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Review Article

Advancing therapeutic approaches for Rett syndrome: investigating trofenitide's role - a comprehensive review

Nikita Gupta[1]*, Kachakayala Ramya[2], Kommuri C. Rao[2], Syeda M. Fatima[2], Khadija A. Siddiqui[2]

[1]Department of Pharmacy Practice, St Paul's College of Pharmacy, Hyderabad, Telangana, India
[2]Department of Pharmacy, St. Paul's College of Pharmacy, Hyderabad, Telangana, India

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***Correspondence:**
Dr. Nikita Gupta,
E-mail: nikitagupta250@gmail.com

ABSTRACT

Rett syndrome is a complex neurodevelopmental disorder that mainly affects girls. It involves the loss of hand skills, walking difficulties, breathing problems, seizures, and repetitive hand movements. The syndrome starts with normal development but then goes through a regression, causing significant disability. It is caused by genetic mutations in the methyl-Cpg-binding protein 2 (MECP2) gene on the X chromosome. Rett syndrome poses challenges for patients and their families, requiring comprehensive support and a multidisciplinary approach involving healthcare professionals, educators, and social support networks. Ongoing research on trofenitide in Rett syndrome focuses on understanding its optimal dosing and long-term efficacy. Recent studies have revealed its neuroprotective and neurotrophic properties, suggesting involvement in important signaling pathways for neuronal development and synaptic plasticity. Future research aims to uncover specific molecular targets and pathways influenced by trofenitide, enabling the development of more personalized treatment strategies. Additionally, exploring the synergistic effects of trofenitide with other therapies, such as histone deacetylase (HDAC) inhibitors and N-methyl D-aspartate (NMDA) receptor modulators, shows promise for improved outcomes. Precision medicine approaches utilizing molecular profiling may aid in patient stratification and the development of targeted therapies.

Keywords: Rett syndrome, Methyl-Cpg-binding protein 2, Histone deacetylase, Nuclear corepressor, Trofenitide

RETT SYNDROME BACKGROUND

Rett syndrome (RS) stands as a rare, severe neurodevelopmental disorder predominantly impacting females, occurring in roughly 1 in 10,000 to 15,000 live female births.[1] Initially identified by Austrian pediatrician Andreas Rett in 1966, who observed distinct features among a cohort of young girls, this syndrome garnered its name from his pioneering work. Typically, RS diagnosis transpires in early childhood, with symptoms emerging between 6 and 18 months of age, subsequent to a phase of seemingly normal development.[2] Clinical manifestations of RS involves regression of acquired skills, loss of purposeful hand movements, stereotyped hand actions like wringing or clapping, gait irregularities, seizures and autonomic dysfunction.[3]

Those afflicted with RS commonly contend with significant impairments in motor coordination, communication, and social interaction, leading to considerable disability and reliance on caregivers for daily tasks. The majority of RS instances stem from mutations in the MECP2 gene, situated on the X chromosome.[4] MECP2 encodes methyl-CpG-binding protein 2, pivotal in governing gene expression and neuronal activity.

Mutations in MECP2 disrupt normal cellular functions, inducing abnormalities in synaptic activity, neuronal growth, and brain connectivity.[5] RS typically arises

sporadically, with mutations occurring de novo in affected individuals. In rare instances, the condition may be inherited in an X-linked dominant pattern, whereby a mother carrying the mutation on one of her X chromosomes passes it to her offspring.

RS presents for mi dable challenges for patients and their families, impacting nearly every facet of daily life. The progressive decline in motor and communication skills, combined with the presence of seizures and other medical conditions, necessitates comprehensive and specialized care. Caregivers frequently grapple with emotional, financial, and social burdens associated with managing the intricate needs of individuals with RS.[6]

OVERVIEW OF TROFENITIDE

Trofenitide, also known by its developmental code name NNZ-2566, stands as a synthetic analogue of insulin-like growth factor 1 (IGF-1).[7] Functioning as a partial agonist of the IGF-1 receptor, it exerts neuroprotective and neurotrophic effects that hold potential in a meliorating neuronal dysfunction observed in RS.[8] By modulating crucial biological pathways linked to neuronal growth, synaptic function, and neuro-inflammation, trofenitide emerges as a promising targeted therapy for RS.[9]

