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Lessons learned from 5 years of experience with pegvaliase in US clinics: a case series

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Background

- Phenylketonuria (PKU) is a rare genetic disorder caused by phenylalanine hydroxylase enzyme deficiency[1]
- Pegvaliase (PALYNZIQ®) is a blood phenylalanine (Phe) lowering enzyme substitution therapy approved for adults with PKU (≥18 years in the US; ≥16 years in Europe) with blood Phe ≥600 µmol/L[2,3]
- This case series illustrates key lessons learned based on up to 5 years of experience with pegvaliase in real-world clinical practice and builds upon recently published literature[4,5]

Methods

- A multidisciplinary panel of 12 healthcare professionals (HCPs) with considerable experience in managing pegvaliase treatment in real-world clinical practice (7 physicians, 4 nurse practitioners, 1 doctor of nursing practice) from 11 different treatment centers in the US participated in a 1-day in-person meeting in April 2023
- All HCPs presented a real-world adult patient case. For each case, challenges with pegvaliase prior to and during treatment, and corresponding strategies to overcome them were discussed. Key learnings from the cases were consolidated

Results

- 12 individuals with PKU receiving pegvaliase for up to 54 months were reviewed and discussed (Table 1)
- All individuals had medical or mental health issues, executive function deficits, challenging social or socio-economic situations, logistical or geographic barriers, or a combination of these; one was considering pregnancy

Table 1. Summary of clinical cases

Case	1	2	3	4	5	6	7	8	9	10	11	12
Demographics and baseline characteristics												
Age, years	19	27	18	26	33	29	22	44	50	68	48	53
Sex	M	F	M	F	F	F	F	F	M	F	F	M
Actual intact protein, g/day[a]	19	60	5	40	8-10	10	6	N/A	40-50	50	55	Unrest.
Actual medical food protein, g/day[b]	121	29	53	30	45-60	40-50	50	15-30	80	15-60	0	0
Phe-restricted diet[c]	Y	N	Y	N	Y	Y	Y	N	N	N	N	N
Blood Phe, µmol/L	988	454	1114	818	777	1089	531	2100	1667	967	1914	1722
Sapropterin dihydrochloride at baseline[d]	Y	N	Y	Y	Y	N	N	N	Y	Y	N	N
Concomitant conditions[e]												
Medical comorbidities	**Y**	**Y**	-	**Y**	**Y**	-	-	**Y**	**Y**	**Y**	**Y**	**Y**
Mental health comorbidities	-	-	**Y**	**Y**	**Y**	**Y**	-	**Y**	**Y**	**Y**	**Y**	**Y**
Executive functioning deficits/ cognitive impairment	-	-	**Y**	**Y**	-	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**
Social/socioeconomic concerns	-	-	**Y**	**Y**	-	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**
Induction/titration												
Pre-medication	H1&H2	H1&H2	H1&H2	H1&H2	H1&H2	H1&H2	H1&H2	H1&H2	H1&H2	H1&H2	H1&H2	H1
Maintenance[f]												
Time to achieve blood Phe ≤360 µmol/L, months[g]	28.6	12.6	NA	4.9	24.4	NA	6.6	6.9	27.3	NA	7.4	2.3
Pegvaliase dose at blood Phe ≤360 µmol/L, mg	60/day	40/day	NA	20/day	40/day	NA	20/day	20/day	60/day	NA	20/day	20/day
Last follow-up												
On treatment, months	43.7	49.3	4.4	22.5	44.1	4.1	12.5	50.5	54.4	Discont.	44.7	13.6
Blood Phe, µmol/L	9	175	1186	376	886	1078	198	147	1193	1454	192	134
Pegvaliase dose, mg	40/day	10/day	40/day	20 5x/wk	40/day	10 mg 2x/wk, 2.5 mg/ wk	20/day	10/day	40/day	Discont.	20/day	20 3x/wk
Actual intact protein intake, g/day[a]	60-80	60	5	75	60	10-15	50-60	80-100	~73	50	65	Unrest.
Medical food intake, g/day[b]	0	0	68	0	0	40-50	0	0	0	60	0	0

F: female; M: male; NA: not achieved; N/A: not available; Phe: phenylalanine; dashes (-) indicate condition is not identified; H1 and H2 refer to H1 and H2 antihistamines

[a]Actual protein intake was derived from diet records and may deviate from prescribed intake. When intact protein provided in mg Phe, 50 mg Phe was considered equivalent to 1 g of intact protein; [b]Actual medical food intake was derived from diet records and may deviate from prescribed intake; [c] >75% of protein from medical food; [d]N= either never tried or non-responder to sapropterin; [e]Case 2 had a pregnancy after initiating pegvaliase; [f]Case 10 discontinued treatment due to poor compliance related to adverse events, family issues and psychological problems; [g]First time blood Phe ≤360 µmol/L

