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A Comprehensive Review of Pegvaliase, an Enzyme Substitution Therapy for the Treatment of Phenylketonuria

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ABSTRACT

OBJECTIVE: To review the pharmacology, pharmacokinetics, efficacy, safety, and place in therapy of a phenylalanine-metabolizing enzyme indicated to reduce blood phenylalanine concentrations, pegvaliase injection.

DATA SOURCES: Searches of MEDLINE (1946–September 1, 2018) were conducted using the terms pegvaliase and phenylalanine ammonia lyase (PAL). Additional data were obtained from the prescribing information, the product dossier obtained from the manufacturer, and Clinicaltrials.gov.

STUDY SELECTION AND DATA EXTRACTION: All English language articles related to pharmacology, pharmacokinetics, efficacy, or safety of the combination therapy in human subjects were reviewed.

DATA SYNTHESIS: Pegvaliase is a pegylated PAL enzyme that converts phenylalanine to ammonia and trans-cinnamic acid. Blood phenylalanine levels were reduced by approximately 50% to 70% in patients receiving therapeutic doses of pegvaliase. However, most patients experienced adverse events.

CONCLUSIONS AND RELEVANCE: The mainstay of therapy in phenylketonuria (PKU) has historically consisted of dietary restriction of phenylalanine. Pegvaliase injection is the first Food and Drug Administration (FDA)–approved enzyme substitution therapy for patients with PKU. The therapy may be a viable option for patients with documented blood phenylalanine >600 μmol/L who have failed existing management strategies.

KEYWORDS: Palynziq, pegvaliase, phenylalanine ammonia lyase, pegvaliase-pqpz, phenylketonuria, PKU

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Introduction

Phenylketonuria (PKU) is a rare autosomal recessive condition affecting about 1 in 13 500 to 19 000 people in the United States.¹ Phenylketonuria is diagnosed through detection of elevated blood phenylalanine concentration.² If untreated, PKU can cause chronic intellectual, neurodevelopmental, and psychiatric disabilities. Excessive phenylalanine is thought to interfere with brain growth, myelination, and neurotransmitter synthesis. Most cases of PKU are detected shortly after birth by newborn screening. As a result, the severe signs and symptoms of classic PKU are rarely seen.²

Elevated phenylalanine levels are caused by a deficiency in the enzyme, phenylalanine hydroxylase (PAH).² The spectrum of severity in untreated PKU ranges from complete enzyme deficiency or classic PKU (phenylalanine concentration > 1200 μmol/L), moderate PKU (phenylalanine concentration = 900–1200 μmol/L), mild PKU (phenylalanine concentration = 600–900 μmol/L), and mild hyperphenylalaninemia (HPA) (phenylalanine concentration = 360–600 μmol/L).³ Although guidelines recommend lifelong treatment to a target blood phenylalanine level of 120 to

360 μmol/L^{4,5} or 120 to 600 μmol/L, (van Wegberg, MacDonald and Ahring, 2017) therapy must be individualized to each patient.

Management of patients with HPA and PKU should be provided by an interdisciplinary team of nutritionists, psychologists, social workers, and metabolic specialists.² Phenylketonuria is a relatively rare disease and patients may require lifelong treatment. The goal of therapy is to lower blood phenylalanine concentrations to minimize the neurocognitive and psychiatric effects of PKU.^{4–7} The mainstay of therapy is dietary restriction of phenylalanine and supplementation with phenylalanine-free medical foods to avoid nutritional deficits.^{4–6} The medical foods are protein substitutes that are phenylalanine-free and fortified in tyrosine and may contain glycomacropptides and other large neutral amino acids as the protein source.³ Adherence to the restrictive diet requires planning and organization, and can be challenging for patients.⁴

Sapropterin was Food and Drug Administration (FDA)–approved on December 13, 2007, and was the first pharmacologic therapy for treatment of PKU.⁸ It is an oral PAH cofactor



Table 1. Summary of pharmacokinetic parameters studied.

