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Management of patients with phenylketonuria (PKU) under enzyme replacement therapy: An Italian model (expert opinion)

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ABSTRACT

Objective: Phenylketonuria (PKU) is a metabolic disorder necessitating lifelong management to prevent severe neurological impairments. This paper synthesises clinical practices from Italian specialist centres to delineate a unified approach for administering pegvaliase, a novel enzyme replacement therapy for PKU.
Methods: Virtual meetings convened in September 2022, gathering a steering committee (SC) of experts from five Italian centres specialising in PKU. The SC reviewed, and discussed clinical practices, and formulated recommendations for pegvaliase treatment.
Results: The SC outlined a comprehensive treatment roadmap for PKU management with pegvaliase, emphasising the importance of multidisciplinary care teams, patient selection, pre-treatment evaluation, and education. Recommendations include initial hospital-based pegvaliase administration, regular monitoring of phenylalanine and tyrosine levels, dietary adjustments, and management of adverse events. A consensus was reached on the need for a digital database to manage treatment plans and enhance communication between healthcare professionals and patients.
Conclusion: The expert panel's consensus highlights the complexity of PKU management and the necessity for a coordinated, patient-centred approach. The recommendations aim to standardise care across Italian centres and provide a framework for integrating pegvaliase therapy into clinical practice, potentially informing international guidelines. Further research is warranted to evaluate the long-term impact of these practices on patient outcomes and quality of life.

1. Introduction

It is estimated that globally, one in 23,930 newborn babies has phenylketonuria (PKU), a rare inborn metabolic disorder preventing the metabolism of phenylalanine (Phe) to tyrosine (Tyr) [1]. Prevalence in Europe, estimated to be 1:10,000 by Blau, van Spronsen [2], varies largely, from 1:4000 live births in Italy to 1:112,000 live births in Finland [1,3].

The conversion of Phe into Tyr requires several components: phenylalanine hydroxylase (PAH), the cofactor tetrahydrobiopterin (BH4), molecular oxygen, and iron [2]. A deficiency in either PAH or BH4 can result in Phe blood levels exceeding 120 μmol/l, a condition called hyperphenylalaninaemia (HPA), and in the accumulation of Phe in the brain [3].

From a clinical standpoint, HPA is classified into two categories: non-PKU HPA, where blood Phe concentration ranges from 120 to 360 μmol/l, and PKU HPA, where blood Phe concentration exceeds 360 μmol/l [4,5].

PKU is mostly caused by pathogenetic variants in the PAH gene [1,6], located on chromosome 12q22-q24.2 [7]. The PAHvdb database, available at http://www.biopku.org/ lists >1000 of such mutations. Defects in BH4 metabolism account for approximately 2% of patients with HPA [8]. The degree of PAH loss of function determines the PKU phenotype and correlates with the severity of the disorder, with residual

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enzyme activity being inversely proportionate to Phe blood levels [8].

If left untreated, PKU (OMIM # 261600) presents with a wide spectrum of clinical manifestations including progressive intellectual disability, autism, epilepsy, behavioural and psychiatric problems, neuromotor deficits, and eczema [2,9], as well as a light pigmentation of the skin and musty odour.

On the other hand, lowering and life-long control of Phe levels may prevent or limit neurological and cognitive disabilities [10–13]. PKU treatment aims to keep blood Phe levels under rigorous control. American guidelines recommend a target range of 120–360 μmol/l for patients of all ages [14], whereas European guidelines recommend a target of 120–360 μmol/l for patients younger than 12 years and during pregnancy, and a target range of 120–600 μmol for patients older than 12 years of age to prevent neurodevelopmental derangement and possible neurocognitive function impairment [9].

PKU control is generally achieved through a lifelong and carefully monitored low-Phe diet, in combination with a Phe-free protein substitute. This is usually supplemented with minerals and vitamins [15]. However, this diet can be unpalatable and unsociable [16], and compliance is often poor [17]. Treatment adherence frequently declines with age, being self-relaxed in late childhood and abandoned during late adolescence and adulthood [16].

To date, the only available pharmacological therapies for PKU are supplementation with sapropterin dihydrochloride (the synthetic form of BH4, marketed as Kuvan® by BioMarin Pharmaceutical Inc., Novato, CA, USA), and enzyme replacement therapy with pegvaliase. However, sapropterin dihydrochloride is effective only in patients with high PAH residual activity. Therefore, it may not work properly in patients with classical PKU who have null residual enzymatic activity and are on strict dietary management [9,14].

On the other hand, pegvaliase is a PEGylated form of the recombinant enzyme phenylalanine ammonia lyase (PAL) derived from *Anabaena variabilis*. This novel and unique enzyme replacement therapy is administered subcutaneously and converts phenylalanine to ammonia and trans-cinnamic acid [18] regardless of residual enzymatic activity [14]. It was approved for use in adult patients with PKU with blood Phe >600 μmol/l by the Food and Drug Administration (FDA) in May 2018 (https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=88195. Accessed 12 November 2023), and 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. Accessed12 November 2023). Pegvaliase is marketed as Palynziq®.

