Molecular Genetics and Metabolism Reports 24 (2020) 100603

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

Short Communication

First 1.5 years of pegvaliase clinic: Experiences and outcomes

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ABSTRACT

We present Boston Children's Hospital's clinic model for pegvaliase therapy in adults with phenylketonuria (PKU) and clinical outcomes in 46 patients over the first 1.5 years of commercial therapy. Approximately 70% (18/26) of patients starting pegvaliase achieved blood phenylalanine (Phe) < 360 μmol/L, with an average of a 68 ± 24% decrease in blood Phe from baseline. All patients experienced at least minor side effects, but in most, management of the side effects allowed for treatment to continue.

1. Introduction

Pegvaliase, an enzyme substitution therapy, reduces blood phenylalanine (Phe) in adults with phenylketonuria (PKU) and often allows for diet normalization [1,2]. It provides an alternative therapeutic approach to PKU when standard treatments, including dietary Phe restriction, medical foods, and cofactor therapy with sapropterin, are inadequate to achieve target blood Phe concentrations (120–360 μmol/L) [3].

Pegvaliase is comprised of pegylated phenylalanine ammonia lyase (PAL), a non-human enzyme that converts Phe to ammonia and trans-cinnamic acid [4,5]. As such, it invariably causes an immune response in humans [6]. Due to risk for anaphylaxis and non-systemic side effects, pegvaliase is initiated and titrated slowly, and patients are advised to pre-dose with H1 and H2 blocking antihistamines and required to carry auto-injectable epinephrine [7].

Here we present our clinic model and clinical outcomes in a large cohort (n = 46) of adults with PKU being treated with pegvaliase in the "PAL Clinic" at Boston Children's Hospital between August 2018 and December 2019.

2. Clinic design

The PAL Clinic is a specialty clinic within the Dr. Harvey Levy Program for PKU and Related Conditions at Boston Children's Hospital that provides care for patients with PKU receiving pegvaliase. Our team includes biochemical geneticists, metabolic dietitians, a psychologist, a clinic nurse and a clinic coordinator. Prior to initiation, patients are required to have a baseline metabolism visit within the previous 12 months and a documented blood Phe ≥600 μmol/L. Group information sessions are offered to help manage patient expectations, including time to efficacy and potential side effects, and to provide Risk Evaluation and Mitigation Strategies (REMS) training for anaphylaxis.

Our clinic provides ongoing education and training during observed injection visits of the initiation phase and with each dosage increase. Pegvaliase doses are sent directly to the hospital pharmacy and provided in clinic for self-injection. Home observer(s) are highly recommended but not mandatory, and are encouraged to attend clinic visits for training. Medical visits occur during dosage increases and approximately every two months; nutrition visits occur every 3–6 months with more frequent visits while making dietary changes; and neuropsychological assessments occur at baseline and every 12 months as needed. Patients have access to 24-hour on-call coverage in the event that a patient experiences medication side effects.

On initiation, baseline labs are obtained including amino acids, chemistry, nutritional labs (e.g., 25-OH vitamin D, vitamin B12, prealbumin, iron studies and zinc) and inflammatory markers (e.g., erythrocyte sedimentation rate and C-reactive protein). Blood Phe and tyrosine are monitored every 4 weeks throughout initiation and titration, and 1–2 weeks after each dosage increase. Weekly blood Phe monitoring is advised as blood Phe decreases in order to make timely modifications to protein intake. Intact protein is generally increased by 10–20 g/day and often accompanied by a concurrent decrease in medical food when blood Phe is < 120 μmol/L [7]. While blood tyrosine concentrations are generally within the reference range, tyrosine concentrations repeatedly below 30 μmol/L are addressed on a case-by-case basis. For the purpose of our discussion, we consider responders to be those with both a Phe decrease > 50% and Phe < 360 μmol/L.

