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RESEARCH REPORT

Extended Experience of Lower Dose Sapropterin in Irish Adults with Mild Phenylketonuria

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Abstract Adherence to dietary and treatment recommendations is a long-standing concern for adults and adolescents with PKU and treating clinicians. In about 20–30% of PKU patients, Phe levels may be controlled by tetrahydrobiopterin (BH4) therapy. The European PKU 2017 Guidelines recommends treatment with BH4 for cases of proven long-term BH4 responsiveness, with a recommended dosage of Sapropterin 10–20 mg/kg/day.

We report four young Irish patients with mild PKU, known to be BH4 responsive, who were treated with lower doses of Sapropterin for over 7 years.

Case 1: Female, currently age 20. Genotype p. 165T/p. F39L, c.[194T>C]; [117C>G]. Newborn Phe: 851 μmol/L. Pre-Sapropterin Phe tolerance: 600 mg Phe/day to maintain Phe levels <400 μmol/L. Commenced on Sapropterin 400 mg (6.5 mg/kg/day) with increase in Phe tolerance to 800 mg/day.

Case 2: Female, currently age 23. Genotype p. 165T/pF39L; c.[194T>C]; [117C>G]. Newborn Phe: 714 μmol/L. Pre-Sapropterin Phe tolerance: 700 mg Phe/day. Commenced on Sapropterin 400 mg (8 mg/kg/day) with increase in Phe tolerance to 800 mg/day.

Case 3: Male, currently age 22. Genotype p. 165T/p. S349P; c.[194T>C][1045T>C]. Newborn Phe: 1,036 μmol/L. Pre-Sapropterin Phe tolerance: 600 mg Phe/day. Commenced on Sapropterin 400 mg (5.4 mg/kg/day). Increased to 1,600 mg Phe/day.

Case 4: Female, currently age 29. Genotype p.R408W/p/p.Y414C; c.[1222C>T], [1241A>G]. Newborn Phe: 1,600 μmol/L. Pre-Sapropterin tolerance: 450 mg/day. Commenced on Sapropterin 400 mg (5.0 mg/kg/day). Increased to 900 mg Phe/day.

Almost 7 years of surveillance for these four patients has shown that this dose of Sapropterin (range 5–8 mg/kg day) was well tolerated and effective with a significant response to treatment and a marked improvement in quality of life at these lower Sapropterin doses.

Background

Adherence to dietary control and treatment recommendations is a long-standing concern to clinicians involved with the care of adult and adolescent PKU patients. In a recent US survey of 182 clinics, it was noted that >60% of adolescents (age 13–17) and >70% of adult PKU patients attending US clinics are non-adherent to target phenylalanine concentrations consistent with earlier international reports (Jurecki et al. 2017; Walter et al. 2002). This is evidenced by non-attendance at clinic and inadequate blood monitoring. Poor adherence leads to social difficulties, mood disorders, attention difficulties and executive functioning difficulties (Burton et al. 2013; Arnold et al. 2004). Patients frequently report poor palatability of the protein substitutes which leads to poor compliance. Furthermore,

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patients report a negative impact of Phenylketonuria (PKU) and its management on their life with high levels of anxiety concerning high phenylalanine levels (Bosch et al. 2015). Pregnancy represents additional challenges in managing PKU with high anxiety reported among expectant mothers (Bosch et al. 2015).

However, recent European guidelines for the treatment and management of patients with PKU advises a 'treatment for life' approach for PKU. For patients over age 12, an upper Phe target of 600 µmol/L is recommended to aim to maintain optimum outcomes and neuropsychological functioning (Van Spronsen et al. 2017). The American College of Genetics and Genomics (Vockley et al. 2014) recommends an upper target Phe concentration of 360 µmol/L for adults with PKU.

At least 890 mutations are now described at the *PAH* locus (BioPKU database, https://www.biopku.org). In about 20–30% of PKU patients, Phe levels may be controlled by tetrahydrobiopterin therapy (Heintz et al. 2013). Sapropterin dihydrochloride is a synthetic formulation of Tetrahydrobiopterin (BH4), a naturally occurring essential cofactor for PAH that acts as a pharmacological chaperone and decreases blood phenylalanine levels and increases dietary phenylalanine tolerance in a subset of patients with milder PKU with BH4 responsive genotypes (Hennermann et al. 2012; Lindegren et al. 2013; Scala et al. 2015).

According to the European PKU Guidelines, treatment with BH4 should only be prescribed in cases of proven long-term BH4 responsiveness defined as the increase in amount of natural protein tolerated of 100% or more or with improved biochemical control (Phe levels >75% in target range) and proven by a trial of up to 6 months. The recommended dosage of Sapropterin is 10–20 mg/kg/day body weight (Van Spronsen et al. 2017). In this case report we retrospectively report our experience with four adult patients with Sapropterin responsive mild PKU treated with lower dose Sapropterin (5–8 mg/kg/day).

