Multi-disciplinary Implementation of Sapropterin for treatment of phenylketonuria patients in a Regional Metabolic Centre

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Introduction

Phenylketonuria (PKU, OMIM #261600) is a rare autosomal recessive metabolic disorder caused by mutations of the *PAH* gene (12q23.2) and deficiency of the enzyme, phenylalanine hydroxylase (PAH). In PKU, the hydroxylation of phenylalanine (Phe) to tyrosine (Tyr) is impaired leading to accumulation of Phe. Exposure of the brain to high concentrations of Phe results in irreversible intellectual disability, behavioural problems, psychiatric symptoms, motor deficits, seizures and eczematous rash. To date, the only treatment to lower Phe has been to follow a **lifelong low phenylalanine diet** (very low natural protein with amino acid supplements).

Sapropterin dihydrochloride

Sapropterin dihydrochloride is a synthetic analogue of the PAH cofactor, tetrahydrobiopterin licensed at doses of 5 to 20mg/kg per day for the treatment of sapropterin-responsive PKU adults and children. Sapropterin responsiveness is determined by presence of at least one *PAH* variant predicting sapropterin-responsiveness, a >30% reduction in Phe level when taking sapropterin alongside their usual low phenylalanine diet, and maintenance of this Phe level after increasing their protein intake in the extension phase (*Fig.1*). In December 2021 NHS England commissioned sapropterin for all PKU patients with proven sapropterin responsiveness. In the inherited metabolic (IMD) service at Queen Elizabeth Hospital Birmingham, Specialist Dieticians and an Advanced Clinical Pharmacist manage the sapropterin responsiveness testing pathway as part of a multi-disciplinary team with Inherited Metabolic Diseases (IMD) consultant oversight.

Results

Since December 2021, 35 patients with at least one *PAH* variant predicting response have been tested for sapropterin responsiveness. 10 were unresponsive or could not complete the extension phase and stopped sapropterin. Four patients started the pathway during pregnancy but did not continue.

Of the 21 patients with proven sapropterin responsiveness after completion of the testing protocol, 15 had one responsive *PAH* variant, 4 patients had two responsive *PAH* variants and 2 patients had one responsive and one unidentified variant (*Fig. 2*). The average Phe blood concentration reduction was 49% (range 30% to 82%). In the extension phase, natural protein intake increased on average by 126% (range 0% to 471%) (*Fig. 3*) .

Of the 10 patients who did not respond to sapropterin 1 had two responsive PAH variants, 7 had one responsive variant. Two patients with 2 non-responsive variants underwent sapropterin responsiveness testing prior to genomic results being available. Average Phe reduction in the non-responsive cohort was 12% (range -4% to 25%, n=8). 2 patients had >30% Phe blood concentration reduction on sapropterin but could not complete the extension phase.