PKU management varies between and within countries, including Italy [17,19]. A recent survey of six Italian experts conducted by Burlina and colleagues [17] showed significant differences in disease management between specialistic centres and highlighted the need for a shared and homogeneous approach to managing PKU patients in specialized centres.

This paper aims to define clinical and biochemical good practices and a shared approach to the management of patients affected by PKU on treatment with pegvaliase, based on the real-life experience of Italian pioneer centres. Additionally, it aims to harmonize patient care at a national level by proposing a shared approach and offering guidance to Italian centres that will have access to this novel therapy for their patients.

2. Materials and methods

In September 2022, BioMarin Pharmaceutical Inc., in conjunction with AIM Education SRL (Milan, Italy), an independent medical communication agency, organized a virtual clinical practice review meeting for a panel of PKU experts (the steering committee or SC) from five specialized Italian centres. This panel was specifically designed to review and discuss clinical practices related to the treatment of PKU patients with pegvaliase. A week later, a virtual consolidation meeting was held to further discuss and consolidate the recommendations made during the initial meeting.

2.1. The expert opinion panel

In Italy, there are several specialistic centres dedicated to the care and assistance of patients with metabolic diseases.

In forming the panel, specific consideration was given to the nationwide representation of the selected centres and to the number of PKU patients managed with pegvaliase.

The expert panel featured representatives from five specialized Italian centres. Participating centres were the: Department of Medical and Surgical Sciences, S. Orsola University Hospital, Bologna, Italy; Clinical Department of Pediatrics, San Paolo Hospital, ASST Santi Paolo e Carlo, University of Milan, Italy; Department of Maternal and Child Health, Federico II University Hospital, Naples, Italy; Unit of Internal Medicine and Rare Diseases, Regional Centre for the Metabolic Rare Disease, University Hospital "Paolo Giaccone", Palermo, Italy; Inherited Metabolic Diseases Division, Regional Centre for Expanded Neonatal Screening, Women and Children's Health Department of Integrated Diagnostic, University Hospital, Padua, Italy.

The SC included three paediatricians (IS, VR, AB), a nutrition science clinician (LB) and an internal medicine clinician (DN), all with specific expertise in the management of PKU patients and each contributing clinical practices and patient experiences from their respective centres.

In Italy, primary care for patients with metabolic diseases such as PKU has traditionally been overseen by reference clinical centres, predominantly staffed by paediatricians. While this organizational model has been the standard since the inception of these centres, it is currently undergoing modifications. Italy has initiated a transition project aimed at improving adult patient care, especially in hospital centres historically focused on paediatric care. In non-paediatric centres, the transition process is more seamless, with paediatric metabolists assuming a consultative role. Therefore, the panel's composition reflects the real-world clinical practice in Italy, providing a comprehensive perspective on PKU management across all age groups. All authors were members of the SC.

The use of this dual-consideration approach for panel formation brought considerable advantages. The geographically diverse distribution of the centres (Fig. 1) reflected the full scope of PKU patient management across Italy. The unique regional contexts of each centre, paired with their significant experience in PKU patient treatment, contributed to a rich and diverse range of insights and expertise, adding valuable depth and breadth to the discussions. Moreover, such variety allowed for an inclusive dialogue, generating comprehensive guidelines capable of catering to varied patient scenarios across Italy. In total, the centres managed 34 patients with an average age of 29.8 years (standard deviation 5.6; median age 27.3 years; age range 14–44 years).

2.2. Virtual meetings

The overall aim of the meetings was to define an effective and flexible approach to the management of PKU patients treated with enzyme replacement therapy. Both meetings were structured as roundtable group discussions and detailed minutes were taken (Table 1).

During the first meeting, the experts shared their real-life clinical experiences in the treatment of PKU patients with pegvaliase. The discussion focused on the various strategies adopted to implement/manage this novel enzyme replacement therapy and on the resources allocated to translate this therapy into clinical practice. The key aspects of the management of PKU patients were thoughtfully deliberated, incorporating the diverse experience and views of the panellists. During the second virtual consolidation meeting, the experts critically reviewed and discussed the previously identified hot topic, developing a set of good clinical practice recommendations on the management of PKU patients on pegvaliase. In the last round of discussion, the practice

Fig. 1. Geographic distribution of the selected specialized centres across Italy involved in the expert panel.

Table 1
Composition of the multidisciplinary core team and role of their members in the treatment of PKU patients on pegvaliase.

