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Promising Treatment Strategies for Rett Syndrome

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Abstract

Background. Rett syndrome (RTT) is a rare, genetic neurological disease caused by a mutation of the methyl-CpG-binding protein 2 (*MECP2*) gene that mainly affects girls. There is no currently available causative treatment for this disease; trofinetide is the only drug dedicated to alleviating symptoms.

Aim. The aim is to present potential medicines in clinical trials that have been observed to have a therapeutic benefit in the treatment of Rett syndrome. The article contains also descriptions of

pathophysiology and symptoms of Rett syndrome, which can be affected by undermentioned pharmaceuticals.

Material and methods. The study used Google Scholar, PubMed, and Scopus databases as its data sources. Other information was obtained from the Clinicaltrials.gov registry and database, and reports of companies conducting drug research. The literature was filtered by keywords: 'Rett syndrome', 'clinical trials' and 'gene therapies'.

Results. The treatment of Rett syndrome focuses on alleviating symptoms and improving the quality of life. Trofinetide is the only substance approved by the US Food and Drug Administration (FDA), which helps to reduce behavioral problems and improve social functioning. Currently, research is underway on genetic therapies, including gene replacement therapy, which may provide more effective treatment options in the future. Additionally, research is being conducted on other drugs that reduce symptoms in patients with RTT.

Conclusions. Great hopes are associated with research on gene therapies, which are currently in clinical trial phases. In the future, this could bring significant benefits to patients; their implementation may not only improve aspects of the disease, such as respiratory issues, but also can result in better survival outcomes.

Keywords: Rett syndrome, gene therapies, clinical trials, MECP2, TSHA-102, NGN-401

Content

1. Introduction

Rett syndrome (RTT) is one of the most common causes of intellectual disability in young females and is rarely diagnosed in males (1,2). RTT prevalence is estimated between 1:10000–15000 live female births (1)·(3). A progressive neurological disorder in patients with RTT results from a mutation in the X-linked, methyl-CpG-binding protein 2 (*MECP2*) gene. Still, the mechanism by which this mutation is responsible for triggering the symptoms of the disease remains unknown (4). Girls with a heterozygous mutation typically survive into their fifth decade of life, whereas in boys, it relates to the karyotype and mutation (2,5). Development appears normal until 6 to 18 months of age, after which a regression in language and motor skills becomes evident. Typical and atypical RTT are distinguished. To diagnose the typical form all four main criteria (loss of spoken language, stereotypic hand movements, gait abnormalities, and loss of purposeful hand skills) must be fulfilled, along with the occurrence of a regression period, followed by stabilization or recovery (6). When a patient does not meet the diagnostic criteria for a typical variant and presents RTT-like symptoms may be diagnosed with atypical RTT depending on the severity of the disease, sequence of clinical profile and the onset of presented symptoms (4). Patients with RTT may require multidisciplinary care due to numerous comorbidities. They also suffer from seizures, breathing irregularities, sleep disturbances, cardiac abnormalities, orthopedic or gastrointestinal disorders (7). Concerns raised by parents of individuals with RTT are an important aspect of patient care. In a study conducted with parents and caregivers of patients with RTT (n=925), they were asked to list the main issues affecting their dependents that they struggle with. The most common concerns involved difficulties in communication with their daughters, followed by seizures, mobility

challenges, lack of hand use, and constipation (8). These problems serve as an important indicator for evaluating the effectiveness of treatment in patients and are crucial in assessing meaningful clinical studies, because of their impact on patients' quality of life (9). The use of animal models provides an opportunity to understand the pathophysiology of RTT better and develop effective therapy, not only by alleviating symptoms but also by modifying the course of the disease (10–12). Due to the introduction of these models, clinical trials in RTT have been conducted that led to the approval of trofinetide by the US Food and Drug Administration (FDA), and gene therapies are currently being pursued, offering significant promise (13–15).

2. Research material and methods

The study used Google Scholar, PubMed, and Scopus databases as its data sources. Other information was obtained from the Clinicaltrials.gov registry and database, and reports of companies conducting drug research. The literature was filtered by keywords: 'Rett syndrome', 'clinical trials' and 'gene therapies'. Articles from the past seven years were searched and included for the review section.