PHARMACOKINETIC PARAMETER	DAILY MAINTENANCE DOSAGE	
	PEGVALIASE 20 MG	PEGVALIASE 40 MG
Median T_{max}	8 hours	
C_{max} at steady state (mean \pm SD)	14.0 \pm 16.3 mg/L	16.7 \pm 19.5 mg/L
Apparent volume of distribution (mean \pm SD)	26.4 \pm 64.8 L	22.2 \pm 19.7 L
Apparent clearance at steady state (mean \pm SD)	0.39 \pm 0.87 L/h	1.25 \pm 2.46 L/h
Half-life (mean \pm SD)	47 \pm 42 hours	60 \pm 45 hours
Steady state plasma concentrations during maintenance treatment (mean \pm SD)	11.2 \pm 9.0 mg/L	10.4 \pm 12.7 mg/L
Metabolism	Catabolic pathways, degraded into small peptides and amino acids	

Abbreviations: C_{max} , peak concentration; T_{max} , time to peak concentration.

indicated to reduce blood phenylalanine concentrations in patients with HPA due to tetrahydrobiopterin (BH4)-responsive PKU. Sapropterin is used in conjunction with a phenylalanine-restricted diet.⁹ The efficacy of sapropterin is based on the presence of residual PAH enzymatic activity. Approximately 25% to 50% of patients with PKU respond to sapropterin.⁴

Phase 3 trials for an enzyme substitution therapy for PKU began in 2013 and showed promise to be effective in any patient with PKU regardless of residual enzymatic activity.⁴ Pegvaliase, FDA-approved on May 24, 2018, acts as a substitute for the deficient PAH enzyme.¹⁰ Pegvaliase is indicated to reduce blood phenylalanine concentrations in adult patients with PKU who have uncontrolled blood phenylalanine concentrations $>600 \mu\text{mol/L}$ on existing management.^{11,12}

Adult patients with PKU whose phenylalanine levels are not appropriately managed may experience adverse neurocognitive and psychiatric outcomes.⁷ The objective of this article is to review the pharmacology, pharmacokinetics, efficacy, safety, and place in therapy of pegvaliase injection. It will also provide an overview of the role of pegvaliase compared with current standard of care.

Data Sources

A search of MEDLINE (1946–September 1, 2018) was conducted using the terms pegvaliase and phenylalanine ammonia lyase (PAL). The 2 terms were combined with the Boolean operator OR. The term pegvaliase was also searched on its own. All English language articles related to pharmacology, pharmacokinetics, efficacy, or safety of the therapy in human subjects were included. The references of included articles were searched to identify additional sources. The product dossier was obtained from the manufacturer, and additional data were obtained from the prescribing information and Clinicaltrials.gov.

Data Synthesis

Pharmacology

PAH catalyzes the irreversible conversion of phenylalanine to tyrosine. In the absence of PAH in PKU, dietary phenylalanine is unable to be converted to tyrosine and undergoes further processing to metabolites including L-dopa, thyroxine, dopamine, noradrenaline, adrenaline, and melanin.¹³ There are 2 modes of enzyme therapy through replacement of the PAH enzyme or substitution with another enzyme to degrade excess phenylalanine.¹² Pegvaliase follows the latter category and is a pegylated PAL enzyme that converts phenylalanine to ammonia and trans-cinnamic acid.⁸ Ammonia is metabolized by the liver. Trans-cinnamic acid and its final product, benzoic acid, are conjugated with glycine and excreted in the urine.^{13,14}

Pharmacokinetics

Due to the heterogeneity of immune response in adults with PKU, the pharmacokinetics of pegvaliase exhibit high interpatient and inpatient variability. High antibody titers correlated with higher apparent clearance. The pharmacokinetic parameters are summarized in Table 1.

Clinical Trials

Phase 1

Clinical trial experience with pegvaliase is summarized in Table 2. The first study of pegvaliase in humans was a phase 1, multicenter, open-label study in patients over the age of 18 with a diagnosis of classic PKU (phenylalanine concentration $>1200 \mu\text{mol/L}$ at diagnosis) and had a history of poor dietary compliance (PAL-001, NCT00634660). The average baseline phenylalanine concentration was $1310 \mu\text{mol/L}$, and the average body mass index (BMI) was 26.4 kg/m^2 . Twenty-five patients were recruited from 7 centers in the United States. Patients were

Table 2. Summary of trials of pegvaliase for the treatment of PKU in adults.