Fig. 1 Treatment Protocol

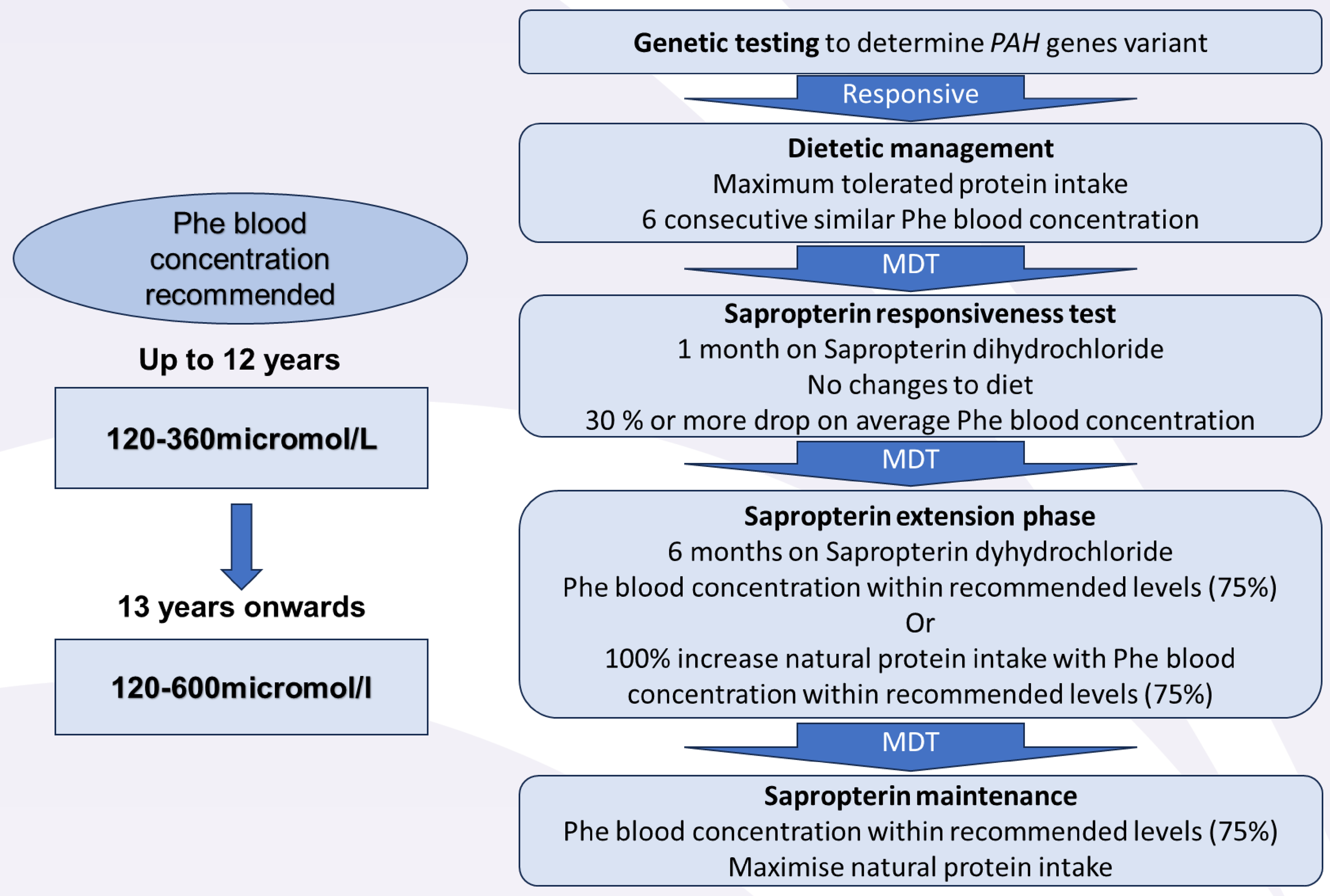

Fig. 3 Reduction in Phe blood concentration (%) and increase in protein intake (%), n=19 patients completing the protocol