Methods

Four Irish patients with mild PKU who were known to be BH4 responsive were treated with lower doses of Sapropterin (BH4) since 2010. Two of these patients (subject numbers 2 and 4) had entered the initial 6 week randomised placebo controlled study of Sapropterin and continued in the 22 week extension study using forced dose titrations of 5, 20 and 10 mg/kg/day (Levy et al. 2007; Lee et al. 2008). The four patients (young adults), one male and three female, had genotypes known to be BH4 responsive (see Table 1). This report outlines their response to treatment as measured by their average Phe level, the amount of natural protein consumed daily as recently assessed, the required intake of synthetic protein, their self-reported improvement in quality of life on BH4 based on a structured interview and a recent evaluation using the adult version of the PKU specific Health-related Quality of Life (HRQoL) questionnaire. The PKU HRQoL questionnaire specifically assesses the impact of PKU on all aspects of PKU patients' lives, including PKU symptoms; the practical social and emotional impact of the condition, the impact of low-protein dietary restrictions and the impact of Phe-free amino acid supplements. Scores of <25% indicate little or no impact of the disease, scores of >25 and <50% indicate a moderate impact, scores of >50 and <75% indicate a major impact and scores of >75% indicate severe impact (Bosch et al. 2015).

Dietary information was collated from a retrospective review of dietetic records for each patient. The current dietary intake was a 'typical day' recall from each patient's last dietetic OPD visit, taken within the past 6 months. Anthropometric measurements and micronutrient status assessment (including ferritin, B12, folate, Hb, and Zn and Se where indicated) were measured before and after Sapropterin use and at each clinic visit.

Table 1 Description of four patients with PKU, biochemical characterisation/Phe tolerance

Case Number and Gender	1 (F)	2 (F)	3 (M)	4 (F)
Newborn Phe level (µmol/L)	851	714	1,036	1,600
Genotype	165T/F39L	165T/F39L	165T/S349P	R408W/Y414C
Pre-Sapropterin Phe tolerance (mg)	600	700	600	450
Recent Phe tolerance (mg)	800	800	1,600	900
Current Sapropterin dose (mg/kg/day)	6.25	8.0	5.4	5
Length of time on Sapropterin (years)	7	7	7	7
Synthetic protein intake g/day. Pre-Sapropterin and post-Sapropterin (in brackets)	60 (40)	50 (42)	60 (40)	75 (50)
Mean (median) Phe level for last 5 years on treatment (µmol/L)	394 (386)	548 (539)	602 (568)	510 (506)
Phe range (min–max) µmol/L)	96–868	201–926	287–1,108	345–690

A dietetic phone questionnaire was conducted with each subject by a qualified dietitian based on a list of common questions/topics. Questions included in the interview addressed how the PKU diet was perceived to be different after the use of Sapropterin; how many exchanges were allowed in the diet before and after Sapropterin; the changes in synthetic protein required; and the changes in intake of low protein foods. In addition, questions were formulated as to how these changes affected the individual's lifestyle: such as the ease of food preparation; the ability to eat out at restaurants; the ease of travel; the ease of socialising; and whether taking Sapropterin had proven to be a positive or negative experience.

In addition to this self-reported structured interview, the four subjects completed the adult PKU specific HRQoL questionnaire. It should be noted that this PKU specific quality of life assessment tool has been available since 2015 and was not available for these individuals before they commenced BH4.

Results

Case 1 Female, currently age 20. Genotype p.165T/p.F39L, c.[194T>C]; [117C>G]. The phenylalanine level in the newborn period was 851 μmol/L (Mild PKU). Pre-Sapropterin at age 13, her Phe tolerance was 600 mg Phe/day to maintain phenylalanine levels <400 μmol/L. She was commenced on maintenance 400 mg Sapropterin (6.25 mg/kg/day) in 2010. This individual has self-reported improved quality of life with improved diet palatability and flexibility since commencing Sapropterin.

Case 2 Female, currently age 23. Genotype p.165T/p.F39L; c.[194T>C]; [117C>G]. The phenylalanine level in the newborn period was 714 μmol/L (mild PKU). Pre-Sapropterin Phe tolerance was 700 mg Phe at age 7. Commenced on Sapropterin 400 mg (8 mg/kg/day) in 2010. This individual reports an ease of meal preparation since starting the treatment facilitating preparation of her own meals which were previously prepared by her parents. She also described increased freedom and choice in relation to food choices resulting in less anxiety around meals.

