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Recommendations for the use of sapropterin in phenylketonuria ☆

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ABSTRACT

Phenylketonuria (PKU) is an inherited disorder of phenylalanine (Phe) metabolism. Until recently, the only treatment for PKU was a Phe-restricted diet. Increasing evidence of suboptimal outcomes in diet-treated individuals, inconsistent PKU management practices, and the recent availability of tetrahydrobiopterin (BH_4) therapy have fueled the need for new management and treatment recommendations for this metabolic disorder. BH_4, now available as sapropterin dihydrochloride (sapropterin), may offer the potential for improved metabolic control as well as enhanced dietary Phe tolerance in some PKU patients. A group of metabolic dietitians from North America convened in June 2011 to draft recommendations for the use of sapropterin therapy in PKU. Physicians with extensive experience in PKU management were invited at a later date to contribute to the development of these recommendations. Based on extensive clinical experience and current evidence, the present recommendations provide guidance from patient selection and determination of sapropterin response to the long-term management of patients on sapropterin therapy. Target Phe levels, nutritional adequacy, neurocognitive screening and adherence to treatment are addressed to optimize patient outcomes.

1. Introduction

Phenylketonuria (PKU; OMIM ID: 261600 and 261630) is an autosomal recessive metabolic disorder characterized by elevated phenylalanine (Phe) levels in the blood and other tissues. This inborn error of Phe metabolism is caused by deficient activity of phenylalanine hydroxylase (PAH; EC 1.14.16.1), the enzyme that catalyzes the hydroxylation of L-Phe to L-tyrosine [1]. Over 500 mutations in the phenylalanine hydroxylase gene (*PAH*) have been identified, giving rise to wide genotypic and phenotypic heterogeneities [2].

If left untreated, PKU can lead to profound mental retardation, seizures, behavioral problems and other symptoms. Newborn screening for PKU enables early diagnosis and dietary intervention and the subsequent prevention of the most severe sequelae. Most clinics worldwide advocate lifelong adherence to a Phe-restricted diet to maintain blood Phe concentrations within recommended treatment ranges. The Phe-restricted diet excludes high-protein natural foods such as meat, dairy products, legumes, nuts and eggs. Limited amounts of Phe-containing intact protein are allowed from calculated amounts of breads and other starchy foods. Remaining protein needs

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are primarily met by consumption of synthetic Phe-free medical foods. Fruits, vegetables, fats, sugars and specially modified low-protein food like breads, pasta, and baked products provide needed energy sources and enhance the quality and variety of food allowed. However, adherence to this highly restrictive and often socially burdensome diet is a significant challenge for many PKU patients, particularly during adolescence and in adulthood [3]. Furthermore, increasing evidence suggests that even PKU individuals treated early and continuously with diet alone may be at risk for suboptimal neurocognitive, psychosocial and nutritional outcomes compared to unaffected peers [4].

Tetrahydrobiopterin (BH_4), a cofactor of PAH, can lower elevated blood Phe levels in a subset of patients with PAH deficiency [5–7]. Sapropterin dihydrochloride (sapropterin), a synthetic formulation of the 6R-isomer of BH_4, has been available as a non-dietary therapy option for patients with BH_4-responsive PKU since 2007 in the United States, 2008 in the European Union, and 2010 in Canada. Sapropterin is a well-tolerated oral medication that can be used as an adjunct to a Phe-restricted diet to reduce elevated blood Phe levels in patients who respond to this therapy [8,9]. For some patients, sapropterin may also increase dietary Phe tolerance to enable consumption of larger amounts of natural protein [10].

Recommendations for determining response to sapropterin and its use in PKU were published by Levy et al. in 2007 [11]. In the following year, Singh and colleagues published recommendations for the dietary management of sapropterin-responsive PKU patients [12]. Both sets of recommendations were consistent with the study protocols leading to FDA approval of sapropterin. In 2009, the European working group on PKU described a protocol for optimizing sapropterin use in PKU management [13]. New evidence and insight from more recent clinical experience as well as recognized inconsistencies in sapropterin use across clinics have prompted the need for a practical and comprehensive set of recommendations for the management of PKU patients on sapropterin therapy. A group of metabolic dietitians from clinics across North America convened in Portland, Oregon, USA in June 2011 to discuss current clinical practices and to develop practical recommendations for various aspects of sapropterin use in PKU, from patient selection and determination of response to the long-term management of patients on therapy. Physicians with expertise in PKU treatment and management were invited at a later date to participate in the formulation of these recommendations and to provide input on medical management. The discussion of common clinical practices and recommendations presented here is a result of this effort and is based on the most current available evidence and the broad range of clinical experience of the author practitioners. Key issues in PKU management are addressed within these recommendations, including optimal Phe levels, nutritional adequacy, neurocognitive testing, and adherence to treatment.

