily premedications during titration even if no injection is given, and some consider discontinuing premedications once a patient has reached efficacy and had not experienced hypersensitivity AEs for 1–2 months, with the plan to resume if hypersensitivity events recur.

Regardless of the premedication regimen, all patients should be counseled on potential side effects of premedications (e.g. sedation may occur even with nominally non-sedating antihistamines); timing of injections in the evening may therefore be preferred (case 7). If premedication is started days before the first injection, the provider can assess any AEs as related to the premedication, as opposed to those related to pegvaliase, and adjust the specific premedication as necessary [12].

4.2.2. Initiation of pegvaliase in patients in geographically remote areas

Initiation of pegvaliase can be challenging in patients living in areas geographically distant from the initial treatment site (case 3). For these patients, it may be helpful to identify a local HCP who is able to provide supervision for the first injection. This can be the patient's primary care provider, or another specialty provider such as urgent care or a local specialist (e.g. an allergist or oncologist) who is comfortable managing hypersensitivity reactions and educated about the risk of and response to anaphylaxis. It is important to make sure that any serious AEs experienced are reported and can be managed adequately. Telehealth tools can increase the cost- and time-efficiency of delivering care to remote areas.

4.2.3. Management of patients during titration

This case series clearly illustrates that each patient's management needs during titration vary, depending on the occurrence of AEs, personal preferences, and emotional factors. Although AEs may present at any time, most of the AEs that occur during titration, such as injection site reactions and joint pain (arthralgia), are mild to moderate in severity, and decrease in frequency and severity over time [6,7,13]. However, some patients may experience severe (e.g. anaphylaxis) or atypical reactions. Patients with acute systemic hypersensitivity events/anaphylaxis are overrepresented in this case series versus previous reports [6,12] because the guidance shared on these cases is important as

they require more specific and tailored care.

AEs related to pegvaliase and best practices for their prevention and management have been described previously [8,13]. HCPs should not be reluctant to increase the dosage of histamine receptor antagonists or prescribe steroids to manage hypersensitivity reactions. Steroids are typically administered over a short period of time, to minimize the effects of long-term use. Patients and caregivers may have a difficult time distinguishing between acute systemic hypersensitivity/anaphylaxis and anxiety (case 5); however, for patient safety, it is best to react as if the patient is having an anaphylactic event in these cases. Managing anxiety by setting proper expectations, offering counseling, and potentially prescribing anxiolytics may help reduce drug discontinuation.

Pegvaliase treatment can be restarted and continued after anaphylaxis or other hypersensitivity reactions (after up to 1 week interruption in this case series), but must be considered on a case-by-case basis. In the EU, restarting treatment is contraindicated after severe anaphylaxis. Patients who experience hypersensitivity reactions early on can still achieve efficacy, although this may require prolonging the titration phase and/or concomitant steroid use (case 13). Achieving efficacy may take longer than 1 year and may require higher doses of pegvaliase. It is important to acknowledge patient frustrations and fears until efficacy is reached. Treatment efficacy is often not achieved until after hypersensitivity symptoms abate (cases 9 and 13), but can also occur while the patient is experiencing significant AEs (case 2). Having a “buddy”, either a family member (case 1 and 2) or a friend, can be helpful in coping with AEs, reinforcing instructions and staying adherent to the regimen. Although the brothers in cases 1 and 2 had similar responses to pegvaliase treatment, that is not always the case for relatives.

Twelve out of 15 patients in this case series remained motivated to continue treatment and achieved efficacy (one patient did not yet complete titration), despite the fact that nine of them experienced severe hypersensitivity reactions. A flexible titration schedule that allows for adjustments when patients experience AEs (i.e. waiting for reactions to resolve before restarting therapy, building up tolerability before advancing to a higher pegvaliase dose) can help avoid discontinuations (cases 9, 10, and 12).

Because of the risk of AEs, travel plans during the titration phase, especially long trips that involve air travel, should be discussed with the patient ahead of time, to plan on timing of the pegvaliase dose in relation to the flight, and to stress the importance of packing medications that may be needed in case of an AE.

4.2.4. Monitoring blood Phe levels and diet

Time to therapeutic response is widely variable between patients, ranging from only five weeks (case 4) to more than a year (case 13). As blood Phe can drop early in some patients, checking levels more than once a month (e.g. every 2 weeks) during induction and titration may be considered. Based on case 11, we also suggest that waiting for two consecutive blood Phe assessments before adjusting the pegvaliase dose may avoid worsening of AEs in some cases.

Close follow-up by a dietitian during titration and maintenance can help with dietary changes and with monitoring weight and body mass index. Early identification and intervention may help prevent rapid weight gain. Initiating dietary changes too early can lead to a “yo-yo” effect in blood Phe levels (case 8).