Case 3 Male, currently age 22. Genotype p165T/p.S349P; c.[194T>C][1045T>C]. The phenylalanine level in the newborn period was 1,036 μmol/L (mild PKU). Pre-Sapropterin Phe tolerance was 600 mg. Commenced on Sapropterin 400 mg (5.4 mg/kg/day) in 2010. This individual reports that he can now eat out with friends more often allowing for improved social life which was important to him. He also described previously hiding his synthetic drinks which is less of an issue now. He feels the treatment has been 'life changing' and allowed him to live a 'normal life'.

Case 4 Female, currently age 29. Genotype: p.R408W/p.Y414C; c.[1222C>T], [1241A>G]. Phenylalanine level in the newborn period was 1,600 μmol/L (mild PKU). Pre-Sapropterin Phe tolerance was 450 mg/day. Commenced on Sapropterin 400 mg (5.0 mg/kg/day) in 2010. This individual is now enjoying eating out which she feels was not possible before starting the treatment due to the restricted diet.

For subjects 2 and 4, these individuals had previously participated in the Sapropterin Phase III extension study (Lee et al. 2008). Thus, they were commenced on a starting dose of 5 mg/kg/day Sapropterin based on the previously identified response at this dose. The phenylalanine levels were measured on a weekly basis and the natural protein exchanges were increased weekly in increments from 100 to 200 mg phenylalanine while maintaining plasma phenylalanine levels <400 μmol/L.

For subject 2, the phenylalanine intake was increased by 100 mg per week to 1,000 mg after 2 months. This individual has had difficulties with recurrent urinary tract infections and subsequently the phenylalanine intake was stabilised at 800 mg/day (Table 1). The initial synthetic protein requirement for subject 2 was 50 g/day which subsequently was decreased to 30 g/day and in recent years to 42 g/day.

Initially, during the first 6 months of Sapropterin, subject 4 tolerated an increase of phenylalanine of 350 mg/day phenylalanine with an increase to 450 mg over the last 2 years. The synthetic protein daily requirement was decreased from 75 to 50 g.

Subjects 1 and 3 had not previously been enrolled in the Sapropterin trial but were known to have BH4 potentially responsive mutations. Both patients initially were started on Sapropterin 10 mg/kg/day for 1 week which determined responsiveness, and then continued on 5 mg/kg/day for 6 weeks as an initial trial period. Subject 1 increased the phenylalanine daily intake from 600 mg phenylalanine/day to 1,000 mg/day initially, then stabilising to 800 mg/day over time. Her synthetic protein intake was reduced from 60 to 40 g/day.

For subject 3, the patient tolerated an increase in phenylalanine by approximately 200 mg/week, from 600 to 2,000 mg/day, then subsequently stabilised on 1,600 mg/day. His synthetic protein requirement and intake decreased from 60 to 40 g/day.

According to the patient's weight, the dose was subsequently rounded for all patients to 400 mg or 500 mg/day (Table 1).

On serial yearly blood monitoring of micronutrient status, two cases required intervention: (Subject 2 and 4) during the last 4 years of treatment. Subject 2 manifested a transient B12 deficiency (154 nmol/L) associated with poor adherence to the prescribed vitamin and mineral supplement in tablet form. Adherence improved with education. Subject 4 manifested chronic sub-optimal zinc levels associated with intermittent reduced intake of the prescribed amino acid supplement and minimal dietary sources of zinc, despite an increase in her natural protein allowance. The zinc status improved after this patient was prescribed additional multi-vitamins to provide an additional 20–40% per day of her vitamin and mineral requirements to ensure ongoing adequacy of her diet.

The above examples highlight the need for ongoing micronutrient monitoring with changes in the dietary prescription associated with a change to Sapropterin. However, it should be noted that poor adherence to intake of the amino acid supplement was well documented in both these individuals prior to starting Sapropterin and indeed was a major rationale to start this therapy.

Height, weight and BMI were monitored and recorded at each OPD visit. In the past 4 years there has been minimal fluctuation in BMI for each patient. Cases 1–3 started Sapropterin in adolescence and therefore earlier BMI records will require interpretation using BMI centile charts and are not included here. Case 4 started therapy in adulthood and has maintained a similar BMI throughout the past 7 years.

The mean phenylalanine levels over the previous 5 years of treatment for all four patients while on Sapropterin are illustrated in Table 1 with the pre-treatment levels, genotype, Sapropterin dose, current natural protein tolerance, changes in synthetic protein intake/requirement and recent PKU HRQoL assessments (Table 2) for three of the four subjects. Other than very occasional high Phe levels with intercurrent illness, the four subjects obtained excellent biochemical control on treatment (Table 1).