The low prevalence of rare diseases poses challenges for conducting large-scale clinical trials. Due to difficulties in selecting sufficient study samples, clinical trials tend to be small. One drug is currently approved in the United States for treating RTT (16). The greatest development in research has appeared in the last 10-15 years, various pharmaceuticals and gene therapies have been investigated (17).

3. Results

3.1. Gene therapies

Genetic therapies for Rett syndrome, such as gene editing, gene replacement, X chromosome reactivation and RNA editing are being researched. The most significant advancements are being made in research on gene replacement therapies, due to elaborating new vectors designed to control the levels of MeCP2 expression (18). A comparison of both gene therapies described in the text is included in Table 1.

Table 1. Comparison of both gene therapies.

Gene therapy	TSHA-102	NGN-401
Company	Taysha Gene Therapies	Neurogene
Type of trial	open-label	open-label
Vector	AAV9	AAV9
Gene delivered	mini*MECP2*	*MECP2*
Technology used	miRARE	EXACT
Drug administration	intrathecal	intraventricular
Clinical trial phase	1/2	1/2
Described study duration	2023–2032	2023–2029

Source: Own resources

3.1.1. TSHA-102

Lonimecgene Renparvovec (TSHA-102) is an experimental gene therapy developed by Taysha Gene Therapies. It is based on the use of a non-replicating self-complementary adeno-associated virus serotype 9 (scAAV9) to deliver a modified, smaller version of the *MECP2* gene, which contains key domains: MBD (methyl-CpG-binding domain) responsible for recognizing methylated DNA fragments, and NID (NCoR/SMRT interaction domain), which mediates gene silencing. To avoid *MECP2* overexpression, miRARE was used for the 3' untranslated region (UTR) (19). The miRARE is a sophisticated genetic tool that helps maintain the safety and efficacy of gene therapies by preventing harmful overexpression while still ensuring the production of sufficient protein for therapeutic benefit. This mechanism is vital for developing safe and effective gene therapies like Rett syndrome (20).

Preclinical data support the efficacy of TSHA-102 gene therapy in mice. Respiratory and survival data were particularly promising (21). Following successful preclinical results, TSHA-102 in 2023 entered phase 1/2 clinical trials under the REVEAL program. These studies are designed to assess the therapy's safety and efficacy. Clinical trials included adolescents and adults (NCT05606614) and expanded to pediatric populations (NCT06152237) after the safety of TSHA-102 was established. Both tests for adults and children involve a single intrathecal administration of

the drug. Two dose levels will be tested sequentially in separate study patients, depending on the outcome of the first dose level (22,23). The first clinical trial reports are promising in adult and pediatric Rett syndrome patients, particularly in motor skills, communication, autonomic function, and seizure control. In adult patients, benefits were seen for up to 52 weeks, including improved sitting, normalized sleep, and reduced seizures. In one case, a patient was seizure-free for 8.5 months on lower medication. For pediatric patients, early improvements were noted by 22 weeks, including better motor coordination, language skills, and an ability to walk upstairs with more seizure-free days. The therapy has an encouraging safety profile (24).

3.1.2. NGN-401

NGN-401 is an experimental gene therapy developed by Neurogene to treat Rett syndrome with a single AAV9 vector dose. It uses the Expression Attenuation via Construct Tuning (EXACT) platform to deliver the full-length human *MECP2* gene while precisely controlling its expression levels. This approach aims to restore necessary *MECP2* function without the risks associated with overexpression (25).

An early-stage phase 1/2 clinical trial (NCT05898620) began in 2023 to evaluate this gene therapy's safety, tolerability, and preliminary efficacy in young female patients aged 4 to 10 years with typical Rett syndrome. The study includes cohort 1 receiving a low dose and cohort 2 receiving a high dose via intraventricular administration (ICV) under general anesthesia (26). Neurogene Inc. has administered NGN-401 to three pediatric patients in a low-dose cohort and one in a high-dose cohort in the U.S. The treatment was mostly well-tolerated, with only mild, transient adverse events reported. Importantly, no indications of *MECP2* overexpression toxicity were observed in any of the patients (27).