4.3. Maintenance

4.3.1. Key issues for establishing a healthy, adequate diet

Many patients hope to control their blood Phe without maintaining a Phe-restricted diet with pegvaliase. The case series highlights that patients' goals for their diet vary. Providers can assist patients with this transition by understanding the challenges they may face when changing their diet. Once patients have achieved efficacy, they may not report all dietary changes (case 14), because they either do not think they are important or lack adequate information on protein sources. Patients may have difficulty liberalizing their diet in a healthy, sustainable way. Due to unfamiliarity with intake of higher protein foods, they may experience early protein satiety, which could lead to catabolism and fluctuating blood Phe levels (case 14). In some patients, dietary changes enabled by pegvaliase may result in significant weight gain (case 7). Providers should also be aware that patients may feel a loss of identity as diet restrictions are lifted and may be anxious about getting enough protein to prevent low Phe levels (case 10). Some patients may feel overwhelmed with drastic changes in their diet or may face additional pressure from family and friends to make changes to their diet during the initial response.

To avoid issues with dietary changes, HCPs should maintain close communication with their patients, make any changes to diet slowly and with specific recommendations of how to increase protein, and avoid making assumptions about the patient's understanding or goals for their new diet. Patients need education on appropriate dietary protein sources and help with healthy eating habits, starting at the time of initial counseling and education for pegvaliase. Medical foods/formula should be maintained until patients can adequately understand and meet their new dietary protein needs, including foods of high biological quality protein sources. Education on nutrition and cooking, with focus on preparation of high protein foods, are imperative for pegvaliase responders. For patients with weight issues, standard weight loss techniques, including weight loss clinics and pharmacotherapy, can be considered and should be coordinated with the metabolic clinic with a proactive approach.

4.3.2. Impact of pegvaliase on patients' lives

This case series underscores the potential for great improvements in quality of life in patients achieving efficacy on a stable maintenance dose. Cases 1 and 2 who had severe socioeconomic challenges reported improvements in neurocognitive and executive function after achieving efficacy. Both brothers received work promotions and, as a result, had better access to food. Other patients showed improvements in studying abilities (cases 8, 12, and 14) (Supplement). Case 4 who had severe functional impairments at baseline was able to perform his own injections and to drive independently; he also became more independent and social. Other patients felt less irritable and had better focus and more energy (case 7), reported improved quality of life from being able to eat a more normal and spontaneous diet (case10), were able to set and achieve personal health goals (case 11), or noted improvements in overall mood (cases 13 and 15).

4.3.3. Ongoing care during maintenance

Several cases underscore the importance of ongoing follow-up of patients during maintenance. Case 12 shows that if unexpected spikes in blood Phe levels are observed in a patient who has responded to pegvaliase, it may be useful to inquire about locations and technique of injections in addition to exploring other factors such as changes in diet or illness. Injecting into areas with dense scar tissue (e.g. when the patient is not rotating injection sites) may limit the dose that enters the patient's bloodstream. Therefore, assessing rotation of injection sites during follow-up visits, as well as offering training to provide more injection site options is important. Patients may also experience blood Phe levels below 30 μmol/L that are not associated with an increase in AEs. In clinical trials, low blood Phe resolved in the majority of subjects with either increased natural protein intake and/or dose adjustments [14]. One patient in this series (case 10) experienced hair loss from telogen effluvium related to low blood Phe that resolved within a few months due to a minor increase in blood Phe after intact protein was increased.

Providers should have continued discussion with patients around life events that might impact pegvaliase use during maintenance, e.g. about birth control and pregnancy plans for women of childbearing years.

4.4. Limitations

The cases presented here do not represent all potential clinical scenarios, nor do the recommendations provided address all challenges which may be encountered when using pegvaliase. These cases and commentary are intended to supplement published clinical trial results, until additional data from registries and independent research can be made publicly available.

5. Conclusions

This case series collects the initial experiences of HCPs from across the US with significant experience in treating adults with PKU with pegvaliase. Until further evidence from registries and independent research become available, the data and proposed recommendations presented herein can be a valuable resource for HCPs to support appropriate management of patients receiving pegvaliase. The very early qualitative data presented here can lead to future, more statistically rigorous studies with larger patient numbers on the impact of pegvaliase on diet, quality of life, and psychiatric and cognitive measures.

Funding

The content of this manuscript was based on presentations and discussions during an advisory board meeting that was coordinated and funded by BioMarin Pharmaceutical Inc. BioMarin also funded the writing of this manuscript.

Data sharing statement

Research data for this case series will not be shared as the data that has been used is confidential.