PHASE	IDENTIFIER	DESIGN	DURATION	DOSING	N	RESULTS
1	NCT00634660 (PAL-001)	OL, single dose	42 days	0.001, 0.003, 0.10, 0.03, and 0.100 mg/kg	25	48.3% reduction in Phe from day 4 to 7 in the highest dosing group
2	NCT00925054 (PAL-002)	OL, multiple dose with induction and titration phases	16 weeks	0.001-0.1 mg/kg given 5 d/wk	40	No significant changes in Phe 5% (2 patients) discontinued due to AEs
2	NCT01212744 (PAL-004)	OL, multiple dose	13 weeks	0.06-0.8 mg/kg/d given 5 d/wk	16	No significant changes in Phe 6.25% (1 patient) discontinued due to AEs
2	NCT01560286 (165-205)	OL, multiple dose with induction, titration, and maintenance phases	24 weeks	2.5 mg weekly × 4-8 weeks, then increased to a maximum of 75 mg daily	24	46% reached maintenance dose 56% reduction in Phe 54% did not reach maintenance dose 8.33% (2 patients) discontinued due to AEs
2	NCT00924703 (PAL-003)	OL, multiple dose extension study	Extended follow-up of phase 2 studies to 264 weeks	Continued or increased from parent studies, up to 375 mg/wk given up to 7 d/wk	68 ^a	58.9% reduction in Phe at 48 weeks 72.3% reduction in Phe at 120 weeks 5.9% (4 patients) discontinued due to AEs
3	NCT01819727 (PRISM-1)	OL, randomized multiple dose with induction, titration, and maintenance phases	24 months	2.5 mg daily titrated to either 20 or 40 mg daily	261	51.1% reduction in Phe at 12 months 68.7% reduction in Phe at 24 months Improvement in mood and inattention scores 11% (29 patients) discontinued due to AEs
3	NCT01889862 (PRISM-2)	PRISM-1 extension study ^b				
	Part 1	OL continuation of PRISM-1		20 or 40 mg daily		Data not published
	Part 2	R discontinuation study	8 weeks	20 mg daily, 40 mg daily, or placebo	86	No change in Phe in the groups that maintained doses 62.6% increase in Phe in placebo 20 mg group 56.4% increase in Phe in placebo 40 mg group No patients discontinued due to AEs
	Part 3	OL, PD, PK		20 or 40 mg daily		Data not published
	Part 4	OL extension	Ongoing	5-60 mg daily		Ongoing

Abbreviations: AEs, adverse events; OL, open label; PD, pharmacodynamics; Phe, phenylalanine; PK, pharmacokinetic; PKU, phenylketonuria; R, randomized.

^aPatients from the other phase 2 studies.

^b12 patients from the phase 2 studies, but their data are not reported.

excluded if they had renal or hepatic dysfunction, had pregnancy or potential pregnancy, or used nicotine, drugs of abuse, or any investigational products in the 30 days prior to screening.¹⁵

Twenty-five patients were assigned to 1 of 5 dosing groups in which they received a single subcutaneous injection of pegvaliase on day 1: 0.001, 0.003, 0.10, 0.03, and 0.100 mg/kg. Patients were followed up for 42 days. In the patients who received the 0.1 mg/kg dose, pegvaliase significantly reduced phenylalanine concentrations (1113 to 575 mmol/L, mean reduction of 48.3%) on day 6. Phenylalanine concentrations increased from day 7 to day 21 and remained relatively consistent through the end of the study.¹⁵

Phase 2

The optimal dosing regimens were explored in 3 phase 2 studies of pegvaliase. PAL-002 (NCT00925054) was an open-label, multicenter study of 40 adults with PKU. Patients entered an 8-week induction phase of various fixed and weight-based doses of pegvaliase administered weekly, followed by an 8-week titration phase during which increasing doses of pegvaliase were administered weekly with the goal of achieving reduced blood phenylalanine concentrations. The doses ranged from 0.001 to 0.1 mg/kg throughout the study. These doses were not sufficient to lower phenylalanine concentrations.