3.2. Blarcamesine

Blarcamesine (ANAVEX2-73) is a sigma-1 receptor agonist and muscarinic receptor modulator (28). It improves calcium homeostasis, ameliorating mitochondrial and synaptic functions in numerous brain regions. Hence, blarcamesine may be perceived as a potential drug for improving core neurologic deficits in RTT. A preclinical study on female *MECP2*-deficient mice proved improvement in motor coordination, balance, acoustic and visual responses, hindlimb clasping, and apnea in expiration. A good safety profile of blarcamesine was demonstrated (29). Three double-blind, randomized, placebo-controlled clinical trials were created for the evaluation of dose escalation safety, tolerability and efficacy. Women between 18 and 45 years of age with

confirmed RTT were included in the phase 3 trial named AVATAR (NCT03941444) and the phase 2 trial (NCT03758924), then children and adolescents 5-17 years of age in 2/3 phase EXCELLENCE trial (NCT04304482) (30–32). Data from a study in the adult population showed patients undergoing treatment with blarcamesine had a statistically significant reduction in disease severity and progression compared to the placebo group (33).

3.3. Cannabidiol

Cannabidiol (CBD) is a phytocannabinoid obtained from Cannabis sativa plant. CBD interacts with various targets such as the neuro-modulatory endocannabinoid system (ECBS) which participates in the GABAergic and glutamatergic neurotransmission (34). ECBS is involved in regulating physiological processes such as anxiety, social behavior, motor coordination or memory, therefore it appears to be a promising pharmaceutical in RTT treatment (35). Due to CBD's ability to regulate inhibition and excitation of the brain, the compound has also been comprehensively researched in connection with its antiseizure properties (34). Epilepsy is a frequent comorbid condition in RTT, occurs in 60-80% of patients. It seems to correlate with the clinical severity of the RTT consequently its effective treatment and prevention of relapses is crucial (35). An observational retrospective study was conducted and included 10 female patients between 7 and 32 years of age with genetically confirmed RTT and pharmacoresistant epilepsy. The patients were initially administered CBD (100 mg/mL, Epidyolex®) at a dose of 5mg/kg/day, which was increased to a maximum of 30 mg/kg/day in case of a lack of side effects. CDB was treated as an adjunct to other prescribed anticonvulsants, including clobazam in 50% of patients. The study showed a good tolerance of patients with RTT to CBD administration and 70% of the cohort recorded a reduction frequency of monthly epileptic seizures (36). The 3-phase clinical study (NCT03848832) aimed at assessing the effectiveness and safety of CBD in 2-18 years of age patients with RTT was conducted. Some of the participants who completed all scheduled visits were qualified for an open-label extension trial (NCT04252586) to analyze the long-term safety of CBD oral solution. The research was interrupted due to the COVID-19 pandemic and the data was not sufficient to conclude (37,38). Positive results from other studies suggest the value of conducting further research.

3.4. Cannabidivarin

Cannabidivarin (CBDV) is a n-propyl analogue of cannabidiol. The mechanism of action of the compound is not fully known. Current studies suggest an antagonistic effect on the G protein-coupled receptor 55 (GPR 55), which presumably modulates motor function, spatial memory and social skills. *MECP2-308* mice, an RTT model, were subjected to systemic CBDV administration, which consequently led to general health status and partial motor coordination improvement and restoration of sociability, and brain weight (39). There is growing interest in CBDV, as an antiepileptic agent, however research, especially in the pediatric population, is limited. Five female patients in the medium age of 12.6 years were enrolled in a small 1-phase clinical trial. The inclusion criteria were pathogenic *MECP2* variant and drug-resistant epilepsy. Treatment with CBDV was started at a dose of 2.5mg/kg/day and titrated to the maximum doses of 9.6–10.1 mg/kg/day. The researchers noted a reduction in the monthly seizure frequency in all five under examination. The CBDV was well tolerated in higher doses of 10mg/kg/day (40).

3.5. Glatiramer acetate

Glatiramer acetate is an immunomodulatory drug, currently used to treat multiple sclerosis (MS). Because of its suspected mechanism of action, involving interaction with myelin proteins and induction of specific suppressor T cells and inhibition of specific effector T cells, glatiramer delays inflammatory disease progression. Moreover, glatiramer has been reported to cause elevated secretion of brain-derived neurotrophic factor (BDNF) both in animal model and in MS patients (41). Studies on mice lacking the *MECP2* gene showed that the use of glatiramer increased BDNF levels (41). Achieving a comparable effect was expected in a clinical trial conducted at SHEBA Medical Center in Israel (NCT02023424), but the study could not be finalized due to four patients developing allergic reactions following the injection of the drug (42).