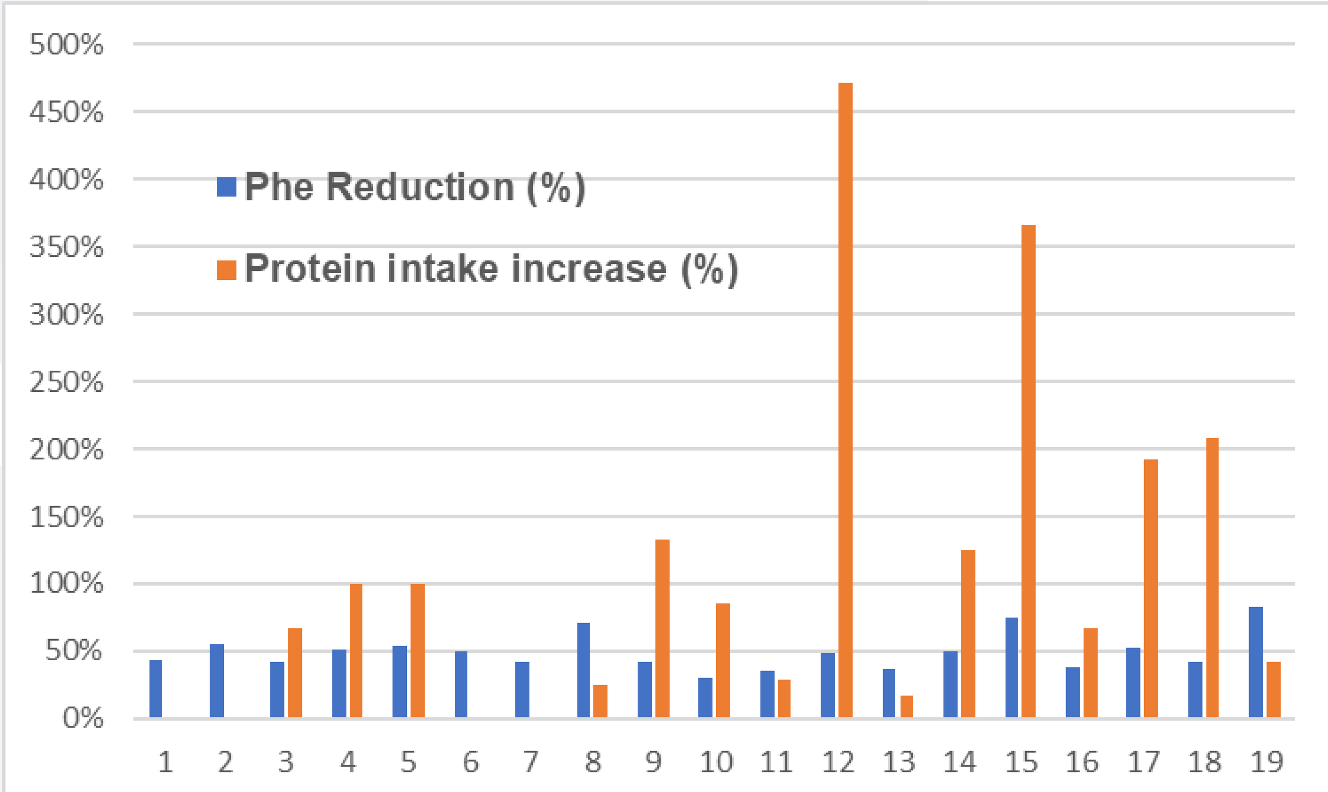

Fig. 2 Reduction in Phenylalanine blood concentration (%) and *PAH* gene variations

Gene variants	c.117C>G p.(Phe38Leu)	c.136G>A p.(Gly46Ser)	c.194T>C p.(Ile65Thr)	c.782G>A p.(Arg261Gln)	c.331C>T p.(Arg111*)	c.838G>A p.(Glu280Lys)	c.842C>T p.(Pro281Leu)	c.873_880del p.(Pro292Ph	c.1222C>T p.(Arg408trp)	c.1315+1G>A (IVS12+1G>A)	c.441+5G>T p.(?)	c.844G>A p.(Asp282Asn)	c.896T>G p.(Phe299Cys)	c.1045T>C p.(Ser349Pro)	c.1205T>C p.(Phe402Ser)	c.(441+20_442-79)_(509+14_510-90)del p.?	Unidentified
c.117C>G p.(Phe38Leu)						33%			-4%								
c.143T>C p.(Leu48Ser)										50%							
c.194T>C p.(Ile65Thr)			51%	25%		32%		54%	14%	36%	52%		43%	42%			30%
c.194T>C p.(Ile65Thr)									40%								
c.194T>C p.(Ile65Thr)									82%								
c.205A>T p.(Arg68Ser)									75%								
c.754C>T p.(Arg252Trp)					42%												
c.754C>T p.(Arg252Trp)					36%												
c.782G>A p.(Arg261Gln)		65%							23%	55%							
c.1042C>G p.(Leu348Val)										16%					42%		
c.1241A>G p.(Tyr414Cys)	41%					71%	50%					48%				23%	
c.331C>T p.(Arg111*)									1%								
c.1222C>T p.(Arg408trp)									-5%								
c.473G>A p.(Arg158Gln)																	37%

PAH gene variants: green – known to respond to sapropterin; red – known not to respond to sapropterin; **black** – unknown response to sapropterin
Phenylalanine blood concentration reduction: green – sapropterin responder; amber – sapropterin responder but not completed extension phase; red – not sapropterin responder
Data of 30 patients, excluding pregnant patients and 1 patient who started sapropterin responsiveness test recently and therefore no data available at the time of writing.

Patient treatment perception / statement

"I feel so lucky to be a responder to sapropterin. My everyday life is so much easier, I am so much more comfortable, happier, less pain and struggle! I am finally able to keep my bloods within a safe range. As an adult with PKU, with sapropterin I am finally able to start seeing the wood for the trees and support my health and well-being in ways that felt unsurmountable since I was teenager."

'Sapropterin has allowed me to have a normal diet where I don't have to think about how much protein I am eating. Taking the tablets is so much easier than any other supplement I have tried. It has been amazing for me'

Conclusions

- Implementation of new treatments for rare disorders like PKU require a multi-disciplinary approach
- Genomic information on responsiveness to treatment allows to target those patients more likely to benefit, optimising resources
- Sapropterin can be life changing for responsive patients, allowing them to eat normally after a lifetime of a very restrictive and challenging diet.