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ACMG THERAPEUTICS BULLETIN

Trofinetide approved for children and adults with Rett syndrome (RTT): A therapeutics bulletin of the American College of Medical Genetics and Genomics (ACMG)

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Background

Rett syndrome (RTT) is an X-linked condition caused by *MECP2* loss-of-function pathogenic variants. *MECP2* is considered to be a crucial regulator for brain development through the encoded protein (methyl-CpG binding protein-2).[1,2] RTT affects 1 in 10,000 to 23,000 females globally, making it one of the most common genetic causes of intellectual and developmental impairment in females.[1,3,4] RTT initially manifests with subtle developmental delay and hypotonia between 6 to 18 months of life (stage 1).[5] This is followed by motor regression (particularly purposeful hand movements) and speech regression (stage 2), leading to pseudo-stabilization (stage 3, 30 months to 20 years of life) and late motor decline

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(stage 4, >20 years of age).[5] To a lesser extent, affected males have also been identified with RTT or a clinical spectrum encompassing early onset neonatal encephalopathy, parkinsonism or severe intellectual disability, usually accompanied by sex chromosome aneuploidies and/or somatic mosaicism.[4] Over 4000 loss-of-function pathogenic variants have been described, although no clear genotype-phenotype correlation has been established.[2] There are other genes, such as *CDKL5* (early infantile epileptic encephalopathy) and *FOXG1* (congenital variant RTT), that are now considered in the differential as atypical RTT.[3]

Management and treatment

Consensus guidelines for RTT management have been published.[6] This involves an individually tailored multidisciplinary approach, focusing on improving quality of life through symptomatic relief.[1,3,6] Strategies include physical therapy to enhance mobility, occupational therapy for daily living skills, and speech therapy to improve communication abilities.[6] Nutritional support, medications to manage seizures, and interventions for breathing irregularities and cardiac arrhythmias (because of risk for prolonged QTc) are also critical.[6,7] Coordination of care among specialists in clinical genetics, neurology, gastroenterology, and orthopedics is essential for comprehensive management.[6]

There were no US Food and Drug Administration (FDA)-approved therapies specifically designed for use in individuals with RTT before 2023.

Newly approved therapy

Indication and approved treatment population

Trofinetide (trade name: DAYBUE) is a synthetic peptidase-resistant analog of glycine-proline-glutamate, an N-terminal tripeptide derived from insulin-like growth factor-1. Trofinetide is expected to improve neuronal and synaptic function and is indicated for use in adults and children aged 2 years and older who have been diagnosed with RTT.[8–10] Trofinetide received FDA priority review, orphan drug, and fast track drug designations.[10] Accelerated approval was obtained through the FDA on March 10, 2023.[10]

Mechanism of action

Trofinetide is administered twice daily by mouth or via gastrostomy tube.[9] Its mechanism of action is uncertain, but clinical studies suggest that it improves and restores synaptic function (increases related gene expression); reduces neuroinflammation (inhibits astrogliosis and microglial activation and enhances antioxidant response, attenuating inflammatory cytokines); reduces apoptosis (interacts with *N*-methyl-D-aspartate receptors); and restores neuron growth and development by amplifying insulin-like growth factor-1 synthesis or activation of the extracellular signal-regulated kinase and phosphoinosite 3-kinase pathways.[8,9,11,12]

Outcomes and efficacy

An anonymized, placebo-controlled, parallel-group study involving 82 female participants (age range 5-15 years) receiving doses between 50 to 200 mg/kg over 42 days showed statistically significant evidence ($P < .05$) of improvement between the highest dose (200 mg/kg) and placebo in 3 measures: Clinical Global Impression Scales, Improvement and Severity (magnitude of effect [MoE] 15% vs 5% placebo); RTT Behavior Questionnaire (MoE 16% vs 6%) and RTT Domain Specific Concerns-Visual Analog Scale (MoE 20% vs 5%).[13]

The LAVENDER study (phase III, anonymized, placebo-controlled trial) involved 187 female participants between 5 to 20 years of age over 12 weeks. Nonplacebo participants showed significant improvement in their coprimary endpoints by Cohen's *d* (effect size): RTT Behavior Questionnaire (0.37) and Clinical Global Impression Scales, Improvement and Severity (0.47).[14] The secondary endpoints, Communication and Symbolic Behavior Scales Developmental Profile Infant-Toddler Checklist-Social Composite Score and RTT clinician rating of ability to communicate choices, also exhibited improvement (Cohen's *d*: 0.43 and 0.36, respectively).[14,15]

Adverse effects and toxicity

The most common adverse effects include diarrhea (80.6%) and vomiting (26.88%), followed by seizures (8.6%), pyrexia (8.6%), transient transaminitis (7.6%), and decreased appetite (5.4%).[14] Severity ranged from mild to moderate. The majority of drug discontinuation cases were due to mild to moderate diarrhea, which proved to be self-limited and resolved upon drug withdrawal.[14] This situation was also addressed by adjusting laxative medications (if RTT-associated constipation was present), starting fiber supplementation, adding antidiarrhea medications, or reducing Trofinetide dosage.[6,14,16] Trofinetide does not carry any boxed warning for prescribers.

Additional considerations

Trofinetide approval was based on improvement of RTT-specific neurodevelopmental scales. At the time of this writing, there are other ongoing clinical trials for RTT exploring alternative therapeutic methods, such as drug repurposing or gene therapy.[17–19] Although Trofinetide has been approved for use in males with RTT, future clinical trials will be needed to assess efficacy. Although Trofinetide has been approved for RTT, it is unclear if this approval includes atypical RTT because these individuals were not part of the clinical trials. Trofinetide is under evaluation for other neurocognitive disorders, such as Fragile X syndrome.[20]

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Conflict of Interest

The authors declare no conflicts of interest.

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