Preclinical investigations have showcased the efficacy of trofenitide in enhancing motor function, cognitive abilities, and synaptic plasticity in animal models of RS, laying the groundwork for its clinical exploration.[10] Early-phase clinical trials have yielded promising preliminary outcomes, indicating enhancements in neuro-developmental skills, communication, and social interaction following trofenitide administration.[11]

Trofenitide presents itself as a novel therapeutic avenue for RS, offering potential advantages in enhancing neurodevelopmental outcomes and enhancing the quality of life for affected individuals. Nonetheless, further research is imperative to unveil its long-term efficacy, safety profile, and optimal dosing regimen.

DISCUSSION

Understanding Rett syndrome

RS represents a multifaceted neurodevelopmental disorder predominantly impacting females, characterized by distinct symptoms, genetic etiology, and profound repercussions for both patients and caregivers. This syndrome manifests with a spectrum of clinical features typically appearing in early childhood. Notable characteristics include the loss of purposeful hand skills, gait irregularities, breathing abnormalities (such as hyperventilation and breath-holding episodes), and seizures. Additionally, individuals with RS commonly display stereotyped hand movements like hand-wringing, clapping, or tapping. The clinical trajectory of RS involves an initial phase of seemingly normal development succeeded by a regression of acquired skills, leading to significant disability.[2]

The genetic foundation of RS primarily lies in mutations within the MECP2 gene, situated on the X chromosome. These mutations disrupt various cellular processes crucial for neuronal function and synaptic plasticity, contributing to the distinctive neurological and developmental abnormalities observed in RS. While most RS casesarisesporadically from denovo mutations, rarefamilial cases can occur with X-linked dominant inheritance patterns.[4]

RS imposes substantial physical, emotional, and financial burdens on both patients and their families. The progressive decline in motor and communication skills, alongside the presence of seizures and other medical conditions, necessitates comprehensive support and management strategies. Caregivers encounter formidable challenges in providing care, addressing symptoms, and accessing suitable medical and therapeutic interventions. The intricate needs of individuals with RS mandate a multidisciplinary approach involving healthcare professionals, educators, and social support networks.

Current treatment approaches for Rett syndrome

Managing RS presents formidable challenges due to its intricate symptomatology and underlying genetic complexities. Present treatment methodologies primarily revolve around symptom alleviation, employing a blend of therapeutic modalities, medications, and supportive care to cater to the diverse needs of RS individuals. Addressing RS symptoms requires a multidisciplinary strategy targeting various facets of the condition. Physical and occupational therapies hold pivotal roles in enhancing mobility, independence, and functional capabilities in RS patients.

These therapies concentrate on enhancing muscle tone, motor coordination, and daily living activities. Speech therapy assumes significance in tackling communication impairments, facilitating alternative communication avenues like augmentative and alternative communication (AAC) systems. Moreover, behavioral interventions like applied behavior analysis (ABA) and positive behavior support (PBS) are instrumental in addressing behavioral challenges and fostering adaptive behaviors.[13]

Pharmacological interventions constitute another cornerstone in managing RS symptoms. Antiepilepticdrugs (AEDs) are commonly prescribed to mitigate seizures, prevalent in RS. Additionally, antidepressants and antipsychotics may be utilized to manage mood fluctuations, anxiety, and behavioral issues such as aggression and irritability. While these medications offer relief for specific symptoms, their efficacy varies among individuals, necessitating vigilant monitoring to mitigate potential side effects.[2]

Despite the array of treatment modalities, existing approaches for RS predominantly target symptoms and do not directly tackle the underlying pathophysiology. This underscores the necessity for innovative therapeutic strategies aimed at addressing RS's molecular mechanisms.

Furthermore, accessing comprehensive care and specialized services remains challenging for many RS individuals, particularly those in underserved communities. Limited comprehension of the disorder's intricate genetic and neurobiological foundations presents hurdles in developing targeted therapies.[12]

Table 1: Various treatment approach for Rett syndrome.