Steering committee recommendations for the composition of the team treating PKU patients on pegvaliase	
Speciality	Role
Physician (with experience in metabolic diseases)	- Conducting patient preliminary assessments - Educating patients and observers on pegvaliase treatment - Performing clinical examinations - Evaluating blood Phe and Tyr test results - Prescribing pegvaliase - Titrating pegvaliase to target maintenance - Adjusting pegvaliase dosing - Monitoring and managing adverse events - Prescribing concomitant medications - Maintaining and adjusting pegvaliase treatment - Assessing treatment progression - Conducting patient follow-up
Dietitian	- ssessing the patient's nutritional status and Phe tolerance - Assessing protein and nutrients intake - Counseling on dietary management - Maintaining and adjusting dietary plans - Educating patients and caregivers on a balanced diet that meets the age-specific nutritional requirements of the patient
Psychologist	- Conducting surveillance and follow-up on neurocognitive deficits and psychological discomfort - Performing neurocognitive testing and quality of life assessments - Providing patient counseling and support - Assessing patients' willingness and readiness to change their eating habits - Monitoring and managing patients' fears, phobias, and expectations

recommendations were further developed and fine-tuned.

The recommendations developed by the SC are based on the real-life clinical experience of the experts and are intended as core treatment requirements.

3. Results

3.1. Management of the PKU patient on pegvaliase

The SC agreed that the goal of pegvaliase treatment is the achievement of the target Phe blood levels set in the European guidelines and Italian consensus [4,9], and that the care of the PKU patient on pegvaliase should be multidisciplinary.

The SC recommended the establishment of a core treatment team. This team should comprise at least a physician with expertise in metabolic diseases, a dietitian, and a psychologist. The team should closely interact with a laboratory with amino acid assay capabilities. This core team would enable the implementation of pegvaliase treatment even in small metabolic centres [20].

The implementation of this team requires the training of healthcare professionals (HCPs) involved with the patient on the drug and its administration, the therapy, and recognising signs and symptoms of adverse events (AEs).

The management of patients undergoing pegvaliase treatment may necessitate more frequent and consistent monitoring than conventional standards. This is crucial for the proper handling of drug-related issues, such as AEs, as well as the timely adjustment of Phe values and/or drug dosages. Therefore, it is essential to have access to rapid communication systems such as home monitoring with remote consultations (e.g., telemedicine).

The composition of this multidisciplinary core team and the role of their members are summarised in Table 2.

3.2. Practice recommendations: key stages of PKU management with pegvaliase

The SC identified ten key stages in the treatment roadmap of PKU patients on pegvaliase therapy:

3.2.1. Patient characteristics

The SC discussed the criteria for identifying patients suitable for pegvaliase therapy for PKU. In addition to clinical parameters, the committee emphasized the importance of considering the patient's overall characteristics, including their expectations and preferences regarding therapy. In line with the Italian national consensus on PKU management and pharmacological treatment, the SC agreed that patients should be able to consent and adhere to treatment.

The decision to initiate pegvaliase therapy should be based on a comprehensive evaluation of the patient's clinical characteristics and an individual assessment of their current disease management. The patient's ability to manage PKU and their history of adherence to previous treatment regimens should be carefully considered. Clinicians should thoroughly assess and discuss the potential clinical and quality-of-life (QoL) benefits of pegvaliase treatment with the patient to determine the suitability of this therapeutic option. The presence of a caregiver who can provide necessary assistance to the patient, as stipulated by the drug label, constitutes a further essential element in the preliminary evaluation of a patient who is eligible to commence treatment.

3.2.2. Patient education on pegvaliase therapy

Pegvaliase is a novel enzyme therapy with commonly occurring AEs, including injection site reactions, arthralgia and, although rarely, hypersensitivity [18]. As such, it is essential that patients are thoroughly educated about the potential risks and benefits of pegvaliase therapy, including the possibility of hypersensitivity (anaphylaxis). This can be achieved through one-to-one preliminary meetings with patients,

Table 2
Minimum requirement for the clinical management of PKU patients on pegvaliase.

Eligibility criteria	Older than 16 years Willing to commit to therapy/follow-up as needed Suitable social context with available caregiver/observer Availability of a general practitioner	Easy access to emergency services within 30 min from the onset of signs and symptoms of anaphylaxis/severe adverse events Anaphylaxis History: No history of misdiagnosed severe anaphylaxis Strong commitment to achieving normal Phe values and unrestricted diet
Exclusion criteria	Planning on becoming pregnant within at least the next 12 months Travelling within the next 12 months to countries where national health services are unable to treat adverse reactions Presence of a psychiatric disorder that could hinder the management of PKU	
Organization of the clinical site	A core team consisting of a physician, dietitian, and psychologist, with support from a nurse, and PKU laboratory Availability of an allergologist, neurologist, and psychiatrist on site Availability of rescue medication and equipment, such as an emergency trolley, IV steroids, antihistamines, and adrenaline Capability to conduct Phe/Tyr dosage within a week	A reference centre responsible for providing a treatment plan A hospital pharmacy able to dispense the drug and epinephrine Ability to communicate with the patient, including through telemedicine if available
Patient therapeutic monitoring	Pre-treatment dried blood spot measurements should be taken at least once a week/every other week for patients who are being routinely monitored Pre-treatment nutritional assessment by a dietitian to understand longstanding eating habits, with follow-up at least once every 6 months based on blood Phe and Tyr levels or anthropometric values For patients on a free diet, the dietary follow-up should not exceed 6 months For patients on a Phe-restricted diet, dietary checks should coincide with any increase in dietary Phe, potentially even 15–30 days after the previous check if necessary Regular biochemical monitoring should be conducted according to pre-treatment guidelines, at least once every three months	Regular anthropometric examination should be conducted according to pre-treatment guidelines, at least once every six months or as needed Regular neuropsychological assessment should be conducted using pre-treatment scales, such as the food neophobia scale and QoL questionnaire, at least once every six months First pegvaliase administration should occur in an outpatient setting with close observation for at least one hour. The treatment plan should be adjusted according to patient's needs and emerging issues Provision of a one-month supply of pegvaliase and an auto-injectable epinephrine device from the hospital pharmacy on the day of the first administration