PAL-004 (NCT01212744) was an open-label, multicenter study of 16 adults with PKU. Patients were given doses of pegvaliase 5 d/wk which ranged from 0.06 to 0.8 mg/kg throughout the 13 weeks of the study. Similar to PAL-002, the doses studied resulted in inadequate control of blood phenylalanine levels. All patients in both studies experienced at least 1 adverse event (AE). The regimens used in PAL-002 were generally well tolerated, but the higher doses in PAL-004 were associated with more frequent hypersensitivity reactions (which included arthralgia, arthritis, eye inflammation, eye irritation, eye pain, joint stiffness, joint swelling, pyrexia, vision blurred, and polyarthritis) and the need for dose reduction.¹⁶

Based on observations made in PAL-002 and PAL-004, a third phase 2 study, 165-205 (NCT01560286), was conducted. This study was an open-label, multicenter study that was 24 weeks in duration. Patients were eligible if they had a blood phenylalanine concentration of $\geq 600 \mu\text{mol/L}$ at screening and an average concentration of $\geq 600 \mu\text{mol/L}$ in the 6 months prior to the screening, and no prior treatment with sapropterin in the 4 months prior to screening. Patients who were pregnant, planning to become pregnant, or breastfeeding were excluded. Patients entered a 4- to 8-week induction phase of 2.5 mg/wk. Afterward, the dose and frequency could be increased over a minimum of 4 weeks to attain a blood phenylalanine concentration of $\leq 600 \mu\text{mol/L}$. The authors defined the “maintenance dose” as the regimen that resulted in target concentrations for 4 weeks without the need for dose adjustments. Once the maintenance dose was determined, patients entered the next phase. In the maintenance phase, the maintenance dose was continued but could still be adjusted for safety or to maintain concentrations below $600 \mu\text{mol/L}$. The maximum dose in the maintenance phase was 75 mg/d given 5 d/wk. However, the protocol was updated to change the maximum frequency to 7 d/wk. Patients experiencing severe hypersensitivity adverse events (HAEs) had their dosing interrupted or adjusted and restarted at the same or a lower dose. Another protocol change allowed patients with treatment-related acute systemic hypersensitivity events to permanently discontinue the study drug. The investigators used a modified intention-to-treat analysis consisting of participants who received at least 1 dose of the study drug and had at least 1 post-treatment blood phenylalanine level.¹⁷

Twenty-four patients enrolled in the study, with 11 patients achieving maintenance dose in the first 24 weeks (group A) and 13 patients not achieving maintenance dose within 24 weeks (group B). Patients had a mean age of approximately 29 years, and baseline blood phenylalanine concentrations were similar in both groups ($1134.8 \mu\text{mol/L}$ in group A vs $1197.5 \mu\text{mol/L}$ in group B). However, group A was comprised mostly of women with a mean weight of 64.6 kg, whereas group B was mostly men with a mean weight of 86.4 kg. Baseline total protein intake and dietary phenylalanine intake were higher in group B. Mean doses of pegvaliase in the 24-week study were 64.7 mg in group A and 89.4 mg in group B. The group A patients'

mean blood phenylalanine concentration reached $< 600 \mu\text{mol/L}$ by week 11 of the study. The mean reduction from baseline was $627 \pm 432 \mu\text{mol/L}$ ($56\% \pm 36\%$ reduction). Furthermore, all patients in group A reached a blood phenylalanine concentration target of $< 120 \mu\text{mol/L}$ during the 24-week study. Group A had lower anti-drug antibody responses, which was likely associated with less immune-related clearance compared with patients in group B with higher anti-drug antibody responses. Ten of the 13 patients in group B continued on to the extension study, during which they achieved a blood phenylalanine concentration of $\leq 600 \mu\text{mol/L}$ by week 48.¹⁷

