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Current Strategies And Emerging Approaches In Treating Prion Diseases: A Systematic Review

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ABSTRACT

Background: Prion disease is a progressive, fatal neurodegenerative disorder caused by the aggregation of misfolded prion proteins (PrP). The normal prion protein (PrPC) has an α-helical structure, while the abnormal form (PrPSc) can lead to severe neurodegenerative disorders. Prion diseases, including sporadic, genetic, and acquired forms, are life-threatening, with affected individuals typically dying within months to a few years after diagnosis. Currently, no effective therapy exists for prion diseases. This review aims to provide insights into current treatments and recent advancements in therapeutic interventions.

Method: We conducted a comprehensive systematic review of published clinical studies on prion diseases, exploring emerging technologies in treatment development. These include immunotherapy, gene therapy, targeted protein degradation therapies, and stem cell technology. We also reviewed clinical studies evaluating the effects of various drugs on prion disease patients.

Conclusion: Over the past 30 years, numerous chemical compounds have been tested for anti-prion effects using cell cultures and animal models. Despite extensive research, only a few compounds advanced to clinical trials, and all failed to show significant therapeutic benefits. The lack of success is largely attributed to disease variability and the challenges in selecting appropriate patient populations for clinical trials, which hindered the achievement of meaningful outcomes.

Keywords: Prion disease, Immunotherapy, Stem cell technology, Protein degradation therapies, Gene therapy.

Introduction

Prion diseases are progressive and fatal neurodegenerative disorders caused by misfolded prion proteins (PrP) that aggregate in the brain. These diseases are characterized by a transformation of the normal prion protein (PrPC), which is predominantly α-helical, into a pathological form known as PrPSc [1][2]. Prion diseases can be classified into sporadic forms (e.g., Creutzfeldt-Jakob disease), genetic forms (e.g., genetic Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker syndrome, and fatal familial insomnia), and acquired forms (e.g., kuru, variant Creutzfeldt-Jakob disease, and iatrogenic Creutzfeldt-Jakob disease) [3].

The PRPN gene, which encodes the human prion protein, is located on chromosome 20 (20p13) and comprises three exons. The open reading frame responsible for the production of PrP mRNA and the known mutations and polymorphisms associated with prion diseases are contained entirely within the third exon [4].

Human prion diseases are categorized into two primary groups based on their pathological features. The first and most prevalent group includes Creutzfeldt-Jakob disease (CJD) and the majority of fatal familial insomnia (FFI) cases. These diseases are characterized by extensive spongiform changes affecting multiple regions of the brain. The second group, known as PrP-amyloidoses, includes Gerstmann-Sträussler-Scheinker syndrome (GSS) and other rare genetic prion diseases. These conditions are marked by cerebral amyloid angiopathy (CAA) in both parenchymal tissues and blood vessels, with or without systemic PrP deposits [5].

A crucial aspect of prion disease pathogenesis is the ability of protein aggregates to propagate throughout the central nervous system (CNS), spreading from cell to cell and across different brain areas. Despite significant advancements over the past fifty years in developing and evaluating various pharmacological tools and interventions aimed at different stages of disease progression, researchers continue to focus on finding effective therapeutic or prophylactic treatments for prion diseases.

As of now, there is no effective therapy for prion diseases. While numerous chemical compounds have demonstrated potential in experimental research, they frequently encounter challenges such as toxicity, limited efficacy, and poor pharmacokinetics at clinical trial level. Initial clinical treatments for Creutzfeldt-Jakob disease (CJD) mainly involved anti-infectious agents, which had little effect on slowing the progression of the disease. Despite the discovery of the pathogenic misfolding of prion protein (PrPSc) and growing understanding of prion diseases, effective treatments remain elusive [6].

This review article provides an overview of the latest developments and advancements in the treatment of prion diseases. It highlights current therapeutic interventions and explores the challenges and knowledge gaps associated with emerging treatment strategies. Through this examination, the article aims to shed light on the progress made in addressing prion diseases and the obstacles that still need to be overcome in developing effective therapies.

Method:

This systematic review provides updated information by analyzing published clinical studies on prion diseases. We discuss emerging technologies and treatment strategies, including immunotherapy, gene therapy, targeted protein degradation therapies, and stem cell technology. Additionally, we outline clinical study findings regarding the effects of various drugs on prion disease patients.