PKU, phenylketonuria; Phe, phenylamine; Tyr, tyrosine.

follow-up meetings with patients and their caregivers/observers and the involvement of the patient's general practitioner (GP).

The meetings should focus on premedication use, the potential for AEs and their management, and similarities and differences in symptoms between anxiety and hypersensitivity. Patients and their caregivers/observers should receive information and support in various formats, including paper-based materials, videos, and in-person demonstrations with staff specialized in pegvaliase treatment.

The paper-based informative material should be designed to cover important aspects of pegvaliase therapy. It should include information on the benefits and risks of pegvaliase therapy, including during pregnancy, how the therapy works, what situations may occur in conjunction with the introduction of the drug, and what are the main focuses that patient should keep when starting treatment. The material should also include notes on blood Phe testing and diet, as well as what to do if a dose is missed and detailed instructions on how and when to use an epinephrine autoinjector.

An example of the outline of the informative material is reported below:

1. Introduction to Pegvaliase Therapy: This section should provide an overview of what pegvaliase is.
2. How Pegvaliase Therapy Works: This part should explain the dose escalation protocol, the need for premedication drugs, the requirement of an observer for 1 h after the injection, the importance of strict interaction with the metabolic team, and the necessity to perform additional dosage of Phe and Tyr if required. It should also emphasise the need to carry an epinephrine autoinjector.
3. Benefits of Therapy: This section should detail the potential benefits of pegvaliase therapy, such as achieving target blood Phe (hopefully physiological Phe values) while maintaining a normoproteic diet.
4. Risks and Side Effects: This part should provide information on the potential risks and side effects of the therapy, including during pregnancy.
5. Pegvaliase Therapy and Pregnancy: This section should explain that there are currently insufficient data on the safety of pegvaliase during pregnancy. It should also highlight that in the first 1–2 years of therapy there is a high risk of blood Phe and Tyr fluctuations. Women who intend to start pegvaliase should be aware of these risks and informed about other therapeutic options for PKU management during pregnancy.
6. Starting Therapy: This part should discuss what to expect when starting pegvaliase and situations that may occur such as recognising anxiety and considerations for travelling.
7. Monitoring Therapy: This section should explain what patients should watch for after starting pegvaliase, including any changes in their clinical status and signs and symptoms of anaphylaxis (Syncope, hypotension, angioedema, dyspnoea, cyanosis, wheezing, chest constriction, tachycardia, vomiting/diarrhoea).
8. Blood Phe Testing: This part should emphasise the importance of regular blood Phe testing.
9. Dietary Considerations: This section should provide notes on diet while on pegvaliase therapy.
10. Missed Doses: This part should give instructions on what to do if a dose is missed. Patients must be informed that they should not take two doses of Palynziq to make up for a missed dose and that clinical evidence suggests that pegvaliase therapy can be resumed at the previous dose for up to 8 week of treatment interruption [21].
11. Use of Epinephrine Autoinjector: This section should offer comprehensive instructions on the usage and timing of an epinephrine autoinjector, which should be always carried by patients undergoing pegvaliase therapy. Valuable information on managing severe AEs associated with pegvaliase treatment can be found in the article authored by Hausmann and colleagues [22].

3.2.3. Pre-treatment clinical investigations

Pegvaliase therapy is indicated for PKU patients older than 16 years

with blood Phe levels >600 μmol/l who are unresponsive to BH4.

The SC agreed that before starting treatment with pegvaliase, certain minimum essential preliminary investigations should be conducted. These include the assessment of anthropometric parameters such as weight, height, and BMI; biochemistry, including nutritional parameters, blood Phe, Tyr, and dried blood spot (DBS) testing; neurocognitive and neurological tests; and an assessment of QoL. Practical recommendations for assessing cognitive, psychological, and neurological outcomes in paediatric, adolescent, and adult patients with PKU can be found in the expert opinion by Manti and colleagues [23]. The SC also agreed on the need to evaluate the patient's suitability for pegvaliase treatment. This evaluation should include an analysis of the patient's social context and any psychiatric or psychological issues that could affect treatment and therefore lead to a decision not to initiate treatment at all (Table 2).