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https://doi.org/10.1016/j.ymgmr.2020.100603
Received 24 January 2020; Received in revised form 3 May 2020

3. Results and discussion

Our team transitioned 20 patients to commercial therapy from the pegvaliase clinical trials [1] and started 25 new patients, two of whom had previous exposure to pegvaliase during the clinical trials. One additional patient transferred to our clinic. The mean age of patients was 35.9 ± 10.5 years (range 19.1–55.4), and 37% (n = 17) were male. Of the 46 patients on therapy, four of the post-trial patients transferred to their local clinics and three patients discontinued therapy, one due to personal choice, one due to anxiety and one due to side effects described below. One female discontinued therapy for pregnancy and resumed after breastfeeding on an accelerated titration schedule [8].

Post-trial patients had been in the trial for an average of 4.8 ± 1.2 years. At the first clinical visit after the study closed, four patients had blood Phe > 360 μmol/L, two had Phe of 30–360 μmol/L and 11 had low blood Phe (< 30 μmol/L). Three patients had no post-study Phe reported due to discontinuation or site transfer. Medication adherence declined after study close-out in six patients, as noted by patient report and worsening metabolic control. Team members increased contact with patients to help reinforce consistent dosing. To help with injection fatigue, we offered weekly dosing reduction by giving a higher dose in a single injection fewer times per week. Phe levels generally remained consistent when maintaining the same weekly dose given in fewer injections. We advised dosing a minimum of twice weekly to avoid potential side effects from dose interruption. No side effects were observed with weekly dosing reduction. Additionally the weekly dose was reduced in patients with low blood Phe (< 30 μmol/L).

Patients initiating commercial therapy started pegvaliase on a rolling basis and were treated for an average of 45 ± 18 weeks (range 10–71 weeks). Mean blood Phe decreased from 1031 ± 385 μmol/L at baseline (n = 26) to 654 ± 509 μmol/L at 12 months of therapy (n = 9). Nearly all patients (24/26) had a ≥ 30% decrease in Phe from baseline with an average decrease of 56 ± 30%. Eighteen patients (69%) had a ≥ 50% decrease in Phe, corresponding to at least one blood Phe concentration < 360 μmol/L (Fig. 1A). The initial blood Phe response (< 360 μmol/L) in these 18 patients occurred while on 10 mg (3/18), 20 mg (8/18), 40 mg (5/18) and 60 mg (2/18) pegvaliase/day at an average of 13 ± 10.5 weeks, 16.1 ± 7.7 weeks, 36.4 ± 2.9 weeks and 58 ± 5.7 weeks after starting pegvaliase therapy, respectively. One patient, who initially responded on 40 mg at 33 weeks, had a rebound increase in blood Phe that remained elevated on 60 mg/day at 62 weeks of therapy. Six patients had low blood Phe concentrations (< 30 μmol/L) on ≥2 samples. There were subjective improvements in quality of life, verbal communication and daily functioning among responders, but objective data were unavailable for the majority of patients. Some patients reported more work-related compliments and being promoted.

At pegvaliase initiation, the majority of patients (16/26) consumed a Phe-restricted diet with medical food (formula), 8/26 consumed a moderate protein restriction with inadequate medical food (≤50% of prescribed) and 2/26 had discontinued all dietary treatment. Most patients had minor fluctuation in BMI (0.14 ± 1.1 kg/m2) after starting pegvaliase; however, 5/26 experienced > 5% weight change that corresponded to an improvement in BMI in 4/5. Of the 18 patients with a blood Phe response, 50% tolerated a normal intact protein intake (≥0.8 g/kg/day) with no medical food. Several patients experienced fluctuations in blood Phe while making diet modifications, which slowed diet liberalization. Patients on a normalized vs. liberalized diet had an earlier blood Phe response prior to data collection (22 ± 19 weeks vs. 16 ± 8 weeks, respectively). At the time of data collection, patients with ongoing diet modifications (n = 9) had a median of a 50% increase in intact protein and 25% decrease in medical food protein.