Treatment approach	Description
Physical therapy	Utilised to promote mobility, muscle tone and motor coordination in individuals with RS
	Focuses on improving activities of daily living and functional abilities through targeted exercises and interventions
Occupational therapy	Aims to enhance independence and quality of life by addressing fine motor skills, sensory processing and self-care abilities
	Interventions may include adaptive equipment, sensory integration techniques and task oriented training
Speech therapy	Addresses communication impairments and facilitates alternative forms of communication, such as augmentation and alternative communication (AAC) systems
	Targets expressive and receptive language skills, articulation, and pragmatic language abilities
Behavioural interventions	Includes applied behaviour analysis (ABA) and positive behaviour support (PBS) strategies to address behavioural challenges and promote adaptive behaviours
	Focuses on reducing maladaptive behaviours, increasing social skills and improving overall functioning
Pharmacological interventions	Involves the use of medications to manage specific symptoms associated with RS
	Antiepileptic drugs (AEDs) are prescribed to control seizures, while antidepressants and antipsychotics may address mood disturbances and behavioral symptoms
Multidisciplinary approach	Encompasses a holistic approach to care, involving collaboration among healthcare professionals, educators, and social support networks
	Addresses diverse needs of individuals with RS through comprehensive assessment and tailored interventions

TROFENITIDE: MECHANISM OF ACTION

Trofenitide, also identified as NNZ-2566, stands as a synthetic analogue of insulin-like growth factor 1 (IGF-1), presenting itself as a prospective therapeutic option for RS. Understanding its mechanism of action entails delving into its pharmacological attributes, targeted biological pathways, and potential benefits in RS. Trofenitide operates as a partial agonist of the IGF-1 receptor, a pivotal regulator of cellular growth, differentiation, and survival within the central nervous system. By binding to the IGF-1 receptor, trofenitide instigates downstream signaling cascades that foster neuronal survival, synaptic plasticity, and neuro-protection. These pharmacological characteristics position trofenitide as a promising contender for alleviating neuronal dysfunction witnessed in RS.

Trofenitide modulates critical biological pathways implicated in neuronal growth, synaptic function, and neuro-inflammation, rendering it a potentially tailored therapy for RS. By fostering neuronal growth and dendritic arborization, trofenitide may enhance synaptic connectivity and neural circuitry, thereby ameliorating neurological function in RS individuals. Moreover, trofenitide's anti-inflammatory attributes could mitigate neuro-inflammatory processes associated with RS's pathogenesis, further bolstering its therapeutic potential.[8]

Preclinical investigations have supplied compelling evidence bolstering trofenitide's potential benefits in RS. Animal models of the disorder have showcased enhancements in neurological deficits and behavioral outcomes post-trofenitide treatment. These findings suggest that trofenitide could mitigate motor impairments, cognitive deficits, and social abnormalities linked with RS, thereby justifying further clinical exploration.

Trofenitide exerts neurotrophic effects by bolstering neuronal survival, dendritic arborization, and synaptogenesis. These effects arise through its interactions with the IGF-1 receptor and downstream signaling pathways implicated in neuronal growth and development. By augmenting neurotrophic support, trofenitide might facilitate neural repair and functional recuperation in RS individuals.[11]

Furthermore, trofenitide enhances synaptic plasticity by modulating synaptic transmission and dendritic spine density. Animal studies have demonstrated that trofenitide treatment yields enhancements in synaptic function and connectivity, potentially underpinning its beneficial impacts on motor function and cognitive abilities in RS.[1]

Trofenitide possesses anti-inflammatory properties that could assuage neuro-inflammation and oxidative stress within the brain. By diminishing inflammatory cytokine levels and suppressing microglialactivation, trofenitide might attenuate neuro-inflammatory processes implicated in RS's pathogenesis.[2]

Lastly, trofenitide showcases neuro-protective effects by forestalling neuronal damage and apoptosis. Animal models of RS have evidenced that trofenitide treatment diminishes neuronal loss and bolsters neuronal survival, hinting at its potential to uphold neurological function and hinder disease progression.[9]

Preclinical and clinical studies of trofenitide in Rett syndrome

Animal studies play a pivotal role as preclinical models for evaluating the efficacy and safety of potential therapeutic agents in RS. Trofenitide, specifically, has exhibited promising outcomes in diverse animal models of the disorder. Preclinical investigations utilizing mouse models with genetic mutations akin to RS have showcased trofenitide's efficacy in mitigating motor deficits, cognitive impairments, and synaptic irregularities associated with the condition.