3.2.4. Patient training on therapy management and administration

Soon after the pre-treatment assessments, or on the day of the first administration, the patient should receive a calendar to remind them of the dosing and schedule of pegvaliase administration, according to their treatment phase.

3.2.5. Engagement of the patient's General Practitioner

The SC agreed on the importance of the involvement of the patient's general practitioner during treatment. GPs should be sent informative materials on pegvaliase and a letter outlining the treatment plan, premedications and possible AEs. Additionally, GPs should receive regular updates on the patient's progress to ensure continuity of care.

3.2.6. Administration of pegvaliase injection(s)

The SC agreed that at least the initial two doses of pegvaliase should be administered as an outpatient procedure in a hospital setting. After administration, patients need to be closely observed to assess their response to the treatment and watch for any immediate adverse reactions, such as anaphylaxis. Patients and observers can receive specific, face-to-face education on pegvaliase treatment during this observation period. In addition, the patient or caregiver must demonstrate competence in administering the injections. The hospital setting should ensure that the patient or caregiver can administer the injections appropriately and should not terminate until this competency is established.

While there are currently no sufficiently robust data available in scientific literature to confidently determine the appropriate observation period for patients after pegvaliase administration, it is important to note that every patient's situation is unique. As such, individual monitoring plans may vary based on several factors, including the patient's response to treatment, potential side effects, and the specific monitoring protocol set by the healthcare provider.

Following the label's guidance, it is recommended that at least an hour of observation is conducted after pegvaliase administration. However, it remains crucial for doctors to be available following dose administrations to ensure medical attention if needed. In case of urgent needs, patients are advised to visit their General Practitioner (GP) and/or the nearest Accident & Emergency (A&E) department. These situations should be considered as potential allergic reactions not specifically linked to the PKU diagnosis and thus need to be treated as such.

3.2.7. Monitoring of Phe/Tyr blood levels

Pegvaliase therapy effectively controls blood phenylalanine (Phe) levels, allowing individuals to consume a healthy diet with sufficient protein, without needing medical food [24]. The therapeutic efficacy of pegvaliase in substituting PAH activity permits a liberalization of dietary restrictions without compromising metabolic health, enhancing patients' QoL, and yielding favourable long-term outcomes. Given the importance of promptly identifying such drug responses, continuous monitoring remains vital even with enzyme treatment to ensure optimal therapeutic results and patient well-being.

For patients on a free diet, starting pegvaliase treatment with high Phe levels (exceeding 1200 μmol/l), monitoring should be conducted at least monthly during the initial 2–3 months. After this period, while on daily 10 mg doses, more frequent monitoring (e.g., every 15 days or weekly) is advisable due to potential fluctuations in Phe levels.

For patients on a restricted diet, monitoring should be conducted at least every 15 days, as they start treatment with Phe levels close to the 600 μmol/l cut-off for initiating pegvaliase treatment.

For patients on long-term therapy, a monthly evaluation may be sufficient once response patterns stabilize.

3.2.8. Pegvaliase dose adjustments

The goal of dose adjustment in pegvaliase therapy is to maintain blood Phe concentration within physiologic levels, which are usually specific to each patient's metabolic needs and treatment objectives.

During the maintenance phase of therapy, pegvaliase doses may be adjusted following the prescribing label if therapy is well tolerated (see below). The maintenance phase begins when patients transition to a 20 mg daily dose.

If there has not been an adequate blood Phe response by 24 weeks on 20 mg daily, it is recommended to increase the dose to 40 mg daily. If there is still no adequate blood Phe response by 16 weeks on 40 mg daily, the dose should be increased to 60 mg daily (3 × 20 mg syringes) for at least another 16 weeks.

If a patient does not respond to therapy after these dose adjustments, alternative treatments or approaches may need to be considered by the clinician. In the event of a partial response, such as achieving lower Phenylalanine (Phe) levels compared to the baseline but still above the target ranges, it's crucial to discuss the potential suspension of therapy with the patient. This discussion should also consider that a full response to pegvaliase may take >30 months as demonstrated in clinical studies [4]. Patients should be informed about this potential timeframe before starting and during the treatment with pegvaliase.

Real-world dosing patterns of pegvaliase may differ from the prescribing label [25]. The relationship between titration timeline, treatment behaviour change, and long-term Phe control is still unclear and, therefore, the exact dose required for each patient cannot always be determined.

Dose adjustment should be tailored to the individual patient's response to treatment, their Phe levels, their dietary intake, and their tolerance to pegvaliase. The specific dose adjustment protocols may vary based on the treating physician's experience and the individual patient's needs.

Even if not explicitly mentioned on the product label, a slowdown should be considered based on individual patient circumstances.