2. Formulation of recommendations

A group of metabolic dietitians who practice in various clinics across the United States and Canada convened for a day in Portland, Oregon, in June 2011 to initiate the development of recommendations for the use of sapropterin in PKU. This meeting was sponsored by BioMarin Pharmaceutical Inc. (BioMarin). Current clinical practices were reviewed and discussed and a preliminary outline of recommendations was drafted during the meeting. A review of the literature was conducted to identify and gather relevant evidence. Continuing discussions and ongoing refinement of the working document revealed a need for the inclusion of medical management considerations, and in the fourth quarter of 2011, several physicians with experience in PKU management were invited to contribute to the development of the recommendations. Draft recommendations were circulated via email to all contributors and their comments and revisions were reviewed and integrated. The final recommendations were approved by all authors prior to submission to *Molecular Genetics and Metabolism* for publication.

While the recommendations presented here reflect a broad consensus among this group of clinicians, areas of disagreement regarding some practice decisions remain. It is not within the authors' ability to resolve inconsistencies across clinics where consensus is still lacking. One intention of this work is to bring issues that lack consensus to attention so that efforts by the clinical community to build consensus will continue.

3. Recommendations

3.1. Patient selection

A trial of sapropterin may be offered to all patients with PKU to determine clinical benefit. A patient's history and current circumstances should be considered to ensure that the patient is able to adhere to the treatment protocol over the 1–2 month trial period. Patients and families should be prepared for the possibility that sapropterin therapy may not be beneficial. Financial/insurance considerations should be addressed.

Special consideration is warranted for the following patient populations:

(i) Mild hyperphenylalaninemia
Currently there is considerable debate among clinicians regarding the need to treat individuals with hyperphenylalaninemia who have persistent blood Phe levels below 600 μmol/L even when catabolically challenged [14–17]. While there is a clear need to address the dearth of research on treatment of patients with mild hyperphenylalaninemia, there is some evidence from studies on treated patients with classical and less severe PKU to suggest that neurocognitive outcomes are optimized when blood Phe is maintained at levels below 360 μmol/L [18–23]. Patients with milder forms of PKU have been found to have higher rates of response to sapropterin (≈50–80%) compared to patients with classical PKU (≈10%) [13]. Because response to sapropterin may be observed in patients throughout the spectrum of PKU classification, patient selection for a trial should be based on the potential for clinical benefit to an individual patient, without regard to anticipation of ability to respond. Patients with blood Phe concentrations in the range of 360–600 μmol/L, particularly those with suboptimal cognitive and psychosocial functioning, should be considered for a trial of sapropterin.

(ii) Infants and young children
Although clinical trials of sapropterin did not include subjects younger than 4 years of age, a recent study suggests that the medication can be used safely and effectively in patients within this age range [24]. Moreover, BH_4 loading tests are routinely performed on infants in many PKU centers in Europe [25] and Canada. A trial may be considered for all infants (0–2 years of age) with pretreatment Phe levels above 360 μmol/L. Sapropterin may enable infants who respond to be fed exclusively with breast milk (which has a lower Phe content than commercial infant formulas) or may allow a greater proportion of intact protein to be derived from breast milk or infant formula. The introduction of a small amount of medical food should be encouraged, however, in order to increase the likelihood of its acceptance later in life if needed. Detecting an adverse reaction in very young patients who cannot describe discomfort is a challenge that should be considered prior to initiating treatment. Additional recommendations may be required when more experience has been obtained using sapropterin in infants with PKU. There is currently a long-term open label study underway that is evaluating the safety and efficacy of sapropterin in children who are 0–6 years of age [26,27].

All children between the ages of 2 and 4 years with PKU may be considered for a trial of sapropterin. The benefits of initiating therapy in children of this age group include the potential to improve metabolic control during this critical time of growth and development, the potential to increase natural protein intake early in life, and the greater likelihood of adherence to treatment. Conducting an accurate sapropterin trial during these years may be challenging, however, because as children grow and protein needs change, it may be difficult to definitively attribute a reduction in blood Phe levels and/or an increase in Phe tolerance to sapropterin responsiveness. An extended trial may be required to determine if a change in blood Phe indicates a temporary response due to the increased anabolism during growth or a more stable and long-lasting effect due to sapropterin responsiveness. Furthermore, as young children are less likely than adolescents and adults to develop an aversion to medical food and more likely to adhere to a Phe-restricted diet [3], postponing a trial for sapropterin response may be considered in 2–4 year old patients who exhibit good metabolic control with dietary therapy alone. This also allows a time period during which parents can educate their child on skills needed to maintain dietary restrictions. The decision to initiate or defer sapropterin treatment should be made jointly by clinicians and families and should balance the advantages and disadvantages.