Historical Development and Evolution of Therapeutic Approaches to Prion Diseases

Prion diseases, recognized as neurodegenerative disorders caused by misfolded proteins, were first identified in the mid-20th century. The discovery of Creutzfeldt-Jakob Disease (CJD) in 1920 marked a significant breakthrough. D. Carleton Gajdusek (1923–2008) identified kuru, the first recognized human prion disease transmitted to chimpanzees, which was categorized as a "transmissible spongiform encephalopathy" (TSE), a slow unconventional virus disease [7]. However, the understanding of these diseases remained limited until the 1960s and 1970s.

A pivotal development occurred when Dr. Stanley Prusiner proposed the prion hypothesis, suggesting that these diseases were caused by misfolded proteins rather than viruses or bacteria. This novel concept challenged existing infectious disease paradigms and underscored the need for new treatment approaches [8].

Over the past 30 years, extensive testing of chemical compounds for anti-prion effects using cell cultures and animal models has occurred. Yet, only a few compounds advanced to human trials, often involving small sample sizes and varied experimental designs, including case reports, observational studies, and randomized placebo-controlled trials. Despite these efforts, effective treatments for human prion disease remain elusive due to inconsistent trial methodologies and limited sample sizes [9].

Although numerous therapeutic strategies have been evaluated in cell cultures and animal models, drugs that showed efficacy in these models often failed to demonstrate the same results in humans. Drugs that

were effective in animals typically worked only during the early, preclinical stages of the disease. When tested in humans, these drugs did not show clear long-term clinical benefits [10].

Currently, prion disease management relies on supportive care and experimental treatments aimed at symptom management and potentially altering disease progression. Continued research and the development of more effective therapies are critical for improving clinical outcomes for prion diseases. This article explores experimental and investigational therapies under consideration for prion disease treatment.

Experimental and Investigational Therapies:

Initial Therapeutic Attempts:

In the early stages of prion disease research, treatments primarily involved conventional approaches used for other neurodegenerative disorders, focusing on symptom management rather than altering the disease trajectory. As understanding of prions evolved, researchers began exploring more targeted therapies. Here, we review various drug trials, noting those that showed some positive results and others that failed to demonstrate effectiveness.

Antiviral and Anti-Prion Drug Trials:

Amantadine

Amantadine, originally used as an antiviral agent and for Parkinson's disease, was among the first drugs tested for prion diseases. Its mechanism of action involves influencing neurotransmitter release and blocking viral replication.

Clinical Trials: In the early 2000s, a study involving nine CJD patients tested amantadine hydrochloride at doses between 3.5 to 15 mg/kg/day for an average of 32 days. The outcomes were disappointing; amantadine did not improve survival rates or clinical outcomes compared to supportive care. Further studies involving over 35 CJD patients also failed to show significant therapeutic benefits, highlighting the complexities of prion diseases and the challenges in developing effective pharmacological treatments [11][12].

Flupirtine

Flupirtine, a pyridine derivative with analgesic and neuroprotective properties, was thought to reduce neuronal cell death due to its anti-apoptotic effects.

Clinical Trials: A double-blind trial with 28 sporadic CJD (sCJD) patients tested Flupirtine, with 13 patients receiving the drug and 15 receiving a placebo. Although Flupirtine showed some cognitive function improvement, it did not extend survival, indicating its benefits were limited to symptom management rather than altering disease progression [13].

Advances and Continued Failures:

Pentosan Polysulphate (PPS)

PPS, a polyanionic compound, showed promise in reducing PrPSc formation in preclinical studies by potentially preventing prion protein aggregation.

Clinical Trials: Despite initial success in laboratory and animal studies, PPS did not significantly improve neurological function in human trials. Although it reduced some prion pathology, it failed to provide clinical benefits, illustrating the challenges in translating preclinical success into effective human therapies [14][15].

Quinacrine

Quinacrine, an antiprotozoal drug used for malaria, was explored for its potential to inhibit PrPSc accumulation.

Clinical Trials: Quinacrine was tested extensively in vitro, in animal studies, and human trials. Early research suggested it might inhibit PrPSc accumulation in animals, but subsequent case-control studies, observational studies, and a randomized trial involving 95 patients did not demonstrate significant clinical benefits. Some trials even suggested Quinacrine might be ineffective in vivo [16][17][18].

Later Developments and New Approaches:

Doxycycline

Doxycycline, a tetracycline-class antibiotic, was investigated for its anti-prion properties, believed to prevent PrPSc assembly into amyloid fibrils and enhance proteolytic degradation.

Clinical Trials: A randomized controlled trial with 121 participants assessed Doxycycline's efficacy but was interrupted without showing significant effects compared to a placebo. A combined analysis of data from two studies in 2006 suggested a slight survival benefit, particularly in individuals with the MM genotype at PRNP codon 129. Doxycycline was also tested in preventive trials with mutation carriers, showing some promise in certain subgroups but overall modest impact [19][20].

