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Long-term safety and efficacy of sapropterin: The PKUDOS registry experience

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On behalf of the, Phenylketonuria Demographics, Outcomes and Safety (PKUDOS) registry

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ABSTRACT

The Phenylketonuria (PKU) Demographics, Outcomes and Safety (PKUDOS) registry is designed to provide longitudinal safety and efficacy data on subjects with PKU who are (or have been) treated with sapropterin dihydrochloride. The PKUDOS population consists of 1189 subjects with PKU: N = 504 who were continuously exposed to sapropterin from date of registry enrollment, N = 211 who had intermittent exposure to the drug, and N = 474 with some other duration of exposure. Subjects continuously exposed to sapropterin showed an average 34% decrease in blood phenylalanine (Phe) — from 591 ± 382 μmol/L at baseline to 392 ± 239 μmol/L ($p = 0.0009$) after 5 years. This drop in blood Phe was associated with an increase in dietary Phe tolerance [from 1000 ± 959 mg/day (pre-sapropterin baseline) to 1539 ± 840 mg/day after 6 years]. Drug-related adverse events (AEs) were reported in 6% of subjects, were mostly considered non-serious, and were identified in the gastrointestinal, respiratory, and nervous systems. Serious drug-related AEs were reported in ≤1% of subjects. Similar safety and efficacy data were observed for children < 4 years. Long-term data from the PKUDOS registry suggest that sapropterin has a tolerable safety profile and that continuous use is associated with a significant and persistent decrease in blood Phe and improvements in dietary Phe tolerance.

1. Introduction

Phenylketonuria (PKU), also referred to as phenylalanine hydroxylase (PAH) deficiency, is an inborn error of metabolism with an incidence of 1:10,000 to 1:15,000 births in the United States [1]. Deficiency of PAH causes hyperphenylalaninemia that can adversely affect brain function [2]. Current treatment is centered on a phenylalanine (Phe)-restricted diet to reduce blood Phe concentrations while providing enough additional protein, vitamins, and minerals to support normal growth. Recent practice guidelines by the American College of Medical Genetics and Genomics (ACMG) identify lifelong maintenance of blood Phe in the range of 120–360 μmol/L as an appropriate target [3,4]. Various classification systems for Phe-related disorders have been developed. In one commonly used system, individuals with Phe concentrations above 1200 μmol/L are considered to have classic PKU while those with a highest untreated blood Phe between 360 and 1200 μmol/L are considered to have milder disease [3,5,6].

Tetrahydrobiopterin (BH_4) is a co-factor for the PAH enzyme and, when given in pharmacological amounts, can improve PAH activity which results in lower blood Phe levels and improved Phe tolerance in some patients with PKU [7]. Sapropterin dihydrochloride (KUVAN®, BioMarin Pharmaceutical Inc., Novato CA, USA), a synthetically-prepared salt of naturally occurring BH_4, at a dose of 20 mg/kg/day can reduce Phe levels in 56% to 75% of pediatric PKU subjects (20% of subjects at 10 mg/kg/day) [8–10]. In BH_4-responsive subjects sapropterin reduces blood Phe levels in adults [8] and in children [10] in a dose-dependent manner [11].

Sapropterin has been assessed in long-term clinical studies. Burton et al. reported the safety of sapropterin and maintenance of blood Phe reduction in a population with PKU (N = 111, age range: 4 to 50 years) for up to 2.6 years at doses of 5 to 20 mg/kg/day. The most common AEs were consistent with previous studies and included

Abbreviations: AE, adverse event; PKU, phenylketonuria; Phe, phenylalanine; BH_4, tetrahydrobiopterin; PKUDOS, phenylketonuria demographics, outcomes and safety; PAH, phenylalanine hydroxylase.

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headache, rhinorrhea, pharyngolaryngeal pain, diarrhea, and vomiting [12]. Keil et al. followed 147 subjects with PKU who were treated with BH_4 or sapropterin for up to 12 years and showed reduced blood Phe ranging from 28% to 89% ($N = 67$, $p < 0.001$) [13]. AEs (relatedness not stated) were observed in 2% of subjects and were classified as: gastric pain, frequent urination, and dizziness. No severe AEs were reported.

While sapropterin is a promising treatment, the strength of the clinical evidence supporting its long-term use is still considered insufficient [6]. This manuscript assesses the short- and long-term safety and efficacy of sapropterin on blood Phe levels and dietary Phe tolerance in a large number of subjects with PKU.

2. Methods

2.1. Description of PKUDOS registry

The Phenylketonuria Demographics, Outcomes and Safety (PKUDOS) registry is a phase 4 voluntary observational study designed to provide up to 15 years of data from adult and maternal [14] subjects with PKU who are (or have been) treated with sapropterin. To participate, subjects must have a diagnosis of PKU and have: previously received sapropterin, are currently receiving sapropterin, or intend to receive sapropterin therapy within 90 days of enrollment. Subjects included in this analysis had a signed informed consent form and had a baseline visit. The rationale for prescribing sapropterin and the subject's disease severity were not assessed.