(iii) Pregnant women

The use of sapropterin has not been evaluated in pregnant women in controlled trials. Good maternal blood Phe control and normal neonatal outcomes have been reported in several case studies of sapropterin use in pregnancy [28–31]. Sapropterin is designated as a Pregnancy Category C drug due to the lack of well-controlled studies [32]. The use of Category C drugs may be justified when a known significant risk to the mother or the fetus can be reduced. To prevent the teratogenic effects associated with hyperphenylalaninemia due to untreated or poorly treated maternal PKU, women with PKU should maintain blood Phe levels between 120 and 360 μmol/L prior to and throughout pregnancy [33]; however, achieving this level of metabolic control may be difficult [34–36]. The initiation of sapropterin therapy during pregnancy should be considered if strict dietary management to maintain blood Phe levels within the recommended range is unattainable or if dietary therapy has been discontinued or relaxed during the years before conception. Ideally, a sapropterin trial should be performed prior to pregnancy because Phe tolerance increases during pregnancy which may compromise the ability to reliably evaluate a response to sapropterin. For women receiving sapropterin therapy who become pregnant, the continued use of sapropterin during pregnancy may be beneficial due to the known risk of increased blood Phe levels that may result from discontinuing therapy. Pregnant women with PKU should be informed about the classification of sapropterin as a Category C medication and should consent to its use during pregnancy.

(iv) Late-treated and untreated adults

Many PKU individuals who were born before newborn screening was introduced in the 1960s were diagnosed late and have severe mental retardation and behavioral problems. For these mentally impaired patients, a reduction in blood Phe levels and possible improvements in behavior may be achieved with a Phe-restricted diet, but dietary treatment may be difficult to implement [37]. Anecdotal evidence suggests that sapropterin therapy may reduce blood Phe levels and/or improve behavior (e.g. reduce anxiety or nervousness) in late-treated and untreated PKU adults [38,39], but sufficient documentation regarding efficacy in this population is still lacking. Successful response to sapropterin based on blood Phe reduction alone may be difficult to determine in individuals who may realistically be unable to adhere to diet or the trial protocol; in such cases, a decision on benefit may be made based on input from the patient's mental health specialist and/or on validated tools designed to assess improvement in behavior in compromised patients [40]. Special issues to consider prior to initiating a trial include the concomitant use of psychotropic drugs and methods of assessing response and adverse events in non-verbal patients. Based on the experience of some of the authors, severely affected PKU adults may react to the introduction of sapropterin with a temporary increase in behavioral problems (e.g. anxiety), but this effect may be reduced or avoided by using a lower starting dose (i.e. 5–10mg/kg/day) and increasing the dose gradually over a longer trial period.

All patients selected as potential candidates for sapropterin therapy should be informed that for the duration of the trial period they will be expected to provide more frequent blood samples, record dietary intake, and stay in contact with the clinic. The willingness and ability of patients/families to comply with clinic requirements should be carefully evaluated in order to ensure an accurate trial for response. In certain situations where family members may be unable to fully engage in the patient's care (e.g. dysfunctional households, joint-custody arrangements), the involvement of an alternative caregiver or other responsible adult, such as a school teacher or school nurse, could be considered. Special attention should be given to patients and families who are considered to be at higher risk of noncompliance; risk factors include low socioeconomic status, low educational achievement, illiteracy or language barriers, co-morbidities or other disabilities, and unemployment. Finally, a trial should not be started if the patient's health is compromised (e.g. by illness, poor nutrition, or stress) or if the patient is undergoing any lifestyle changes (e.g. a new job or school, a new exercise routine) because these circumstances may interfere with the patient's ability to follow the clinical protocol and prevent reliable determination of a blood Phe response to sapropterin.

3.2. Baseline assessment

A careful and thorough initial evaluation of the patient is essential for ensuring an accurate trial of sapropterin responsiveness. The evaluation should be comprehensive and include obtaining a complete medical history, performing a physical examination, collecting baseline laboratory and dietary intake data, and identifying cognitive deficits and psychosocial factors that may compromise adherence to treatment.

