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Research paper

The novel first-line therapy for rett syndrome

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Abstract

Rett Syndrome (RTT) is a neurodevelopmental disorder predominantly affecting females and characterized by hyperkinetic movement disorders and related symptoms. At present, the available treatments for RTT primarily focus on managing symptoms and providing supportive care. This article examines the emergence of trofinetide as an innovative therapeutic approach targeting the underlying molecular and synaptic abnormalities associated with RTT. The approval of trofinetide, marketed as DAYBUE™, as the primary treatment for Rett Syndrome by the US Food and Drug Administration (FDA) is based on encouraging outcomes from clinical trials. Ongoing open-label studies are currently underway to evaluate the long-term efficacy and safety of trofinetide in various age groups, thus providing valuable insights into its sustained benefits. These advancements in research, along with other potential treatments under investigation, offer promising prospects for the development of improved and personalized management strategies for individuals with Rett Syndrome.

Keywords: *Cognitive Disabilities; Developmental Disorder; Neurological Deficits; Rett Syndrome; Trofinetide*.

1. The novel first-line therapy for rett syndrome

Rett Syndrome is a neurodevelopmental disorder that primarily affects females, and it is due to an X-linked mutation in the methyl-CpG-binding protein 2 (MECP2). The symptoms manifest in early childhood, and are typically associated with hyperkinetic movement disorders (HMD), which have been described as a core feature of Rett, along with tremor, dystonia, chorea and myoclonus [1].

Currently, therapeutic options for Rett syndrome focus solely on symptomatic management and supportive treatment, which include timely visits to the clinic for the evaluation of neurologic, cardiologic, urologic and respiratory systems of the patients. For common problems such as constipation and reflux, laxatives and H2 blockers are used empirically. Several behavioral therapies have been recommended if the patients suffers from difficulties in chewing, defecation and cognition [2].

Trofinetide is the first drug approved by the US Food and Drug Administration (FDA) for the therapeutic treatment of Rett syndrome [3]. It is an analogue of the N-terminal tripeptide of insulin-like growth factor-1 (IGF-1), an essential growth factor for the proper growth and function of the brain that is found naturally in the brain. It is believed that trofinetide mimics IGF-1, the levels of which are reported to be low in individuals with Rett Syndrome. Another benefit is that it reduces neuro-inflammation and inhibits the release of pro-inflammatory cytokines [4].

The effectiveness and safety of trofinetide was assessed over 12 weeks in a randomized, double-blind, placebo-controlled trial carried out by Neul et al., in the female population aged between 5-20 years. The main effectiveness measures of the study were the Clinical Global Impression-Improvement (CGI-I) score and the Rett Syndrome Behaviour Questionnaire (RSBQ) score. By the end of the trial, trofinetide had significantly outperformed the placebo in both co-primary outcomes [5]. Another study's findings revealed that trofinetide showed significant improvement over the placebo in the MBA change index, the CGI-I score, and the Caregiver Top 3 Concerns VAS score [6]. This was supported by another trial that showed that trofinetide was well tolerated at three different dosage levels and statistically significant improvement ($p<0.05$) was observed over placebo in RSBQ, CGI-I and Rett Syndrome-Domain Specific Concerns (RTT-DSC) [7].

The most common side-effects associated with the use of trofinetide were diarrhea and weight loss, with around 85% of patients suffering from diarrhea and 12% experiencing weight loss of greater than 7% from baseline. Hence patients were advised to stop laxatives before starting the medication. Currently trofinetide is recommended to be given twice daily, with the dosages varying according to patient weight. It is an oral solution which can be administered orally as well as through a G tube [8].

As of now two open-label trials are ongoing to study the long-term efficacy of trofinetide in girls from two to five (2-5) years of age and women from five to twenty two (5-22) years of age. These trials will be fundamental in proving the effectiveness and safety of trofinetide in the long run.

Although trofinetide has been approved by the FDA, several other emerging treatments are currently being studied, including Glatiramer Acetate, which is a medicine used to treat multiple sclerosis and has shown remarkable results in improving the gait speed, breathe hold index and recognition memory of patients with Rett syndrome [9]. Aside from that, Virtual Reality system GRAIL is also being devel-

oped to better the gait and cognition of these individuals [10]. As these studies progress, we can hope for more effective and personalized treatment strategies for Rett syndrome.

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