- Pegvaliase was initiated successfully by anticipating potential challenges and implementing individualized strategies to overcome (potential) barriers and stimulate compliance to the therapy in the long term
  - 9 achieved treatment response (maintenance phase with blood Phe ≤360 µmol/L, discontinuation of medical food, and increase/maintenance of intact protein intake)
  - 2 have not yet achieved treatment response (after 4.1 and 4.4 months of treatment)
  - 1 discontinued treatment due to poor compliance related to adverse events (AEs), family issues and psychological challenges
- In several cases, lowering blood Phe levels improved PKU-related symptoms, including neurological issues, even in late-diagnosed individuals
- Figures 1 and 2 summarize key learnings from the cases pre- and post-initiation of pegvaliase

Figure 1. Key learnings from the case series *prior to initiating* pegvaliase

Considerations for starting pegvaliase

- Medical or mental health issues, executive function deficits, social or socioeconomic complexities, older age, or concomitant medications should not prevent individuals from being offered pegvaliase[4,5]
- Women of childbearing age and those contemplating pregnancy may be offered pegvaliase, provided they are well informed and understand the uncertainties and potential associated risks of both maternal PKU syndrome and continuing pegvaliase while trying to become pregnant/during pregnancy[6,7]
- Identifying and setting up additional support such as regular telemedicine or local provider visits, or connecting with a local support organization ahead of starting pegvaliase can be reassuring and help overcome logistical issues

Education of candidates for pegvaliase treatment

- Individualization of education is especially important for individuals with more complex backgrounds
- In cases of impaired executive or cognitive function, the teach-back method or clear, simple written resources with images, such as side effect and medication action sheets, and emergency protocols can help confirm and support learning
- Set realistic expectations regarding time to efficacy, number of injections, and possibility of modifying the dosing schedule[4]

Figure 2. Key learnings from the case series *after initiating* pegvaliase

Managing adverse events

- Individualization of dosing is important for individuals with complex backgrounds. The induction and titration phase can be modified in an attempt to reduce the risk of AEs. A prolonged and/or simplified induction and titration schedule can also help address executive function and psychosocial issues
- Start premedication prior to pegvaliase to maximize AE prevention and to distinguish between premedication- and pegvaliase-related AEs
- Comorbid conditions should be monitored closely during pegvaliase treatment and may require collaboration with HCPs involved in managing underlying comorbid conditions

Managing treatment adherence

- A good relationship with the clinic, ongoing education, and supportive relatives or friends can help individuals to remain adherent while utilizing pegavaliase
- Supporting adherence may be addressed by a daily reminder system, telemedicine, in-home support, or a simplified or shortened treatment plan
- In the absence of a dedicated support person, in-home support, social workers, and/or support organizations may ensure access to medications and continued connection with the treatment team
- Increased touch points with individuals and tailoring pegvaliase management to their social determinants of health can allow for successful management even after a treatment interruption

Adjusting diet and pegvaliase dosing during maintenance

- Additional dietetic support and education on how to transition to a nutritionally balanced and healthy diet may be required, particularly in those with disordered eating
- Some individuals may tolerate a reduction in the dose and number of daily injections over time while maintaining blood Phe levels ≤360 µmol/L. A dose reduction should also be considered in case of blood Phe levels <30 µmol/L

Managing pegvaliase during pregnancy

- Use of pegvaliase during pregnancy has not been studied and requires a benefit/risk discussion and assessment[7]. A surveillance program (PALominostudy.com) is ongoing and evidence continues to emerge[6]
- If the decision is made to continue pegvaliase during pregnancy, it is preferable that a stable dose and efficacy have been achieved prior to pregnancy. Blood Phe levels should be monitored frequently prior to and during pregnancy to maintain blood Phe within treatment range[6]

Conclusions

- The learnings from the presented cases and up to 5 years of expert experience in real-world clinical practice provide insight and guidance for HCPs initiating and managing pegvaliase treatment in complex PKU cases
- These cases demonstrate that, with comprehensive assessment and addressing barriers, pegvaliase treatment can be successful in adults with PKU, regardless of previous treatment, age, socioeconomic, cognitive, or executive function challenges, as well as in those with comorbidities or considering pregnancy
- These recommendations are applicable to all patients on pegvaliase and should be individualized according to need
- Ongoing documentation of clinical experience is crucial for advancing the management of individuals receiving this treatment

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