2.2. Clinical assessments

Assessments were performed according to current medical practice at each participating medical center (Supplement Table 1). The investigators evaluated the seriousness and relatedness of all AEs. Various sample types and methods were utilized for laboratory measurements according to clinical practice at each site. Blood Phe/Tyrosine ratios were not calculated because the timing of the measurements for the two analytes was not always known.

2.3. Statistical analysis

This interim analysis focused on two populations based on the use of sapropterin:

- Uninterrupted use population: subjects who have continuously been on sapropterin.
- Short-term use population: subjects who were on sapropterin ≤3 months. Dose gaps were allowed within 3 months of exposure.

Analysis of variance (ANOVA) at 95% confidence assessed the significance of blood and dietary Phe values. A Fisher's exact test was used to compare peak blood Phe by cohort. For subjects with multiple Phe values during a defined time interval, the median Phe was calculated. For patient populations, the mean of median values was calculated. Sapropterin recorded dosages that were missing or outside the range of 5–25 mg/kg/day, outlier blood Phe values (>5400 μmol/L) at birth and (>3000 μmol/L) at all other ages were excluded. Peak blood Phe refers to the highest recorded blood Phe concentration from newborn screening, confirmatory testing, and any other source since registry entry. This value was calculated from registry entries and may not reflect highest lifetime blood Phe. Sapropterin-responsiveness was defined as ≥20% reduction in blood Phe within 3 months of initial exposure. If more than one value was reported, the mean blood Phe concentration was used.

3. Results

3.1. PKUDOS registry and demographics

As of June 2013, 1224 subjects were enrolled in the registry from 52 active sites within the United States. Of these, 1189 subjects were eligible for analysis. The population was predominantly Caucasian (89%) and 52% were females. Age distribution, assessed at first sapropterin dose, ranged from 0 to 63 years, and 97/1189 (8%) were children < 4 years of age. At registry entry, half of the population was reported to be enrolled in school, 22% were employed, and a small fraction (2%) was disabled. Demographic information specific for the uninterrupted use population and short-term use population is shown in Supplement Table 2.

3.2. Sapropterin usage

Of the 1189 subjects, 42% (504/1189) were on continuous sapropterin use (uninterrupted use population) and 18% (211/1189) discontinued the drug within 3-months (short-term use population). In the uninterrupted use population, the first recorded median sapropterin dose was 20 mg/kg/day for a median duration of 4 years. Duration of exposure ranged from 0.9 to 7.2 years. The first recorded median dose for the short-term use population was 20 mg/kg/day and the duration of exposure ranged from 0.03 to 3 months. Sapropterin dosages did not change throughout the time period analyzed in either population.

3.3. Blood and dietary phenylalanine

More than half (56%) of all subjects had a peak blood Phe ≥ 1200 μmol/L, about a third (34%) had peak blood Phe between 600 and 1200 μmol/L and the rest (9%) had peak blood Phe < 600 μmol/L. In the uninterrupted use population, 43% had peak blood Phe ≥ 1200 μmol/L, 42% had peak blood Phe between 600 and 1200 μmol/L, and 15% had peak blood Phe < 600 μmol/L. In the short-term use population, the majority (82%) had a peak blood Phe ≥ 1200 μmol/L (significantly different from uninterrupted use cohort, $p = 0.0001$), 16% had a peak blood Phe between 600 and 1200 μmol/L, and 3% had a peak blood Phe < 600 μmol/L.

Table 1 shows changes in mean blood Phe from pre-sapropterin (baseline) to 6 years for both uninterrupted use and short-term use populations. For the uninterrupted use population, the data show significant ($p = 0.0009$ to 0.0001) and sustained (−25% to −34%) decreases in blood Phe from 1 to 6 years after starting sapropterin compared to baseline. For the short-term use population, blood Phe data over this same time interval show smaller (−1% to −9%) decreases, and none are significantly different from baseline.

In the uninterrupted use population, 71% (69/97) are sapropterin-responsive compared to 27% (12/45) in the short-term use population. This difference was significant ($p = 0.001$). Overall, the response rate for these two populations is 57% (81/142).

Table 2 shows that, for the uninterrupted use population, average actual dietary Phe intake increases from 1000 mg/day (pre-sapropterin exposure) to 1539 mg/day after 6 years from baseline. For the short-term use population, average actual dietary Phe intake decreases from 815 mg/day to 725 mg/day over the same time interval.

Fig. 1 shows changes in median blood Phe concentrations and actual dietary Phe intake for a subgroup of the uninterrupted and short-term use populations, who had diet Phe intake and blood Phe both measured at the same time points. For the uninterrupted use population, the median blood Phe data show significant and sustained decreases compared to baseline (mean of median decrease: 43%, range: 37%–48%). In addition, this cohort shows increases in actual dietary Phe intake (mean of median increase: 48%, range: 28%–67%) over this same time period. Blood Phe concentrations for the short-term use