The following assessments, most of which are important in the routine care of PKU patients, are recommended prior to the start of a sapropterin trial and summarized in Table 1:

- Blood Phe concentrations—Ideally, 3 or more blood Phe levels should be obtained within the month prior to the start of the trial. Every effort should be made to ensure that blood samples are obtained by the same method and at a consistent time of day that is at least 2h after food intake. More data should be obtained if initial blood Phe levels are inconsistent or if the methods used for testing blood Phe differ (i.e. filter paper fluorometric, venous HPLC, etc.). The purpose of obtaining multiple blood Phe levels is to determine the normal range of variation in an individual patient before the trial. It is recommended to use the same analytical assay each time a blood Phe level is obtained. If baseline blood Phe levels are low (<120–240 μmol/L), increasing dietary Phe intake prior to the trial may be considered to ensure that increases in Phe tolerance can be attributed to sapropterin response and not to over-restriction of Phe.
- Dietary intake—Patients should be instructed not to change their eating habits prior to a trial of sapropterin unless directed to do so

Table 1
Recommended assessments for PKU patients on sapropterin therapy. Most of these assessments are recommended for routine care of all individuals with PKU.

	Baseline	Sapropterin trial	Long-term therapy
Blood Phe levels	X	X	X
Dietary intake	X	X	X
Medical history	X		
Physical examination	X		X
Weight, height	X	X	X
Nutritional status	X	X	X
Metabolic status[a]	X	X	X
Dietary Phe tolerance	X	X	X
Mental health screening	X	X	X
Adverse reactions		X	X
Pregnancy status	X	X	X
Illness	X	X	X
Concomitant medications	X	X	X
Changes to daily routine	X	X	X
Adherence to treatment	X	X	X

[a] Blood Phe/Tyr, plasma amino acids.

by their dietitian. Ideally, a 3-day diet record or a food frequency questionnaire (FFQ) [41] should be completed prior to each blood test and used to estimate nutrient intake and assess nutritional status. The choice of assessment tool should be based on the willingness and abilities of the patient. Patient burden can be high for food records, which require time and thought to complete, and the act of maintaining records may affect eating behavior. The FFQ method typically requires less patient burden than the 3-day diet record and may be more appropriate for patients who may have difficulties with completing more detailed assessments. Diet counseling prior to the trial should be considered for patients with suboptimal nutritional status. For vegetarian patients who are not consuming medical food, dietary counseling may be appropriate to improve nutritional adequacy prior to the trial. When significant dietary changes prior to the trial are considered essential for improving nutritional adequacy, the trial should be postponed in order to ensure that a change in blood Phe is not due to changes in dietary intake.

- Medications and supplements—Concomitant use of drugs that inhibit folate metabolism (e.g. methotrexate), drugs that affect nitric oxide-mediated vasorelaxation (e.g. PDE-5 inhibitors), and levodopa require caution [32].
- Medical history—For patients with a history of gastrointestinal disorders, particular attention should be paid to the administration of sapropterin. The medication should be taken with food, and starting with lower doses may ameliorate gastrointestinal distress, which has been reported as an adverse event [42]. More frequent monitoring during the trial should be considered. Previous allergic reactions to medications should be noted.
- Pregnancy status—For women who are pregnant or planning a pregnancy, a sapropterin trial should be considered if dietary management alone does not adequately control blood Phe levels or if dietary adherence is problematic. These patients should be informed that sapropterin is a Category C medication.
- Mental health screening—When possible, patients should be screened for cognitive impairment and psychosocial problems, which may impact adherence to treatment. Appropriate screening tools can include the Behavior Rating Inventory of Executive Function (BRIEF) [43] and the Pediatric Symptom Checklist (PSC) [44] for children, and the BRIEF and Brief Symptom Inventory (BSI) [45] for adults [46,47]. If these tools are not available or are impractical to administer, then feedback from patients and their teachers, spouses, and employers may be helpful for assessment. If relevant, input from a patient's mental health specialist should also be used to determine benefit. Referral to a mental health specialist should be considered if warranted.
- Physical examination—A routine physical examination should be performed, and anthropometric data (weight, height, and, for children under 3 years of age, occipitofrontal circumference (OFC)) collected.
- Complete blood count and blood chemistry profile—A complete blood count as well as appropriate blood tests to determine nutritional and metabolic status (e.g. RBC folate, vitamin B12, ferritin, albumin, 25-hydroxyvitamin D, prealbumin, plasma amino acids, essential fatty acids) should be obtained if these have not been performed within one year.
- Adherence to treatment—The patient's ability to comprehend instructions and to adhere to the clinic protocol (e.g. keep diet records, check Phe levels) should be assessed. Barriers to adherence should be identified and addressed accordingly.