A landmark study by Tropea et al demonstrated that trofenitide treatment partially reversed RS-like symptoms in MeCP2 mutant mice. Notable enhancements in motor coordination, cognitive function, and synaptic plasticity were observed post- trofenitide administration, providing compelling evidence for its therapeutic potential in RS.[9] Additionally, further preclinical studies have elucidated the underlying mechanisms of trofenitide's effects in RS. For instance, Deogracias et al exhibited that trofenitide treatment augmented brain-derived neurotrophic factor (BDNF) levels and fostered neurogenesis in a mouse model of RS. These neurotrophic effects are believed to contribute to trofenitide's ability to bolster neuronal survival and synaptic connectivity in RS.[8]

Phase 1 clinical trials are tailored to assess the safety, tolerability, and pharmacokinetics of investigational drugs in humans. In the case of trofenitide, phase 1 clinical trials have affirmed its safety profile and provided valuable insights into its potential therapeutic effects in individuals with RS. Glaze et al conducted phase 1 clinical trials to gauge the safety and tolerability of trofenitide in RS patients, reporting its well-tolerated nature with no serious adverse events noted during the trial period. These findings supported further exploration of trofenitide in larger-scale clinical trials to evaluate its efficacy in enhancing clinical outcomes in RS individuals.[14]

Phase 2 and phase 3 clinical trials are tailored to evaluate the efficacy and safety of investigational drugs in broader populations of patients with the target condition. Early-phase clinical trials of trofenitide in RS have yielded promising initial outcomes, indicating improvements across various domains including motor function, cognitive abilities, communication, and social interaction. Glaze et al reported positive outcomes from Phase2 and Phase3 clinical trials of trofenitide in RS individuals, showcasing enhancements in motor function, communication skills, and behavioral outcomes in participants receiving trofenitide treatment compared to placebo. These findings suggested the potential efficacy of trofenitide in ameliorating functional outcomes and enhancing the quality of life in RS individuals.[11]

Table 2: An overview on key findings done at various clinical trials.

Study/author	Study type	Key findings
Tropea et al (2009)	Preclinical	Trofenitide treatment leads to a partial reversal of RS like symptoms in MeCP2 mutant mice
		Improvements observed in motor coordination, cognitive function and synaptic plasticity
Deogracis et al (2012)	Preclinical	Trofenitide increased brain derived neurotrophic factor (BDNF) levels and promoted neurogenesis in a mouse model of rest syndrome
		Believed to enhance neuronal survival and synaptic connectivity in RS
Glaze et al (2019)	Phase I clinical trial	Trofenitide was well tolerated in individuals with RS
		No serious adverse events reported during the trial period
Glaze et al (2017)	Phase 2 and 3 clinical trial	Trofenitide showed improvements in motor function, communication skills and behavioural outcomes in individuals with RS compared to placebo
		Positive outcomes observed in functional outcomes and quality of life

EFFICACY AND SAFETY OF TROFENITIDE

Improvement in neuro-developmental skills

Recent research, exemplified by studies such as those conducted by Castro et al and Grillo et al, suggests that progenitive holds promise in alleviating neurodevelopmental deficits associated with RS. These studies illustrate that trofenitide treatment leads to functional recovery and structural preservation of neurons in mouse models of RS. Specifically, trofenitide has demonstrated the potential to enhance motor function, cognitive abilities, and adaptive behaviour. Such improvements are pivotal as they target core symptoms of

RS, offering optimism for enhanced independence and improved quality of life for affected individuals.[15]

Impact on communication and social interaction

Emerging evidence from clinical trials, including those discussed by Pini et al indicates that trofenitide may have a positive impact on communication skills, social interaction, and overall quality of life in individuals with RS. These studies have observed enhancements in expressive and receptive language abilities, as well as increased engagement in social activities following trofenitide treatment. Such improvements are significant as they not only facilitate better communication but also foster social connections, promoting emotional well-being and integration within the community.[17]

Evaluation of adverse effects

While initial findings suggest that trofenitide is generally well tolerated, ongoing investigations highlighted by O'Leary et al and Naviaux et al underscore the importance of assessing its long-term safety profile. It is imperative to understand potential adverse effects and drug interactions associated with trofenitide treatment to ensure the well-being of individuals with RS. Comprehensive evaluation and monitoring of adverse effects are essential for optimizing treatment outcomes and minimizing potential risks, thereby supporting the safe and effective use of trofenitide in clinical practice.[18,19]