A study conducted at Montefiore Medical Center, New York (NCT02153723), involving ten girls with RTT, six of whom were being treated for epilepsy, came up with more promising results. A standardized walk test measured the primary outcome, while secondary endpoints included change in respiratory and cognitive function, quality of life and electroencephalography (EEG). Gait speed improved significantly in treated patients. Memory and breath-hold rate also improved ($p \leq 0.03$). Epileptic discharges decreased in all four patients who had them at the start of treatment. A trend toward improved quality of life was also observed, but this did not reach statistical significance (43).

The results of these two studies are inconclusive, but given the partial therapeutic success, further rigorous clinical trials on the use of glatiramer acetate in patients with RTT are recommended.

3.6. Esketamine and ketamine

One of the characteristic symptoms of Rett syndrome that significantly affects patients' quality of life is respiratory distress (1). Improvement in this symptom would be the target of using esketamine in RTT therapy (44). Esketamine is the more potent S-isomer of the racemic drug, ketamine, and an antagonist of muscarinic receptors in the CNS, a non-competitive antagonist of NMDA receptors stimulated by L-glutamate, as well as interacting with opioid receptors μ, and σ (45). Studies in RTT patients and mouse models have shown reduced expression of N-methyl-D-aspartate receptors (NMDAR). Genetic deletion of the NMDAR subunit, GluN2A, in mice lacking the *MECP2* gene has been shown to prevent some of the symptoms of RTT (46). A possible therapeutic effect of ketamine and its derivatives in RTT involves antagonizing NMDA receptors, inhibiting GABA-ergic interneurons and reduction of adverse synaptic activity in brainstem centers responsible for respiration, and autonomic control.(44) The above effects on the CNS were sought to be exploited by researchers in a multicenter clinical trial in the United States conducted on patients with RTT (NCT03633058) (47). No significant adverse effects were reported at either dose. The results are now available and researchers are developing them. A study on the effects of esketamine on RTT patients at the University Children's Hospital of Fudan University is also currently underway (NCT06199700) (48).

Research on the effects of administering ketamine with donepezil, as a possibly more effective combination, is also planned.

3.7. Triheptanoin

It has been proven that, patients with RTT have evidence of mitochondrial dysfunction, as well as abnormal levels of the adipokines leptin and adiponectin, which indicates an overall metabolic imbalance. Thus, restoring balance in lipid metabolism and regulating oxidative processes has been recognized, as a possible drug target in RTT therapy (35). Consequently, triheptanoin, as a drug indicated for the treatment of children and adults with molecularly confirmed disorders of long-chain fatty acid oxidation, provides a potential therapeutic option also for RTT patients. Studies on mice hemizygous for *Mecp2* knockout, demonstrated, that dietary therapy with triheptanoin significantly increased longevity, as well as improved motor function and social interaction of mice. This anaplerotic therapy in *Mecp2* knockout mice also decreased adiposity,

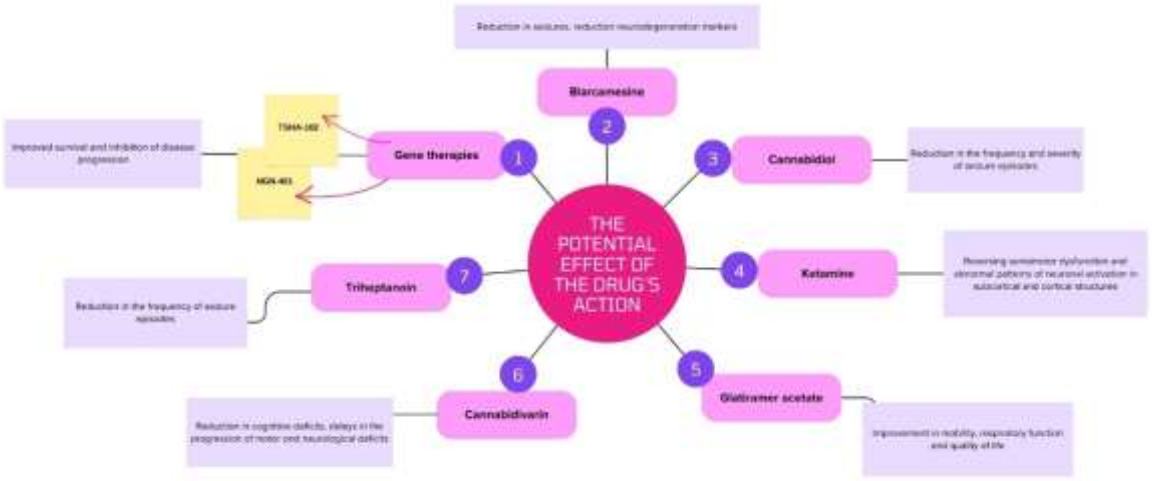
increased glucose tolerance and insulin sensitivity, decreased levels of leptin and insulin, and improved mitochondrial morphology in skeletal muscle (49).