Patients in the 3 phase 2 dosing finding studies (will be referred to hereon as “parent studies”) were invited to continue on in an extension study (PAL-003, NCT00924703) if they were willing to continue stable protein intake. Patients taking any other injectable drug containing polyethylene glycol (PEG) and patients with a history of systemic hypersensitivity events to a PEG-containing product were excluded. However, patients with a previous reaction to pegvaliase could be eligible for the study on a case by case basis. Doses for individuals were either continued from the parent study or increased and were adjusted throughout the study to attain or maintain phenylalanine concentrations between 60 and $600 \mu\text{mol/L}$. In addition, doses could be adjusted to manage AEs. Initially, dosing ranged from 2.5 to 375 mg/wk or 0.001 to 5 mg/kg/wk, but a protocol changed limited weekly dosing to 375 mg/wk. The authors used a modified intention-to-treat analysis for efficacy which included all patients who received 1 dose of pegvaliase and had at least 1 phenylalanine concentration measurement taken after treatment.¹⁷

Sixty-eight of the 80 participants in the parent studies enrolled in the extension study. The baseline phenylalanine concentration was $1022.4 \mu\text{mol/L}$. The mean daily dose of pegvaliase in the parent studies was 5.3 mg/d (SD = 6.8 mg/d), and this increased to 26.2 mg/d (SD = 17.9 mg/d) in the extension study. Doses remained relatively stable from week 48 to week 120 of the study. The average duration of treatment in all of the phase 2 studies was approximately 3.4 years. Mean phenylalanine concentrations decreased throughout the study by more than half (58.9%) at week 48 of treatment and by 72% at week 120 ($1022.4 \mu\text{mol/L}$ at baseline, $541.6 \mu\text{mol/L}$ at week 48, and $372 \mu\text{mol/L}$ at week 120).¹⁷

Approximately one-third of patients (36.8%) had their pegvaliase dosing reduced or held during the study. A small number of patients ($n = 4$, 5.9%) discontinued the study due to AEs. All 4 patients reported resolution of the AEs after discontinuing treatment. Hypersensitivity adverse events were highest during early treatment in phase 2 studies and correlated with the timing of highest IgM, PEG IgM, and PEG IgG antibodies.¹⁷

Phase 3

Pegvaliase was evaluated in a phase 3 study, PRISM-1 (NCT01819727). In this multicenter, open-label study, patients

naïve to pegvaliase were randomized to receive 1 of 2 regimens of pegvaliase. Patients with a blood phenylalanine concentration of 600 $\mu\text{mol/L}$ or higher for at least 6 months prior to the study were eligible. It is unclear if allocation to treatment groups was concealed. Both groups received 2.5 mg once per week of pegvaliase subcutaneously for 4 weeks during the induction period. Dosing and frequency were increased gradually to either 20 mg/d or to 40 mg/d. Titration was performed over a period of 5 to 30 weeks. The schedule was described for the 20 mg/d group: 2.5 mg twice weekly, 10 mg weekly, 10 mg twice weekly, 10 mg 4 times weekly, 10 mg daily, and then 20 mg daily. Doses were continued in the maintenance phase, which ranged from 24 to 36 weeks in duration. Phenylalanine levels, safety, immunogenicity, and neuropsychiatric symptoms were assessed by trained study staff at each site using tools validated for use in PKU.¹⁸

PRISM-1 included 261 patients: 131 in the 20 mg/d group and 130 in the 40 mg/d group. Patients had a mean age of approximately 30 years at baseline and were mostly white, and approximately half of them were women. Mean phenylalanine levels at baseline were 1232.7 $\mu\text{mol/L}$. The mean number of weeks to reach maintenance doses was 11.5 and 14 in the 20 mg/d and 40 mg/d groups, respectively.¹⁸

