Compatibility of Trofinetide With Ketogenic Diets in Patients With Rett Syndrome: Case Reports

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Poster #44

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INTRODUCTION

- Rett syndrome (RTT) is a rare neurodevelopmental disease characterized by developmental regression, hand stereotypies, behavioral and communication issues, and impaired motor skills[1]
- Patients with RTT have multiple RTT-related comorbidities, including epilepsy, which occurs in approximately 60–90% of patients[2]
- In patients with RTT, seizures are primarily managed with pharmacologic therapy but non-pharmacologic options, such as ketogenic diet therapy, are common[3]
  - Ketogenic diets are high-fat, low-carbohydrate, and moderate-protein diets that promote ketosis to reduce seizures[3]
  - When following a ketogenic diet, all sources of carbohydrates, including those from medications, must be accounted for[3]
- Trofinetide (DAYBUE®) is approved for the treatment of RTT in patients aged ≥2 years in the United States and patients aged ≥2 years weighing ≥9 kg in Canada[4,5]
  - DAYBUE® oral solution contains 0.03 g of carbohydrates per 1 mL of medication
  - With recommended weight-banded doses ranging from 25–60 mL twice a day (BID),[4,5] trofinetide may contribute 1.5–3.6 g carbohydrates/ day toward a patient's daily carbohydrate allowance
- The feasibility of maintaining ketosis through ketogenic diets while on trofinetide is unknown

OBJECTIVE

- To describe the successful induction of ketogenic diets amid trofinetide treatment in 3 anecdotal patient cases

RESULTS

- The cases presented are of 3 female patients, aged 5–11 years, with RTT and comorbid intractable epilepsy, who are currently receiving trofinetide for the treatment of RTT symptoms (Table 1)

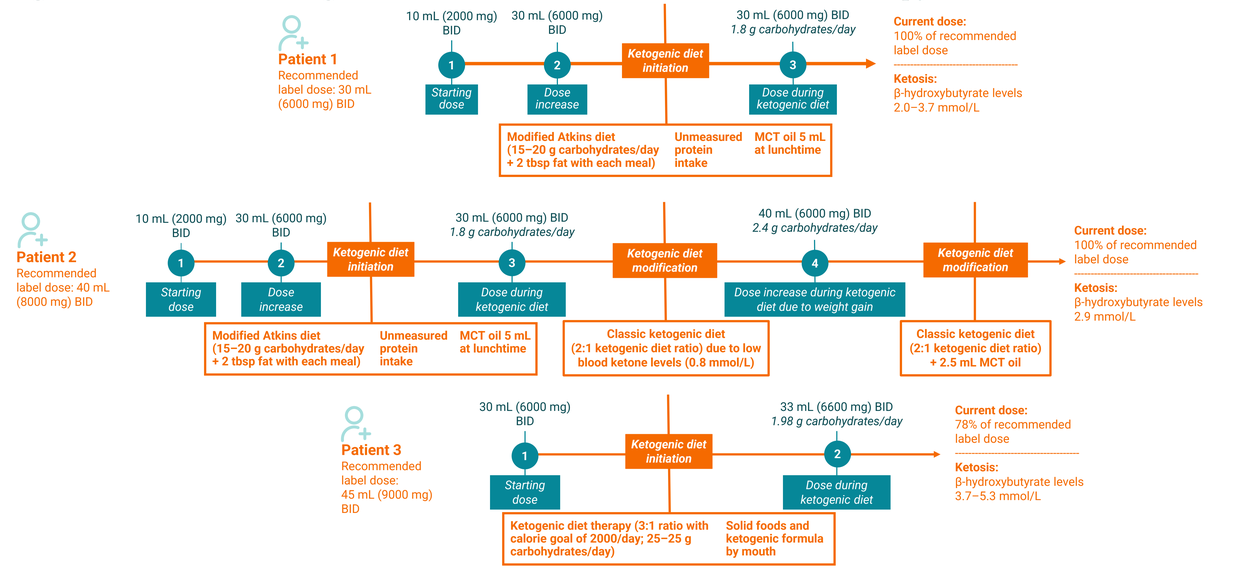
Table 1. Patient Characteristics and Medical History