3.3. Patient education prior to a sapropterin trial

Before initiation of the trial, patients should be counseled on the common side effects of sapropterin and the clinic protocol for the trial, including how to take sapropterin and the importance of timely submission of blood samples. They should be informed that any changes to diet or lifestyle may invalidate the trial and should therefore be avoided. The importance of adherence prior to and during treatment should be emphasized and appropriate interventions to enhance adherence should be considered; for example, patients may receive phone or email reminders to obtain blood Phe tests and to submit blood test results and diet records. Information should be tailored to the age and cognitive ability of the patient. For patients new to clinic or who have not been seen for an extended period, ideally at least two initial clinic visits prior to the trial are recommended in order to establish a supportive relationship.

The following materials and tools are recommended for patient use prior to and during a sapropterin trial:

- Educational materials about sapropterin (e.g. how it works, its safety and efficacy)
- Clinic-specific instruction sheet detailing how to take and store sapropterin, and how to contact the PKU clinic for questions or concerns
- Educational video or in-clinic demonstration on how to perform a blood Phe test
- Lab slips/filter papers
- Diet records/FFQ forms
- Calendar to remind patients to take medication
- Diary to record sapropterin intake, diet, behavioral changes, and/or adverse events
- Weekly pill box

3.4. Implementation of sapropterin

An initial dose of 20mg/kg/day is recommended. A lower starting dose (5–10mg/kg/day) may be considered in infants or patients with gastrointestinal issues or other risk factors (e.g. concomitant drugs). The dose may be titrated between 5 and 20mg/kg/day to achieve optimal clinical benefit. For obese and overweight patients, an initial dose based on adjusted body weight rather than actual body weight may be recommended; however, if this is deemed ineffective, the dose should be increased to reflect actual weight [48]. Splitting the total dose should be considered if taking a large number of tablets is difficult for the patient or if a patient experiences gastrointestinal issues.

Sapropterin is recommended to be administered orally once daily, at the same time each day, and with a meal. Ideally the medication should be taken with the meal of the day that contains the greatest amount of Phe. Because sapropterin is acidic, it is better absorbed and tolerated with food and may be less effective when taken with medical food alone. The tablets may be swallowed whole, crushed

and dissolved in water, apple juice or other appropriate beverage, or crushed and mixed in soft foods. For infants and young children, sapropterin may be more effectively administered by mixing crushed tablets in formula or soft food or by administering dissolved tablets via syringe with a feeding.

3.5. Patient monitoring during a sapropterin trial

The patient's health and response to sapropterin as well as factors that may invalidate the trial should be evaluated throughout the trial period (Table 1). Patient monitoring should include:

- Blood Phe concentrations—Blood Phe tests should be performed prior to initiation of treatment and weekly thereafter until completion of the trial. For infants and young children, a blood Phe test is best obtained at day 1 or 2 of the trial; more frequent monitoring is recommended for this age group in order to avoid Phe deficiency. Blood samples should be obtained at a consistent time of day that is at least 2h after food intake in order to minimize any impact of diurnal fluctuation or dietary Phe ingestion on blood Phe level. The same analysis method to determine blood Phe levels should be used throughout the trial period. Patients should be informed that regular blood Phe testing is required to evaluate responsiveness and to determine proper dosage.
- Dietary intake—Patients should be instructed to maintain their usual diet during the trial period in order to ensure an accurate trial for response. Dietary intake should be assessed prior to each blood Phe test if possible.
- Mental health—Patients should be encouraged to record their mood and sense of well-being in a diary throughout the course of the trial. If possible, a follow-up evaluation of cognitive and psychosocial functioning should be conducted at approximately 4 weeks using appropriate screening tools. Obtaining input from third party observers such as teachers, spouses, and employers is beneficial. For patients being followed by a psychologist or psychiatrist, consider contacting their mental health specialist for input.
- Weight—Patients should be counseled on the importance of weight maintenance during the trial period. Changes in weight may affect response to sapropterin as dosing is based on weight. For young patients who are growing, weight gain or loss outside of the normal growth rate may affect the validity of the trial and necessitate adjustments to sapropterin dose. Weight should be monitored throughout the duration of the trial, and more frequently in younger patients.
- Adverse events—Patients should be educated on the most common side effects of sapropterin and should be assessed for any signs and symptoms of an adverse reaction at every clinic visit. Since adverse events may be difficult to determine in infants and very young children who do not have the ability to verbally describe discomfort, it is important to counsel families to watch closely for any signs of irritability and intolerance. Any patient experiencing an adverse reaction should be treated appropriately and closely monitored until symptoms have stabilized or subsided. The adverse events associated with sapropterin have been reported to typically be mild and primarily associated with gastrointestinal issues or headache [42].
- Adherence to treatment—Barriers to adherence may arise at any point during the trial period. Reasons for nonadherence should be identified (e.g. failure to understand dosing instructions, adverse reaction, psychosocial problem) and addressed accordingly.
- Illness—Patients who become ill during the trial should be closely monitored and examined to determine if symptoms are related to the medication. For patients with mild symptoms, the trial does not necessarily need to be stopped, but may need to be extended to reliably evaluate responsiveness.
- Changes to daily routine—Patients should be instructed not to make any lifestyle changes (e.g. starting a new exercise regimen or a new job, traveling) during the trial period which may lead to changes in blood Phe and invalidate the trial for response.