The decision to implement a slowdown in pegvaliase therapy should be personalized and based primarily on the patient's adverse reactions to treatment. Other factors, such as the patient's overall metabolic control and response to treatment, should also be considered. Physicians may consider either scaling down the daily dose or trying an alternate-day dosing approach as potential options during the slowdown phase.

In the context of dose adjustment for patients experiencing hypophenylalaninemia, the approach may differ depending on the patient's dietary intake. Pegvaliase dose should be reduced for patients on a normoproteic diet to find the minimum effective dose that maintains phenylalanine levels within physiologic levels. On the other hand, if a patient is still on a low-Phe diet, the focus may shift to improving the diet's nutritional balance. Nutritional counseling and ensuring a balanced diet appropriate for the patient's age and activity level should be prioritized. Dose adjustments, including eventual tyrosine supplementation if required, can be considered as necessary [18,26].

3.2.9. Adjustment of diet

Clinical practice has shown that pegvaliase therapy is effective for patients with phenylketonuria. However, it's been observed that patients, driven by enthusiasm, may tend to liberalize their diet. This

possible lack of adherence to the dietary regimen can result in a rapid increase in blood Phe levels. Therefore, it's crucial to define the strategy for increasing the dietary Phe content even before starting treatment.

For patients with blood Phe levels <360 μmol/l on a Phe-restricted diet, protein intake should be increased in increments of 10–20 g [27]. Patients not on a Phe-restricted diet should continue their previous dietary regimen. Dietary adjustments may also be agreed with the patient, considering the need to maintain compliance throughout treatment.

The outcome of a diet adjustment should be monitored using DBS measurements. A positive outcome may be defined as two consecutive blood Phe measurements via DBS following a dietary change that show no changes in value and that were taken at least one week apart from each other for a period of at least three weeks.

However, as indicative as these findings may be of a response, having achieved them does not necessarily mean that the patient is destined to keep them as such. Therefore, the possibility of observing subsequent increases in value, even independently of any changes that may have been implemented, is to be expected.

It is worth noting that achieving treatment effectiveness (i.e., Phe levels lower than 600 μmol/l) allows but does not guarantee the possibility for patients to consume a free diet while still maintaining blood phenylalanine control. This highlights the importance of continuous monitoring and adjustment as necessary in the treatment process.

3.2.10. Adverse events prevention and management

The management of AEs with pegvaliase therapy in PKU patients involves premedication with an H1 antagonist (cetirizine 10 mg/day or fexofanedine 120 mg/day), with or without an H2 antagonist (famotidine 40 mg/day), and antipyretic/analgesic agents (acetaminophen, 1000 mg/day) prior to each pegvaliase dose during induction and titration. Premedication during maintenance should be considered based on patient tolerability.

In the event of an acute severe hypersensitivity reaction, pegvaliase should be interrupted, and reintroduction may be evaluated by the clinician in agreement with the patient. Rechallenge should occur in a controlled setting with a lower dose and frequency of administration.

During the induction and titration phase, daily intake of premedication is recommended to reduce hypersensitivity risks.

Common AEs during this phase may persist beyond this phase for some patients. If hypersensitivity reactions persist, short-term use of oral glucocorticoids such as prednisone (10–50 mg) and/or reverting to the last well-tolerated dose can be considered. Managing injection site reactions involves increasing antihistaminic doses, applying cooling and using topical glucocorticoids or oral glucocorticoid. For arthralgia and fever, NSAIDs are recommended. In the maintenance phase, persistence of AEs warrants evaluating medication compliance and correct injection site rotation.

The recommended treatment roadmap of the PKU patient on pegvaliase is summarised in Fig. 2.

3.3. Minimum requirements for pegvaliase therapy

The Steering Committee discussed the significant differences in disease management between specialized centres and recognized the need for a shared and homogeneous approach to managing PKU patients. To