Declaration of competing interest

DA reports grants from BioMarin outside the submitted work. HCA and KC received payments from BioMarin to participate in the advisory board meeting related to the submitted work. HB reports personal fees from BioMarin related to the submitted work and personal fees from BioMarin, Cambrooke, Horizon, Nutricia, Ultragenyx, and Vitaflo outside the submitted work. CE received payments from BioMarin to participate in the advisory board meeting related to the submitted work, and payments from BioMarin outside the submitted work. ML received personal fees to participate in the advisory board meeting related to the submitted work; payments from BioMarin outside the submitted work; and is an investigator in clinical trials sponsored by BioMarin. JL and KW are employees of BioMarin. KL received payments from BioMarin for participating in the advisory board meeting related to the submitted work; she is currently an employee of BioMarin. MM reports personal fees and non-financial support from BioMarin related to the submitted work and personal fees from Applied Therapeutics, Cycle Pharmaceuticals and Rhythm Pharmaceuticals, personal fees and non-financial support from Aeglea Biotherapeutics and Horizon Therapeutics, and grants from Censa Pharmaceuticals outside the submitted work. JWR received payments and travel support from BioMarin for participating in the advisory board meeting related to the submitted work. HS received payments and travel support from BioMarin related to the submitted work, was involved as an investigator in clinical trials for BioMarin, and received payments from BioMarin, Vitaflo, MetEd and Symbiotics outside the submitted work. SS received consulting fees, speaker fees, and travel support from BioMarin and was involved as an investigator in clinical trials for BioMarin. DS received personal fees from BioMarin related to the submitted work and personal fees from BioMarin, Cambrooke, Horizon, Nutricia, Ultragenyx, Cycle Pharmaceuticals and Vitaflo outside the submitted work. JT-A received personal fees for participating in the advisory board related to the submitted work and personal fees from BioMarin outside the submitted work. JT was involved as an investigator in clinical trials for BioMarin and was a member of the Phase III advisory board. EV received personal fees for participating in the advisory board related to the submitted work and personal fees from BioMarin outside the submitted work. LBW received personal fees from BioMarin for participating in the advisory board and virtual platform meeting related to the submitted work, and personal fees from BioMarin and Nutricia outside the submitted work.

Acknowledgements

The authors are grateful to Cheryl Clow (Albany Medical Center) for her contribution to the advisory board meeting and to Ismar Healthcare NV for their assistance in the writing of this manuscript, which was funded by BioMarin Pharmaceutical Inc. The authors are also grateful to Sarah Rose (BioMarin) for her assistance in finalizing the case details, Gillian Clague (BioMarin) for her assistance in finalizing the manuscript and implementing graphic updates, and Terry Manspeaker (Show Your Science, LLC) for graphic support. The authors are grateful to BioMarin for coordinating and funding the advisory board meeting related to this publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgmr.2021.100790.

References

[1] N. Blau, F.J. van Spronsen, H.L. Levy, Phenylketonuria, Lancet 376 (2010) 1417–1427.
[2] V.L. Brumm, D. Bilder, S.E. Waisbren, Psychiatric symptoms and disorders in phenylketonuria, Mol. Genet. Metab. 99 (Suppl. 1) (2010) S59–S63.
[3] J. Vockley, H.C. Andersson, K.M. Antshel, et al., Phenylalanine hydroxylase deficiency: diagnosis and management guideline, Genet. Med. 16 (2014) 188–200.
[4] Palynziq (pegvaliase-pqpz) [US prescribing information], BioMarin Pharmaceutical Inc, Novato, CA, 2018.
[5] Palynziq (pegvaliase) [EU product information], BioMarin International Ltd, Shanbally, Ireland, 2019.
[6] J. Thomas, H. Levy, S. Amato, et al., Pegvaliase for the treatment of phenylketonuria: results of a long-term phase 3 clinical trial program (PRISM), Mol. Genet. Metab. 124 (2018) 27–38.
[7] R. Zori, J.A. Thomas, N. Shur, et al., Induction, titration, and maintenance dosing regimen in a phase 2 study of pegvaliase for control of blood phenylalanine in adults with phenylketonuria, Mol. Genet. Metab. 125 (2018) 217–227.
[8] N. Longo, D. Dimmock, H. Levy, et al., Evidence- and consensus-based recommendations for the use of pegvaliase in adults with phenylketonuria, Genet. Med. 21 (2019) 1851–1867.
[9] R. Zori, K. Ahring, B. Burton, et al., Long-term comparative effectiveness of pegvaliase versus standard of care comparators in adults with phenylketonuria, Mol. Genet. Metab. 128 (2019) 92–101.
[10] A.M.J. van Wegberg, A. MacDonald, K. Ahring, et al., The complete European guidelines on phenylketonuria: diagnosis and treatment, Orphanet. J. Rare Dis. 12 (2017) 162.
[11] A.G. Florek, R.P. Dellavalle, Case reports in medical education: a platform for training medical students, residents, and fellows in scientific writing and critical thinking, Springer, 2016.
[12] S. Sacharow, C. Papaleo, K. Almeida, et al., First 1.5 years of pegvaliase clinic: Experiences and outcomes, Mol. Genet. Metab. Rep. 24 (2020) 100603.
[13] O. Hausmann, M. Daha, N. Longo, et al., Pegvaliase: immunological profile and recommendations for the clinical management of hypersensitivity reactions in patients with phenylketonuria treated with this enzyme substitution therapy, Mol. Genet. Metab. 128 (2019) 84–91.
[14] J.A. Thomas, E. Jurecki, K.B. Whitehall, et al., Dietary intakes and adverse events in pegvaliase-treated phenylketonuria adults who had low blood phenylalanine concentrations, in: Poster 183 presented at ACMG 2020, 2020. https://www.acmgeducation.net/Users/LearningActivityAssetSingleViewer.aspx?LearningActivityAssetID=xHQ0EkDW9ADf%2fkbgLwwMFw%3d%3d.