3.6. Dietary phenylalanine challenge

If a patient responds to sapropterin with a clinically meaningful reduction in blood Phe (discussed in the next section) and consistent Phe concentrations within the targeted range, a dietary Phe challenge should be considered. During any period of dietary adjustment, blood Phe must be regularly monitored and the diet assessed for adequate intake of calories, protein, vitamins and minerals.

3.6.1. Determination of dietary Phe tolerance

Dietary Phe can be added to the patient's food or medical food in the form of dry or liquid milk; if lactose intolerance is noted, egg white powder or soy milk can be used instead. This approach allows controlled increases of dietary Phe in a form that is accurately measured and does not involve introducing high Phe foods that may need to be discontinued if there is no significant increase in Phe tolerance. These products should be gradually added to the diet, and in suggested increments of 10% of usual Phe intake or in increments of 50mg/day (for children) or 100mg/day (for adults). If dietary Phe tolerance increases markedly, increments of added Phe may need to be larger in order to evaluate total tolerance without extending the trial period unduly. Medical food intake should remain unchanged to avoid any effect on blood Phe levels other than adding dietary Phe. Blood Phe should be frequently monitored and dietary Phe should be adjusted weekly until blood Phe concentrations are maintained within the individualized target range over a 4-week period. If dietary Phe tolerance increases substantially, the amount of dry or liquid milk required to achieve maximum tolerance may become difficult for the patient to consume, especially if it is added to medical food formulas. Natural foods may then need to be introduced as well; in these cases, it is recommended to utilize foods that are consistently pre-portioned (e.g. eggs, pre-packaged cheese slices, yogurt, etc.). To ensure that Phe tolerance is maximized in well-controlled patients who are able to maintain Phe levels within the targeted range with diet alone, it may be advisable to increase dietary Phe until blood Phe levels are just above the recommended range [49]; dietary Phe can then be adjusted downward to achieve blood Phe in the targeted range.

The process described above represents the most well controlled approach to determining dietary Phe tolerance and may not be feasible to implement in every clinical situation. A less accurate determination of dietary Phe tolerance may be achieved through a less controlled advancement of dietary Phe using foods that are already being consumed; for example, if a person derives 10g of protein from food, then an incremental increase of 10% of usual Phe intake may be roughly equivalent to adding half a slice of bread ($\approx$1g protein).

3.6.2. Diet modification

After the patient's dietary Phe tolerance with sapropterin has been established, the dry or liquid milk (or other product(s) used to trial tolerance) may be gradually replaced with natural foods. Dietary modification should be an incremental process, beginning with the replacement of modified low protein food products (e.g. bread, pasta, cereal) with regular foods. If these substitutions are not sufficient to fulfill an increased dietary Phe tolerance, high-quality proteins such as egg and cheese may then be introduced. Patients should be advised that as small errors in measuring higher protein food can result in a large increase in dietary Phe, foods that are easy to consistently portion and measure (e.g. a cheese slice, a container of yogurt) are preferable. Meat is not recommended as it contains high concentrations of Phe and is difficult to consistently portion; it is best reserved for those patients who demonstrate an increase in

dietary Phe tolerance approaching an unrestricted diet. Adding previously prohibited foods to the diet may cause anxiety in some patients/parents and should be anticipated and addressed. Additionally, patients who develop a substantially increased Phe tolerance may find it burdensome to manage their restriction by counting milligrams of Phe intake, so counting grams of protein instead may be recommended.