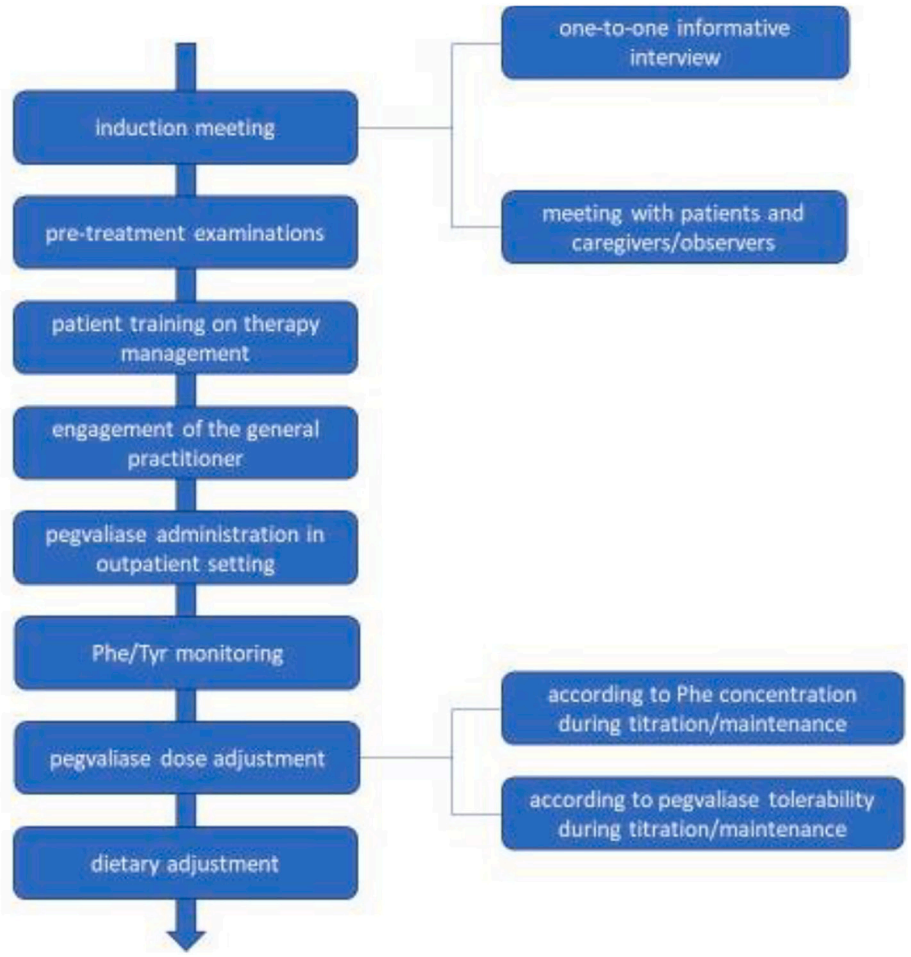

Fig. 2. Treatment roadmap of the PKU patient on pegvaliase. PKU, phenylketonuria; Phe, phenylamine; Tyr, tyrosine.

address this, the committee considered the practical aspects of managing PKU patients with pegvaliase and defined a set of minimum requirements for the selection of patients, the organization of the clinical site, and the patient's therapeutic journey. These requirements, which aim to ensure that all patients receive consistent and high-quality care, regardless of the specialized centre they visit, are summarised in Table 2.

3.4. Additional strategies and actions

The SC agreed that PKU patient management would benefit from the implementation of a digital database and direct communication with the HCPs, the health system, and the centre. A digital, searchable database for internal use, to be updated each week/fortnight, would ease the management of the medication schedule, the treatment plan and all the practicalities related to the administration of pegvaliase.

Additionally, the implementation of timely and ongoing communication (via email/phone/texts and remote consulting) during treatment would engage the patient and improve their treatment adherence. The SC also agreed that HCPs should be engaged more frequently during dose escalation.

4. Discussion

This expert opinion aims to provide practical recommendations for managing PKU flexibly with pegvaliase. Various aspects of PKU clinical care in Italy were discussed and analysed by experts, revealing a shared approach and convergence towards a unified strategy. The composition of the treatment team, clinical management, patient education on enzyme substitution therapy, barriers to management, and potential solutions were all discussed. The Scientific Committee (SC) offered insights into the practical organization of clinical sites and the therapeutic journey of PKU patients.

Phenylalanine plays a significant role in brain development and function throughout life [28–31]. Elevated levels of this amino acid can lead to various complications, including intellectual disability, microcephaly, and seizures [32]. In pregnant women with PKU, high phenylalanine levels can cause complications for the foetus, such as microcephaly and congenital heart disease [28–30].

After birth, untreated PKU can lead to epilepsy, cognitive impairment, and motor deficits [32]. High phenylalanine levels can interfere with the transport of large neutral amino acids (LNAAs) across the blood-brain barrier, affecting protein synthesis and neurotransmitter production [33–35]. A high phenylalanine concentration in the brain also may compete with tyrosine and tryptophan for binding to tyrosine hydroxylase and tryptophan hydroxylase respectively, further decreasing dopamine and serotonin neurotransmitter synthesis [36].

As individuals with PKU age, they may encounter neurodevelopmental challenges. These can include speech delays, language production difficulties, and attention deficits with hyperactivity (ADHD). Autistic behaviours and ADHD are particularly common among PKU patients, with the frequency of ADHD being roughly twice that of the general population [37].

Dietary treatment is fundamental in managing PKU and is recommended for life. If dietary treatment is discontinued, PKU patients may develop behavioural and psychiatric issues like depression and anxiety during childhood or adolescence, with problems tending to worsen with age. However, these issues can be prevented with strict monitoring and control of Phe levels. While some issues may have limited reversibility, others related to abnormal myelination often respond positively to interventions that reduce phenylalanine levels [31]. Long-term dietary treatments can also result in unfavourable outcomes. A growing body of evidence supports the need of tailoring dietary treatments to the individual, rather than adopting a one-size-fits-all approach [38–41].