All patients experienced side effects, which included injection-site reaction (including erythema, 23/26), arthralgia (18/26), rash (18/26), fatigue (12/26), headache (9/26), gastrointestinal symptoms (7/26), chills (6/26), hair loss (5/26), inguinal or axillary lymphadenopathy (4/26), dizziness (2/26) and anaphylaxis (1/26). There were often reactions 1–2 weeks after initiation, and the frequency decreased over the course of treatment (Fig. 1B).

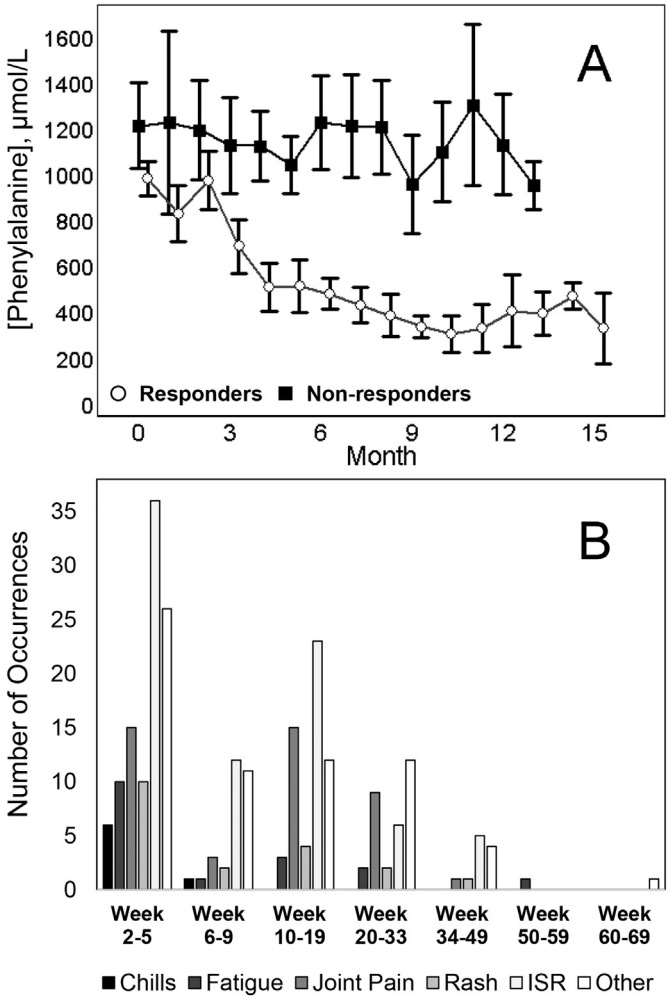

Fig. 1. Blood phenylalanine (Phe) concentrations (A) and side effects (B) in 26 adults with phenylketonuria on commercial pegvaliase therapy. (A) Treatment response classified as having ≥1 blood Phe concentration < 360 μmol/L. Mean ± SD blood Phe concentrations demonstrated an overall decrease of 68 ± 24% for responders (n = 18) and 24 ± 18% for non-responders (n = 8) when comparing most recent blood Phe to baseline. (B) Rate of side effects for treatment naïve patients. For most, pegvaliase was increased to 10 mg at 6 weeks, 20 mg at 10 weeks and 40 mg at 34 weeks. *ISR, injection site reactions.

Side effects were managed allowing continuation of therapy for most. One patient experienced gastrointestinal symptoms from the premedication, which lead us to start premedication dosing prior to initiation in subsequent patients. The titration schedule [7] was slowed due to side effects in 4/26 patients, including one patient who experienced anaphylaxis at 6 weeks of therapy and was successfully re-challenged at week 10. One patient was concurrently receiving immunotherapy for environmental allergies, and developed an injection site reaction that became cellulitic with central scabbing, and later severe joint pain, leading to discontinuation. Oral steroids were prescribed to treat joint pain, hives or marked injection site reaction in 11/26 patients. Substantial hair loss characterized by global thinning without alopecia was noted in one patient after a period of low blood Phe combined with suboptimal total protein intake. Symptoms improved after an increase in dietary protein.

