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Letter to the Editor

Trofinetide providing a promising avenue for the treatment of Rett syndrome

Sir,

Rett syndrome (RTT) is a developmental disability associated primarily with the abnormal functioning of the nervous system. Affecting 1 in 10,000-15,000 women, it results from an inactivating modification in the X-linked genetic code, methyl-CpG-binding protein 2 (MECP2), which codes for a protein that binds to DNA and regulates transcription.[1,2] Girls with RTT are born with normal prenatal and perinatal periods and appear to be in good health. Their psychomotor growth is typical up to their first or second year of life, at which point brain functional regression starts. Clinical signs of the regression include the emergence of stereotyped hand movements, a loss of fine motor skills, gait apraxia, verbal and nonverbal communication deficits, and epileptic seizures.[3]

There is no specific treatment for RTT at the moment.[4] Due to a lack of diagnostic tests, it was previously misdiagnosed as autism, cerebral palsy, or a developmental delay, which was one of the reasons it didn't have therapy. Since the MECP2 gene was identified, a blood test may be used to determine whether a kid has a gene mutation that causes RTT. The clinical characteristics and family history of the kid must be taken into consideration because the mere existence of this mutation is insufficient to confirm RTT.[5]

For the control and management of the disease, preventive measures are applied. These measures include nutritional support with a focus on caloric intake and vitamin D levels, prevention of gastrointestinal and orthopedic complications, and individualized therapeutic interventions in addition to conventional drug treatments (e.g., selective serotonin reuptake inhibitors for anxiety, antiepileptic drugs for seizures).[6]

Trofinetide, a novel medication, was given FDA approval on March 24, 2023 to treat RTT in adults and children 2 years of age and older. Trofinetide, also named glycyl-L-2-methyl prolyl-L-glutamic acid, is a tripeptide similar to insulin-like growth factor 1 (IGF1). This drug can cure RTT by restoring dendritic morphology, synaptic protein synthesis, and neuronal signaling, and antioxidant response. These effects result from the anti-inflammatory and trophic actions that suppress pathological microglial activation and astrogliosis.[7]

Some researchers conducted a randomized, multi-centered, phase 2, double-blind, placebo-controlled trial to compare the safety and tolerability, pharmacokinetics, and clinical response of twice-daily oral administration of trofinetide with a placebo in children with RTT aged 5 to 15 years. There was statistically significant proof of clinical improvement ($p<0.05$) with 200 mg/kg twice daily dosages of trofinetide over placebo. It was via three main metrics: The RTT Behavior Questionnaire ($p=0.042$), the clinical global impression scale improvement ($p=0.029$), and the RTT-clinician domain specific concerns-visual analog scale ($p=0.025$).[7]

Another phase 2 study conducted in adult females with RTT revealed outstanding safety, tolerability, and early proof of the efficacy of trofinetide at 70 mg/kg twice a day for 28 days. Even though some participants had advanced illnesses and symptoms, all fundamental endpoints exhibited either progress or constancy.[5]

The most typical adverse reaction seen in all individuals with the administration of the daily oral dose of trofinetide was diarrhea.[5,7] Additionally, reported were an upper respiratory tract infection, fever, loss of weight, nasopharyngitis, and vomiting. Most adverse events were mild in intensity, and most of them were deemed unrelated to the medication used. There were no known life-threatening incidents. In individuals with RTT, all dose levels of trofinetide were generally safe and well-tolerated.[7]

Given the lack of medical therapy for RTT, trofinetide seems to be a promising option for slowing the course of the disease along with addressing the primary symptoms of the disease.[5] These findings, plus those from a prior study, justify additional research into trofinetide's effectiveness in resolving RTT.

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