3.6.3. Medical food adjustment

If dietary Phe tolerance is increased sufficiently so that age-appropriate dietary reference intakes (DRIs) for protein are met with natural foods, then the amount of medical food may be reduced in 25% increments. If less than 50% of protein intake is then derived from medical food, high biological value protein sources should be incorporated in the diet to ensure adequate intake of essential amino acids. Elimination of medical food may be an option for some patients, but the decision to do so must weigh both the advantages and disadvantages. While medical food is expensive and inconvenient and adherence can be difficult, it may provide a valuable protein source during times when Phe intake cannot be increased (e.g. illness, puberty), or if sapropterin treatment is interrupted. Discontinuing medical food altogether may compromise taste acceptability if it becomes necessary to re-introduce it in the future. Maintaining small amounts of medical food in the dietary regime may help to avoid these potential consequences. As medical food is reduced or discontinued, blood Phe, plasma amino acids and nutrient status should be closely monitored. The need for vitamin and mineral supplements should also be considered.

3.6.4. Patient education

Because the PKU diet allows for only a very limited choice of intact protein sources, patients may not be adept at selecting appropriate natural foods to ensure a nutritionally balanced diet. Patients who have an increased Phe tolerance and are able to consume a wider range of natural foods should be taught the basic principles of nutrition as well as how to count grams of protein, read food labels, and determine the protein content of foods when eating out. The importance of careful measurement of high-protein foods should be emphasized. Patients should be cautioned against excessive relaxation of dietary restrictions and dependence on sapropterin alone to maintain blood Phe within therapeutic range. Patients should also be encouraged and educated to seek additional nutritional information from online and other resources (e.g. the USDA website [50], Bowes and Church's food values [51]).

3.7. Determination of clinical benefit of sapropterin

A clinically significant response to sapropterin will vary depending on the protocol of the clinical center and on individual patient status and treatment goals. While a reduction in blood Phe is the most widely accepted criterion for response, a survey has revealed that other measures of response, including improvements in dietary Phe tolerance and behavior, are being used by clinicians [52]. A clinical benefit may be demonstrated if one or more of the following response criteria are met:

- Reduced blood Phe concentrations—In clinical trials, a ≥30% decrease in blood Phe concentration was used to define sapropterin responsiveness [8,9]. However, a smaller reduction may be clinically meaningful, especially if accompanied with an increase in dietary Phe tolerance and/or an improvement in neurocognitive/psychosocial functioning. There is currently a lack of consensus regarding which blood Phe levels are the most appropriate to use in determining response. Results may be best interpreted by comparing mean baseline blood Phe to a mean of blood Phe collected during the trial, with exclusion of any levels known to be associated with diet change, illness, etc. This is most relevant in patients who respond significantly and rapidly, but may not capture slower responders. In patients who respond with gradual decreases in blood Phe during the trial period, a more effective evaluation may include the trend exhibited and/or comparison of baseline blood Phe with final trial blood Phe. Evaluating response in a patient whose baseline blood Phe levels are between 120 and 360 μmol/L may be more difficult and a change in dietary Phe tolerance may be a more reliable indicator of response [53].
- Increased dietary Phe tolerance—For an accurate determination of response, dietary Phe tolerance should be maximized prior to the trial to ensure that any increase in tolerance of dietary Phe is due to sapropterin and not due to over-restriction prior to the trial. For children in periods of rapid growth, it is important to determine if an increase in dietary Phe tolerance is due solely to sapropterin response or if it is influenced by increased anabolism.
- Improved neurocognitive and/or psychosocial functioning—Anecdotal reports suggest that sapropterin may improve neurocognitive and psychosocial functioning in individuals with PKU [38,54,55]. Behavioral improvements have anecdotally been associated with sapropterin even in the absence of a reduction in blood Phe [39], but the mechanism for such an effect has not been elucidated. Subjective reports of improvements in neurocognitive and psychosocial functioning are susceptible to misinterpretation and should therefore be verified with objective clinical measures in order to ensure an accurate determination of sapropterin response. Appropriate validated assessments include the BRIEF, BSI, and PSC. If relevant, input from a patient's mental health specialist may also be used to determine benefit. Currently, a double-blind, placebo-controlled randomized trial is underway to objectively evaluate the therapeutic effects of sapropterin on neuropsychiatric symptoms in patients with PKU [56,57].
- Improved blood Phe stability—High variability in blood Phe levels has been associated with more severe PKU phenotypes [58]. Reduced long-term variability of blood Phe levels may be associated with improved cognitive outcomes [59]. Sapropterin has been shown to increase blood Phe stability in patients with BH4-responsive PKU [60,61]. While the mechanism of this effect has not been elucidated, it may be related to the ability of sapropterin to enhance residual PAH activity [5]. Stability in blood Phe concentrations should be demonstrated over an extended period of time.