Mean phenylalanine concentrations decreased by 51.1% from baseline to 564.5 $\mu\text{mol/L}$ at 12 months of follow-up, and by 68.7% from baseline to 311.4 $\mu\text{mol/L}$ at 24 months of follow-up. Inattention and mood scores improved while on treatment with pegvaliase and correlated with a decrease in phenylalanine levels. Similar to previous studies, all patients experienced at least 1 AE. However, in this study, 99% of events were mild to moderate in nature, and 96% resolved without dose reduction or interruption. This represents an improvement in the safety profile compared with previous regimens studied. The most common AEs were arthralgia (70.5%), injection site reactions (62.1%), injection site erythema (47.9%), and headache (47.1%). Of the AEs leading to discontinuation, 2.7% were anaphylaxis, 2.7% were arthralgia, 1.1% were injection site reactions, and 0.8% were generalized rash. Twelve patients (4.6%) experienced 1 or more acute systemic HAEs which were independently adjudicated by an allergist/immunologist. The median time after pegvaliase administration to acute systemic HAE was 1.8 minutes, and all occurred within the first 50 days of dosing and were resolved quickly.¹⁸

Patients enrolled in PRISM-1 could continue to PRISM-2 (NCT01889862), a study to evaluate the safety and efficacy of long-term treatment. Patients reaching maintenance dosing in PRISM-1 entered part 1 of PRISM-2, and continued their assigned doses, either 20 mg or 40 mg daily. Part 2 was a randomized, double-blinded, placebo-controlled discontinuation study which will be described below. Part 3 was an open-label pharmacodynamics and pharmacokinetic study, and part 4 is an open-label extension study which is ongoing. Patients who did not reach maintenance dosing in PRISM-1 could enter directly

in to part 4 of PRISM-2, in which the open-label dosing ranges from 5 to 60 mg daily.¹⁸

Eighty-six patients who received pegvaliase in PRISM-2 part 1 enrolled in the double-blinded PRISM-2 part 2 discontinuation trial. An additional 9 patients were enrolled but were not included in the efficacy analysis. Patients were randomized via concealed allocation to receive either their current pegvaliase dose (either 20 or 40 mg/d) or matched placebo containing either 20 mg or 40 mg of Dextran 40 (22% Dextran 40). The study drugs were self-administered daily for 8 weeks, rotating subcutaneous injection sites.¹⁹

The pooled active pegvaliase group phenylalanine concentrations remained stable from baseline to week 8 (503.9-559 $\mu\text{mol/L}$), while levels in both placebo groups increased (563.9-1509 $\mu\text{mol/L}$ in the placebo 20 mg group and 508.2-1164.4 $\mu\text{mol/L}$ in the placebo 40 mg group). However, no significant changes in mood or inattention were observed, perhaps due to the short duration of the trial or to the tools used to measure these symptoms in the trial.¹⁹ Patients in PRISM-1 demonstrated improvements in attention deficit hyperactivity disorder (ADHD) scores at 3 months of treatment.¹⁶

Overall, clinical trial experience from phase 1 to phase 3 suggests substantial reductions in blood phenylalanine concentrations and improvement in inattention and mood symptoms with the use of pegvaliase. However, these benefits must be weighed against the risk of common and sometimes serious AEs.

Dosing and Administration

The package insert for Palyzqi recommends to obtain baseline blood phenylalanine concentrations prior to treatment initiation.¹¹ The induction dosage for pegvaliase is 2.5 mg subcutaneously once weekly for 4 weeks under the supervision of a health care provider. The dosage should be titrated based on tolerability over at least 5 weeks to achieve a dosage of 20 mg subcutaneously once daily. Therapeutic response may not be achieved until the patient is titrated to an effective maintenance dose.

During treatment, patient tolerability, blood phenylalanine concentrations, dietary protein, and phenylalanine intake should be monitored. Studies in adult PKU patients have shown a variation in phenylalanine levels can be observed without any change in treatment.²⁰ In clinical trials, the response to sapropterin treatment was defined as a 30% reduction in blood phenylalanine concentration from baseline.²¹ In contrast, therapeutic response with pegvaliase was based on a 20% reduction in blood phenylalanine concentration from baseline or a blood phenylalanine concentration $\leq 600 \mu\text{mol/L}$ after 24 weeks. If not achieved, increasing the pegvaliase dose to a maximum dosage of 40 mg subcutaneously once daily can be considered. If therapeutic response has not been achieved after 16 weeks on the maximum dosage, discontinuation of pegvaliase is recommended. If

patients experience blood phenylalanine concentrations $<30 \mu\text{mol/L}$ during titration and maintenance, the dosage of pegvaliase may be reduced or the dietary protein and phenylalanine intake may be modified.¹¹