The survey, conducted by the Center for Rare Neurological Diseases, Norcross, GA provided the following results. Two of four patients with intractable seizures achieved a more than 50% seizure reduction. In the other two participants, seizure frequency did not improve and worsened, respectively. Of the two patients with frequent dystonia, the total number of dystonia days decreased and remained unchanged in one (50).

Further studies on triheptanoin may be considered, because of the inconclusive results, given by the described clinical trial and the agent's safety profile.

4. Discussion

The treatment of Rett syndrome focuses on alleviating patients' symptoms and improving the quality of life. At present, Trofinetide is the only substance approved by the FDA, which helps to reduce behavioral problems and improve social functioning. Nevertheless, currently undergoing research on new therapies, including gene replacement therapies, seem to provide an effective treatment options in the future. TSHA-102 and NGN-401 therapies revealed promising results, as well as positive safety profile, which will hopefully encourage other clinicians to conduct further, broadscale and multicenter studies. It is even more important because the trials conducted so far have mostly included only small groups of patients. Additionally, research is being conducted on other drugs that reduce symptoms in patients with RTT, such as blarcamesine, cannabidiol, cannabidivarin, glatiramer acetate, triheptanoin, esketamine and ketamine. Although not every drug tested in described clinical trials has already a significant impact on patients' health, the researchers are significantly emerging the knowledge about the possible ways to treat Rett syndrome. The potential effects of those medicines are summarized and presented below (Figure 1).



Source: Own resources

Figure 1. The potential effect of the drug's action in Rett syndrome

5. Conclusions

1) The clinical trials of the aforementioned pharmaceuticals offer a promising and useful foundation for the development of RTT therapies, with the potential to significantly enhance patients' quality of life.
2) Gene replacement therapies for MECP2 mutation have the greatest potential in future therapy of Rett syndrome, with the ability to control a wide range of symptoms simultaneously. This is particularly promising for TSHA-102.
3) RTT is a very rare genetic disorder, which makes the conduct of clinical trials significantly hampered, by the small groups of patients included in the surveys.
4) The effect of cannabinoid derivatives tested in clinical trials is mainly to reduce the frequency of epileptic seizures. Comparable outcome is expected to occur with triheptanoin.
5) Glatiramer acetate intake may have positive influence on function of the brain, due to increasing BDNF level. It is highly probable that this enabled the improvement of motor and cognitive functions in described survey.
6) RTT therapy involving esketamine aims primarily to alleviate symptoms associated with respiratory distress, in consequence of regulating the activation of brainstem NMDAR and opioid receptor.

7) It is recommended that these drugs and gene therapies, targeted on the treatment of RTT, continue to be studied in larger, broadscale multi-centred trials.
8) The vast majority of the above-mentioned drugs that have been included in clinical trials have achieved an acceptable safety profile, with gastrointestinal complaints being the most common side effect.

Disclosure

Author's contribution

Conceptualization: MK,WM,NZ, and PM; methodology: WM, NZ and MK; software: MK and NZ; check: MK, MChK and NZ; formal analysis: MChK; investigation: MK and PM; writing - rough preparation: MK,WM, NZ and PM; writing - review and editing: MK, NZ and PM; visualization: MK and NZ; supervision: MChK;
All authors have read and agreed with the published version of the manuscript.

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