	Patient 1	Patient 2	Patient 3
RTT medical history			
Approximate age at diagnosis	1 year 10 months	1 year 3 months	1 year 6 months
***MECP2* mutation**	473C>T	Exon 4 deletion	c.763C>T, p.R255X
RTT features	Development regression and stagnation at 1 year 6 months of age	Development delays and stagnation	Development regression with stagnation at 1 year 6 months of age; crying for communication, eye contact, follows simple commands
Seizure medical history			
Approximate age at diagnosis	2 years 11 months[a]	2 years 6 months[b]	10 years 6 months[c]
Diagnosis	Intractable focal epilepsy	Intractable focal epilepsy (motor and nonmotor with impaired awareness)	Intractable focal epilepsy
Seizure frequency at diagnosis	1 seizure/month	1 seizure/day	3–4 seizures/day
Management	Phenobarbital and clobazam	Oxcarbazepine and brivaracetam	Levetiracetam, perampanel, and lamotrigine
Trofinetide for the treatment of RTT			
Approximate age at initiation	3 years	2 years 9 months	9 years
Administration route	Oral	Oral	Oral
Duration of trofinetide treatment to present	2 years 6 months	2 years 5 months	1 year 11 months
Duration of concomitant trofinetide and ketogenic diet therapy	4 months	6 months	1 year 3 months

[a]Seizures diagnosed approximately 1 month prior to trofinetide initiation. [b]Seizures diagnosed approximately 3 months prior to trofinetide initiation. [c]Seizures diagnosed approximately 18 months after trofinetide initiation.
RTT, Rett syndrome.

- Ketogenic diets were successfully initiated and maintained amid concomitant trofinetide therapy for the treatment of intractable epilepsy (Figure 1)
  - Prior to ketogenic diet induction, trofinetide was initiated at 10 mL (2000 mg), 10 mL (2000 mg), and 30 mL (6000 mg) BID, which is 33%, 25%, and 66% of their recommended weight-banded dose, respectively
  - One patient's trofinetide dose was further increased to 30 mL (6000 mg) prior to ketogenic diet induction, which is 100% of their recommended weight-banded dose
  - For the remaining 2 patients, after ketogenic diet induction, trofinetide was further increased to 40 mL (8000 mg) and 33 mL (6600 mg) BID, respectively, which is 100% and 78% of their recommended weight-banded dose, respectively
  - The final BID trofinetide regimens contributed 1.8 g, 2.4 g, and 2.0 g carbohydrates/ day, respectively
  - In all 3 cases, ketosis was achieved and maintained while on trofinetide treatment, as evidenced by β-hydroxybutyrate levels ranging from 2.0–5.3 mmol/L

Figure 1. Initiation of Ketogenic Diets Amid Concomitant Trofinetide Therapy



BID, twice a day; **MCT,** medium-chain triglycerides.

Across cases, RTT symptoms improved in all patients, comorbid seizures improved in 2 of 3 patients, and seizure incidence did not worsen post trofinetide initiation (Table 2)

Table 2. Impact of Concomitant Ketogenic Diets and Trofinetide Treatment on Symptoms of RTT and Seizure Frequency

	Patient 1	Patient 2	Patient 3
Age at last evaluation	5 years	5 years	11 years
RTT clinical improvement	No further RTT regression; currently standing with support and making monosyllable sounds	No further RTT regression; can sit with support and has a radial grasp	Uses words like "no" and "yeah"; more engaged
Seizure frequency	Seizure clusters every 3–4 months	Seizures once every 3–4 months or longer interval	No change
Concomitant antiseizure medication	Phenobarbital, clonazepam, and clobazam	Brivaracetam, clonazepam, oxcarbazepine, and diazepam	Lamotrigine and perampanel

RTT, Rett syndrome.

CONCLUSIONS

In these anecdotal cases, patients with RTT were successfully initiated and maintained on ketogenic diets for intractable epilepsy despite concomitant RTT-related trofinetide therapy

All patients achieved ketosis, as evidenced by optimal β-hydroxybutyrate levels; 2 of 3 patients experienced reductions in seizure frequency

It is possible that trofinetide aided in the reduction of seizure frequency in 2 of the 3 patients; further research is required as the direct impact of trofinetide on seizure frequency has not been studied

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DISCLOSURES

HL, **KU**, and **VP** have no disclosures. **SK** is no longer an employee at Acadia Pharmaceuticals Inc but was at the time of abstract submission.

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