However, a recent survey designed to characterize the dietary habits of Italian adult PKU patients found that adherence to the PKU diet is unsatisfactory; only 42% of PKU patients were compliant with dietary recommendations. Patients also reported increased consumption of natural protein sources and reduced daily use of amino-acid supplements [42].

Interestingly, patients have an altered perception and awareness of the disease and its consequences; about 40% of them do not consider PKU a disease. Nearly half of them reported a high plasma value over the last six months (> 600 μmol/l). The main factors affecting compliance with dietary recommendations were inappropriate perception and knowledge of the disease and a lack of awareness of the negative impact of poor metabolic control in adult life.

To address these issues, educational initiatives to increase awareness about PKU are recommended along with regular follow-up visits and psychological interventions [42]. Efforts should also be made to make dietary treatment more acceptable.

Patient education, a multidisciplinary treatment team, and effective communication between patients and HCPs are crucial for managing PKU with pegvaliase. Preliminary meetings can enhance dialogue and increase patient awareness about the therapy's demands. Patients can strengthen their commitment to treatment and assess available resources through interviews and collaboration with their general practitioner. Both patients and primary care physicians can benefit from supplemental information. BioMarin is creating a website with guides on pegvaliase dosing, administration, risk evaluation, and mitigation strategies (available at https://www.pku.com).

During the discussion, the SC heavily focused on patient selection and preparation phases for therapy. It is believed that proper selection and patient education ensure successful outcomes for this complex treatment, whose benefits are appreciated even after several months of daily injections.

Among the patient selection criteria, it should also be emphasized that while an ongoing psychiatric condition may require exclusion from treatment, this is not the case for patients who have a history of psychiatric pathology treated pharmacologically with a good outcome. These patients could benefit from the reduction of Phe levels, provided that the doctor still assesses the patient's ability to adhere to prescriptions.

The SC recognized that PKU's complex nature requires a multidisciplinary approach, as reported by several authors [4,5,43,44]. To provide optimal care, internal training for HCPs involved in treating PKU patients is essential.

A crucial and distinctive feature of the Italian management approach, as underscored by the SC, is the need to differentiate the management of PKU patients depending on whether they are on an unrestricted or restricted diet while starting pegvaliase. Those on a restricted diet necessitate heightened attention, encompassing more frequent monitoring of Phe levels, increased consultations with nutritionists to ensure dietary education, and enhanced focus from psychologists to address potential eating disorders [15].

It is also noteworthy that PKU patients may experience psychological distress and a diminished sense of overall well-being, often due to the dietary treatment [42,45]. Therefore, a holistic approach PKU management should include psychological support and well-being assessments.

However, as PKU management shifts from being primarily diet-based to a polypharmacological approach, the impact on patients' perceived well-being is not fully understood. This shift in the treatment paradigm requires the continuous monitoring of the QoL of patients undergoing pharmacological therapy.

PKU patients who respond to pegvaliase can maintain a diet unrestricted in protein, micronutrients, and fatty acids. However, when liberalizing the diet, food neophobia and potential barriers to introducing protein should be evaluated [46]. As patients adapt to this change, nutrition education remains an important component of care. This is because a normal diet involves not only the normalization of protein intake but also the adoption of healthy dietary patterns [47]. Therefore, it's legitimate to question whether the effectiveness of drug-

derived treatment might inadvertently lead to a worsened perception of QoL by the patient. It's also important to gauge any stress that may result from taking a drug that carries potential severe AEs.

According to the label, patients should be pre-medicated with an H1-receptor antagonist, H2-receptor antagonist, and antipyretic. However, real-world practice suggests that H1 antagonists are likely the most effective in reducing the effects of adverse events [22]. Therefore, the use of H2 antagonists is not strictly recommended [20].

The SC suggested potential solutions to barriers in using pegvaliase. Remote consultations with HCPs are recommended when feasible and available.

The implementation of a digital database for managing patient therapy and direct and timely communication between HCPs and patients using personal management tools such as calendars can effectively address issues with adherence to therapy and diet, a problem commonly reported by the centres.

These recommendations are based on Italian clinical practice and are a strength of this expert review. However, the SC did not include neurocognitive experts despite their importance in treating PKU patients.

In conclusion, this expert opinion offers practical recommendations for treating PKU patients with pegvaliase based on successful practices in Italian PKU centres. As clinical experience with pegvaliase grows, these recommendations could contribute to a more standardized and systematic approach to managing PKU.

Author contributions

Each author was a member of the SC and actively participated in all virtual meetings. They all significantly contributed to the work, from its conception and execution to the development and discussion of the analysed topics. Every author was involved in the drafting, revision, and critical review of the article. They all approved the final version to be published, agreed on the chosen journal for submission, and are willing to take responsibility for all aspects of the work.

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CRediT authorship contribution statement

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Declaration of competing interest

None.

Data availability

No data was used for the research described in the article.

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