If a clinically significant response to sapropterin is not attained, it is important to verify that factors such as illness, dietary noncompliance or improper administration of sapropterin did not invalidate the trial.

3.8. Long-term management of patients on sapropterin therapy

Optimal patient outcomes are best achieved through continuous assessment, modification of treatment plans and monitoring by collaborative and multidisciplinary health care teams. Ideally, the frequency of clinic visits and assessments should be tailored to meet the individual needs of each patient.

The assessments outlined below and summarized in Table 1, many of which are already part of routine care, are recommended for PKU patients on long-term sapropterin therapy:

- Blood Phe concentrations—Monthly blood Phe tests are recommended, but more may be required depending on age and individual patient circumstances. Patients should be informed that regular blood Phe testing may be required for continued insurance coverage of sapropterin.
- Dietary intake—Ideally, dietary intake should be assessed prior to each blood Phe test using a 3-day diet record or FFQ. Nutritional counseling should be ongoing, particularly for patients whose diets have been significantly modified due to increased dietary Phe tolerance.

- Dietary Phe tolerance—Periodic reassessment of dietary Phe tolerance is recommended, particularly when there are changes in body mass or lifestyle [62].
- Metabolic status—Phe/tyrosine ratio and other plasma amino acid levels should be monitored regularly.
- Nutritional status—Blood tests (e.g. CBC, albumin, prealbumin, ferritin, vitamin D, vitamin B12, etc.) should be performed on a regular basis to ensure nutritional adequacy.
- Mental health—Evaluations of cognitive and psychosocial functioning should be conducted at regular intervals if possible, particularly as impairments can impact self-management and adherence to treatment.
- Anthropometric measurements—Growth and changes in weight and height should be monitored and sapropterin dose adjusted accordingly. Dietary Phe tolerance should be reassessed when body mass changes [62].
- Adverse events—Patients should be monitored for any adverse reaction to the medication on an ongoing basis.
- Illness—Elevations in blood Phe during periods of illness may require adjustments to diet and sapropterin dose.
- Pregnancy status—For patients on sapropterin therapy who become pregnant, the continuation of sapropterin should be considered based on the individual patient's risk for teratogenic blood Phe levels. Pregnant women with PKU should be informed that sapropterin is a Category C drug and should consent to its use during pregnancy. The pregnancy should be closely monitored and care should be coordinated with the patient's obstetrician.
- Adherence to treatment—Patient adherence to every aspect of treatment (i.e. sapropterin therapy, diet, clinic visits, blood Phe tests, etc.) should be continually assessed in order to optimize outcomes. Reasons for suboptimal adherence include issues related to treatment regimens (e.g. pill burden, frequency of blood tests, burden of diet records), patient factors (e.g. cognitive or psychosocial deficits, problems at work or home, low socioeconomic status, low educational level), and health system-related issues (e.g. interruptions in access to sapropterin, inadequate access to healthcare professionals and treatment resources). The reasons for nonadherence must be identified in order to implement appropriate patient-specific interventions. Resources and approaches that may be utilized to enhance adherence include:
  - Peer support groups
  - Family support
  - Case management services
  - A multidisciplinary health care team that includes a metabolic dietitian, metabolic physician, metabolic nurse, psychologist, genetic counselor, and social worker
  - Improved access to clinics and healthcare providers
  - Referrals to appropriate specialists (e.g. mental health)
  - Phone counseling to reduce the need for multiple clinic visits
  - Ongoing PKU self-management education tailored to the age and needs of the patient
  - Reminders for prescription refills, blood Phe tests, etc.

4. Conclusions

Sapropterin has the potential to improve patient outcomes in PKU through improved control of blood Phe, possible subsequent enhancements in neurocognitive/psychosocial function, and/or increased tolerance of dietary Phe. The recommendations described here represent an attempt to develop a uniform and practical approach to the use of sapropterin for treating PKU in conjunction with diet and could serve as a useful adjunct to any future national consensus statement that may emerge from ongoing efforts (e.g. by the National Institutes of Health, the American College of Medical Genetics, the Health Resources and Services Administration-funded collaboration between Genetic Metabolic Dietitians International and Southeast Regional Newborn Screening and Genetics Collaborative) to revise current PKU management guidelines. While these recommendations represent current practice, experience, and knowledge regarding sapropterin treatment, it is recognized that further experience and future research may alter the understanding of the optimal use of sapropterin and necessitate changes to these recommendations.

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