4. Conclusion

While there are many challenges with pegvaliase therapy, including a significant side-effect profile and delay of drug efficacy, it has proven to be a powerful new treatment for adults with PKU. Given the potential for cognitive and psychiatric co-morbidities in adults with PKU, this clinic model has offered patients ongoing education, emotional support and close monitoring throughout the phases of therapy. The majority of our patients were able to achieve efficacy (Phe < 360 μmol/L) with diet liberalization or normalization and continue on therapy even through side effects, including one case of anaphylaxis. A multidisciplinary clinic with excellent psychosocial support is beneficial for patient experience and adherence. As our clinic expands in the future with a broader PKU population base, we hope to continually improve clinic practices involving this new treatment modality.

References

[1] J. Thomas, H. Levy, S. Amato, J. Vockley, R. Zori, D. Dimmock, C.O. Harding, D.A. Bilder, H.H. Weng, J. Olbertz, et al., Pegvaliase for the treatment of phenylketonuria: results of a long-term phase 3 clinical trial program (PRISM), Mol. Genet. Metab. 124 (1) (2018) 27–38, https://doi.org/10.1016/j.ymgme.2018.03.006.

[2] C.O. Harding, R.S. Amato, M. Stuy, N. Longo, B.K. Burton, J. Posner, H.H. Weng, M. Merilainen, Z. Gu, J. Jiang, et al., Pegvaliase for the treatment of phenylketonuria: a pivotal, double-blind randomized discontinuation phase 3 clinical trial, Mol. Genet. Metab. 124 (1) (2018) 20–26, https://doi.org/10.1016/j.ymgme.2018.03.003.

[3] E.R. Jurecki, S. Cederbaum, J. Kopesky, K. Perry, F. Rohr, A. Sanchez-Valle, K.S. Viau, M.Y. Sheinin, J.L. Cohen-Pfeffer, Adherence to clinic recommendations among patients with phenylketonuria in the United States, Mol. Genet. Metab. 120 (3) (2017) 190–197, https://doi.org/10.1016/j.ymgme.2017.01.001.

[4] J.A. Hoskins, S.B. Holliday, A.M. Greenway, The metabolism of cinnamic acid by healthy and phenylketonuric adults: a kinetic study, Biomed Mass Spectrom. 11 (6) (1984) 296–300, https://doi.org/10.1002/bms.1200110609.

[5] H.L. Levy, C.N. Sarkissian, C.R. Scriver, Phenylalanine ammonia lyase (PAL): from discovery to enzyme substitution therapy for phenylketonuria, Mol. Genet. Metab. 124 (4) (2018) 223–229, https://doi.org/10.1016/j.ymgme.2018.06.002.

[6] S. Gupta, K. Lau, C.O. Harding, G. Shepherd, R. Boyer, J.P. Atkinson, V. Knight, J. Olbertz, K. Larimore, Z. Gu, et al., Association of immune response with efficacy and safety outcomes in adults with phenylketonuria administered pegvaliase in phase 3 clinical trials, EBioMedicine 37 (2018) 366–373, https://doi.org/10.1016/j.ebiom.2018.10.038.

[7] N. Longo, D. Dimmock, H. Levy, K. Viau, H. Bausell, D.A. Bilder, B. Burton, C. Gross, H. Northrup, F. Rohr, et al., Evidence- and consensus-based recommendations for the use of pegvaliase in adults with phenylketonuria, Genet. Med. 21 (8) (2019) 1851–1867, https://doi.org/10.1038/s41436-018-0403-z.

[8] F. Rohr, A. Kritzer, C.O. Harding, K. Viau, H.L. Levy, Discontinuation of Pegvaliase therapy during maternal PKU pregnancy and postnatal breastfeeding: a case report, Mol. Genet. Metab. Rep. 22 (2020) 100555, https://doi.org/10.1016/j.ymgmr.2019.100555.