The Quality of Life as self-reported by all four subjects was noted to be improved post treatment with Sapropterin. All respondents indicated that travel was now much easier without having the necessity to bring vast amounts of low protein foods and all respondents recommended the treatment and reported that it had a positive impact on their lives. The PKU HRQoL domains studied for the three individuals all noted little or no current impact of the disease. Table 2 shows the results for all four domains for the three respondents that answered the questionnaire.

From a review of the most recent dietary record taken in out-patients and a patient phone questionnaire, all four individuals reported improved variety in regular foods they are able to consume and less reliance on specialised low protein prescription foods such as bread, pasta, biscuits, flours, milks. This involved the use of normal bread/wraps, chips and pasta/noodles and increased flexibility of choices, for example toppings on pizzas, ability to eat out at restaurants and to take small quantities of higher protein foods such as meat on occasion for subjects 2 and 3.

Discussion

Almost 7 years of surveillance for these four patients has shown that this dose of Sapropterin (range 5–8 mg/kg day) was well tolerated and effective. There were no adverse effects noted and all four subjects reported a marked improvement of their Quality of Life with optimum Phe levels and adherence during this time period. All four subjects considered that the liberalised diet possible as a result of Sapropterin treatment had a positive impact on their life.

The literature cites differing experiences with Quality of Life assessments in PKU patients that are shown to be responsive to Sapropterin. In a US based study, Douglas

Table 2 PKU health-related quality of life score under domain and categorisation

Quality of Life (QoL) score under domain (%) followed by category	Case 1	Case 2	Case 3	Case 4
Symptoms	4% Minimum impact QoL	0 No impact QoL	16% Little or no impact QoL	25% Little or no impact QoL
Adherence	20% Little or no impact QoL	4.5% Little or no impact QoL	7.6% Little or no impact QoL	29% Moderate impact on QoL
Supplement use (synthetic formula and products)	15% Little or no impact QoL	20% Little or no impact QoL	12.5% Little or no impact QoL	25% Little or no impact QoL
Protein restriction	15.5% Little or no impact QoL	4.8% Little or no impact QoL	6.25% Little or no impact QoL	21.5% Little or no impact QoL

et al. (2013) reported significant improved Quality of Life (QoL) for definitive Sapropterin PKU responders in their study (17 BH4 responders). The areas of improvement noted by the patients described in this report include: reduced planning required for meals, more freedom around eating out allowing more socialising, and increased independence around food preparation. Cazzoria et al. (2014) reported the experience of 22 Italian PKU patients with mild PKU who were respondent to BH4 in comparison to 21 patients with classical PKU treated with diet. Global QoL scores were found to be within the normal range both in patients with mild and classical PKU but global QoL was found to be significantly higher in patients with mild PKU under BH4 treatment as compared to the classical PKU group under a complete dietary Phe restriction regime (Cazzoria et al. 2014). In the study reported by Demirdas et al. (2013) of Dutch patents attending eight metabolic centres, overall PKU patients demonstrated normal health-related quality of life (HRQoL), however for the 10 BH4 responsive PKU patients in their study, improvement in their HRQoL after relaxation of diet could not be demonstrated (Demirdas et al. 2013). A recent study by Feldmann et al. (2017) reporting on 112 German BH4 patients (children and adolescents) with PKU measured the QoL for the patients and their carers before the start of BH4 therapy and after 6 months of therapy. This group reported that Sapropterin did not seem to improve the QoL in PKU patients and their carers.

In our current study, three of the four patients showed a significant response to treatment at these lower Sapropterin doses with reduced requirement for synthetic protein and reduced costs associated with using low protein products and self-reported improved quality of life. However, the economic benefit of this improvement of quality of life is difficult to quantify. Ireland is one of the few countries worldwide that has an explicit cost-effectiveness threshold (O'Mahony and Coughlan 2016). In Ireland generally only medicines that are more expensive than existing treatments for similar patients undergo a Health Technology Assessment (HTA) that measures Quality of Life adjusted years (QALYs) with other economic evaluations. A QALY is: 'A measure of an individual's length of life that has been adjusted for the health-related quality of life'. Essentially a QALY equates to 1 year of good health. Quality of Life is measured by quality of life questionnaires. This assessment is challenging for diseases which are not life-threatening when there are alternative treatments (such as dietary in PKU).

While Sapropterin at a dose of 10 mg/kg day has not to date received reimbursement approval in Ireland by the HTA assessment process, we consider that this lower dose schedule may represent a more cost-effective treatment for patients with responsive mutations, allowing a less restrictive diet with improved Quality of Life and improved adherence.

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