For hypersensitivity reactions, premedication can be considered with an H1-receptor antagonist, H2-receptor antagonist, and/or antipyretic prior to administration based on tolerability. Patients should be observed during and for at least 60 minutes after receiving pegvaliase injection. Patients should also be trained on recognition of signs and symptoms of anaphylaxis, how to administer injectable epinephrine, and how to seek emergency care, if needed. If the decision is made to readminister pegvaliase after an episode of anaphylaxis, the subsequent dose should be administered under the supervision of a health care provider after titrating based on patient tolerability and therapeutic response.¹¹

Due to the risks of anaphylaxis, pegvaliase is only available through a Risk Evaluation and Mitigation Strategies (REMS) program which includes prescriber and pharmacy certification requirements and patient educational enrollment. In clinical trials, most patients developed anti-PEG IgM and IgG antibodies after treatment. The clinical effects of concomitant treatment with other pegylated products are unknown. Therefore, if patients are treated in combination with other pegylated products, further monitoring for hypersensitivity reactions and anaphylaxis is recommended.¹¹

Relevance to Patient Care and Clinical Practice

The risk of adverse outcomes in PKU is related to disease severity, blood phenylalanine concentration, and adherence to treatment.⁴ The assessment of blood phenylalanine concentrations may also be indicative of patient adherence to therapy.²² Poor adherence can manifest as failure to take medical foods or prescribed medications, and missing regular clinic appointments or blood phenylalanine testing.²³ A presentation released by BioMarin Pharmaceuticals suggests there are 125 PKU clinics in the United States currently managing patients through dietary counseling and/or sapropterin.²⁴ A study of 45 PKU clinics showed that non-adherence to clinic-recommended target phenylalanine concentrations increased with age. Most adults had blood phenylalanine concentrations $>360 \mu\text{mol/L}$ with 15% of patients aged 18 to 29 years and 20% of patients aged 30+ years reported to have concentrations $>1200 \mu\text{mol/L}$.²³ Given that PKU can cause neurocognitive and psychiatric symptoms, there may be an unmet need for additional therapeutic approaches in adults with uncontrolled disease.

Dietary treatment consists of dietary restriction of phenylalanine, phenylalanine-free protein substitutes (L-amino acid mixtures), and modified low-protein foods.^{4,6} Patients with residual enzymatic activity of PAH may respond to sapropterin which increases metabolism of phenylalanine to tyrosine. Safety and efficacy of sapropterin have been established in pediatric patients as young as 1 month of age.²¹ Prior to routine

treatment with sapropterin, a test should be conducted to determine if the patient is sapropterin-responsive, defined as a rapid decline in phenylalanine or increase in phenylalanine tolerance. Sapropterin can provide better phenylalanine control and increase dietary phenylalanine tolerance.²⁵ Clinical guidelines have recently been updated on to address the role of pegvaliase in management of PKU. The goal of pegvaliase treatment is to provide maintenance of blood phenylalanine concentrations while normalizing diet. Pegvaliase can be considered for all adult patients with PKU who can adhere to therapy, including requirement for monitoring of AEs.²⁶ No head-to-head trials were conducted comparing the safety and efficacy of sapropterin with pegvaliase. Given patients in the clinical trials were unable to continue sapropterin in the pegvaliase trials, it is unclear whether the combination is statistically and clinically more beneficial than either treatment alone.