FUTURE DIRECTIONS AND CHALLENGES

Pharmacokinetic and clinical findings

Recent reviews such as Darwish et al and Darwish suggested that increased trofinetide exposure correlates with improvements in RSBQ, CSBS-DP-IT Social Composite, and RTT-COMC scores, suggesting a dose-response relationship. Specifically, assuming target trofinetide AUC0–12 values of 800–1200 µg·h/ml, the reductions in RSBQ total scores at week 12 were approximately five- to seven-fold greater with trofinetide (range 3.55–4.94) compared to placebo (0.76). Furthermore, significant exposure-response (E-R) relationships were observed for the CSBS-DP-IT social composite and RTT-COMC scores, emphasizing the therapeutic potential of trofinetide across multiple outcome measures.

Additionally, bioequivalence criteria were met for all tested conditions, indicating consistent drug exposure regardless of dosing conditions such as fed versus fasted states and morning versus evening administration. However, C_{max} in the fed versus fasted condition was slightly below the bioequivalence limit (75.49%), suggesting a minimal impact of food intake on trofinetide bioavailability. Trofinetide's primary excretion pathway is unchanged in the urine, contributing to its favorable pharmacokinetic profile.[20,21]

Synergistic effects with other treatments

Trofenitide shows promise for RS treatment, particularly when combined with other therapies. Recent reviews such as Silva-Reis et al and Wang et al underscore the potential synergies between trofenitide and emerging pharmacological interventions, such as neuropeptides like glypromate and novel drugs highlighted in recent advancements. This combination therapy approach holds the potential for enhanced efficacy in symptom management and warrants further exploration in clinical studies to advance precision medicine strategies for RS.[22,23]

Precision medicine approaches

Advances in molecular profiling technologies, such as transcriptomics and proteomics, hold promise for advancing precision medicine approaches in RS. Recent studies, such as those by Sanfeliu et al and Urdinguio et al have identified molecular signatures linked with RS pathophysiology and treatment response, providing potential biomarkers for patient stratification and treatment monitoring. Integrating these molecular insights with clinical data and treatment outcomes can inform the development of targeted therapies and predictive models for optimizing treatment selection and monitoring disease progression.[24,25]

CONCLUSION

In conclusion, the investigation of trofenitide as a therapeutic intervention for RS marks a significant advancement in the quest for effective treatments for this intricate neurodevelopmental disorder. With a thorough understanding of RS's clinical manifestations, genetic foundations, and its profound impact on individuals and families, researchers and clinicians have acknowledged the pressing need for innovative therapeutic strategies. Trofenitide, with its distinctive mechanism of action targeting crucial pathways involved in neuronal growth and synaptic function, has exhibited promising outcomes in preclinical and early clinical investigations. These findings instil hope for enhanced neurodevelopmental outcomes, motor function, and communication skills in individuals with RS.

Furthermore, trofenitide's potential to alleviate neuroinflammation and exert neuroprotective effects suggests broader implications for disease modification and progression. Its implications extend beyond symptomatic relief, offering the prospect of enhancing the overall quality of life for individuals with RS and their families. Nevertheless, while the preliminary evidence is encouraging, challenges and uncertainties remain to be addressed. These include delineating the optimal dosing regimen, evaluating long-term safety and efficacy, and navigating regulatory pathways for clinical translation.

Moving forward, collaborative efforts among researchers, clinicians, industry partners, and advocacy groups are crucial to propel the development and implementation of trofenitide and other targeted therapies for RS. Furthermore, sustained investment in research and clinical trials, coupled with a dedication to personalized medicine approaches, will be pivotal in maximizing the potential benefits of trofenitide and ultimately improving outcomes for individuals living with RS.

In essence, trofenitide emerges as a beacon of hope for the RS community—a potential breakthrough with the capacity to transform lives and pave the way for a brighter future. As we embark on this journey of exploration and innovation, let us remain steadfast in our pursuit of effective treatments, fueled by compassion, collaboration, and unwavering determination to make a meaningful difference in the lives of those affected by RS.

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