Although the package insert for pegvaliase does not specify use to be in conjunction with a phenylalanine-restricted diet, it is indicated in patients with uncontrolled blood phenylalanine concentrations “on existing management”¹¹ which can be inferred as guideline-recommended dietary therapy and/or sapropterin pharmacotherapy. Furthermore, in pegvaliase clinical trials, patients were stable in protein intake and in many instances received counseling from a dietician.^{15–19} However, while Thomas et al observed stable total dietary protein intake, there was a decrease in medical food protein (from 26.3 to 18.4 g/d) and an increase in dietary phenylalanine intake (from 1700.2 to 2679.7 mg/d). This shift may indicate a decreased need for medical food.¹⁸ Efficacy of pegvaliase without dietary therapy was not assessed in clinical trials. Due to the potential shifts in dosing from changing dietary protein and phenylalanine intake, continuation of nutritional and blood phenylalanine monitoring is warranted in patients treated with pegvaliase.^{11,26}

Given only 25% to 50% of patients with PKU respond to sapropterin,³ the availability of additional pharmacologic options is necessary to improve the quality of life in patients with uncontrolled PKU. In 2015, the National PKU Alliance conducted a survey of adults and children with PKU in the United States. The survey confirmed that dietary therapy is the mainstay of clinical treatment. Approximately 6% of survey respondents stated they were not treating PKU with medical foods or pharmacotherapy. Most survey respondents (91%) stated the importance of development of new products for PKU. Respondents generally preferred oral therapy over injectable therapy, and home injections over injections, at a medical facility.²⁷ Pegvaliase is a novel enzyme substitution therapy which can be used in patients with more severe disease and in part meets the needs of the PKU community. The subcutaneous prefilled syringe can be self-administered if patients demonstrate adequate competency.¹¹ Although an oral pegylated PAL formulation has been investigated in animal studies,²⁸ similar trials have not been conducted in humans. It is recommended that multidisciplinary teams continue involvement in

care of patients with PKU, including monitoring therapeutic response, adverse effects, and medication adherence.

Cost

As of June 2018, pegvaliase has been launched. For cost considerations, the average wholesale price (AWP) for pegvaliase-pqpz prefilled syringes are US\$585.60 which includes 3 strengths: 2.5 mg/0.5 mL, 10 mg/0.5 mL, and 20 mg/mL, whereas the AWP of sapropterin 100 and 500 mg tablets are US\$44.28 and US\$221.40 per tablet, respectively.^{29,30} Using these AWP cost figures, the 30-day cost for a 70 kg patient at the maximum recommended sapropterin dose (20 mg/kg once daily) is US\$5314 and at the maximum recommended pegvaliase-pqpz dose (40 mg once daily) is US\$35136. BioMarin Pharmaceuticals predicts the average annual net cost of therapy for a typical patient to be approximately US\$192000 per year based on an average of 1.5 units per patient at maintenance dosing.²⁴ Dietary treatments used in conjunction with currently available pharmacotherapy pose an additional cost burden to patients and payers.

Conclusions

Patient characteristics and preferences should be considered to help guide treatment of PKU. Pegvaliase reduces blood phenylalanine concentrations independent of PAH activity compared with previously available therapeutic alternatives.⁴ In pivotal phase 3 clinical studies, treatment with pegvaliase was associated with overall safety and statistically significant improvements in blood phenylalanine concentrations.^{18,19} Patients also had sustained reductions in blood phenylalanine concentrations that reached guideline-recommended levels. However, due to risks of anaphylaxis, pegvaliase is only available through a restricted program under REMS.¹¹ The injectable route of administration, potential risks, and factors related to insurance coverage may limit the use of pegvaliase. At the present time, pegvaliase is only FDA-approved for use in adults who have uncontrolled blood phenylalanine concentrations >600 μmol/L.¹¹ Clinical guidelines have been updated to address the role of pegvaliase in management of PKU.²⁶ Given the high cost, therapy may be a viable option for patients who have failed existing management strategies due to inadequate response or desire for dietary relaxation. Further research should be conducted to evaluate the safety and efficacy in younger patients, those with milder forms of PKU, in combination with sapropterin, and with limited dietary therapy.

Author Contributions

TH and VAC wrote, reviewed, and approved the final manuscript.

Ethical Approval

Given there was no human participation or use of personal data involved in the writing of this review article, no ethical permission was applied for.

Informed Consent

Given the writing of this review article was non-human subject research and based on the availability of published clinical trial data, written/verbal consent from patients and/or caregivers was not necessary.

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