Ongoing Challenges and Future Directions:

The history of prion disease treatments underscores several significant challenges:

Disease Complexity: Prion diseases involve complex mechanisms and misfolded proteins leading to neurodegeneration. This complexity makes it challenging to develop treatments that address all aspects of the disease [21].

Translational Difficulties: Many treatments that show promise in preclinical models do not produce similar results in human trials. Disparities between models and human disease mechanisms, along with difficulties in drug delivery to the brain, contribute to this challenge [22].

Biomarker Limitations: The lack of reliable biomarkers for early diagnosis and disease monitoring hampers the accurate evaluation of treatment efficacy.

Genetic Variability: Prion diseases exhibit genetic variability, which affects disease progression and treatment response. This variability complicates the development of universal treatments and necessitates tailored approaches for different patient populations [23].

Vaccine Development for Prion Diseases:

Historically, vaccines have proven to be highly effective in managing infectious diseases in both humans and animals. There is growing optimism about developing vaccines for prion diseases, driven by the fact that these diseases present a well-defined, cell surface-accessible target for immunotherapy. Recent studies have demonstrated that antibodies targeting PrP can impede prion propagation in vitro. However, creating an effective vaccine for prion diseases remains challenging due to unique factors such as overcoming immunological tolerance and establishing appropriate benchmarks for vaccine success, which may differ between humans and animals [24].

The development of vaccines for prion diseases focuses on strategies aimed at either preventing the conversion of PrPC to PrPSc or enhancing the immune system's ability to clear misfolded proteins. Recent advances have introduced several promising approaches:

1. Immunotherapy:

Immunotherapy, known for its specificity and relatively mild side effects, is considered a promising approach for treating prion diseases. Significant efforts have been made to develop immunotherapies [25], including vaccines and monoclonal antibodies, to stabilize the normal PrPC protein and prevent its conversion into the disease-associated form. In prion diseases, the immune system's activation is often suppressed due to self-tolerance. Researchers have explored strategies to counteract this self-tolerance, and studies have shown that anti-PrP monoclonal antibodies can inhibit the incorporation of PrPC into expanding prion aggregates, thereby delaying the progression of the disease [5].

*Courtesy: *Ling Liu et al., 2024*

FIGURE-1: Immunotherapies for Prion diseases target the conversion of PrPC to PrPSc, which likely starts on the plasma membrane and enters the cytoplasm via endocytosis. Vaccines and anti-PrP monoclonal antibodies aim to prevent this harmful conversion of PrPC into PrPSc [5].

2. Gene Cell Therapy:

Genetic prion diseases, such as CJD, GSS, and FFI, result from mutations in the PRNP gene and account for approximately 15% of prion diseases [5]. Various therapeutic approaches to reduce PrP expression have been explored, but effective methods for human use remain limited. ***Antisense oligonucleotides (ASOs):***

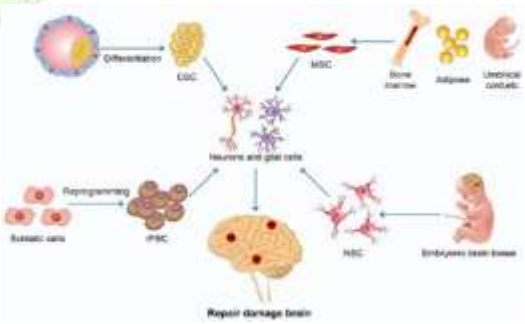
Antisense oligonucleotides (ASOs) have emerged as a promising near-term therapeutic strategy. ASOs are short, chemically modified oligonucleotides that specifically bind to complementary RNA sequences, leading to RNA degradation and reduced protein production [26]. However, no gene therapy-based vaccines for prion diseases are currently available, and the diagnosis of genetically incurable prion diseases remains devastating for individuals and families [5].

3. Advanced Targeted Protein Degradation (ATPD):

Advanced Targeted Protein Degradation (ATPD) is a novel therapeutic strategy with potential for treating prion diseases. ATPD involves designing molecules, such as proteolysis-targeting chimeras (PROTACs), that selectively target and degrade pathological proteins responsible for disease. In prion diseases, ATPD aims to specifically identify and eliminate misfolded prion proteins while preserving normal cellular functions. This approach could potentially reduce prion protein levels, slow disease progression, and possibly reverse some of the damage caused by prion accumulation. Although still in the research and early development stages, ATPD offers a promising avenue for addressing unmet medical needs in prion disease treatment [5].

4. Stem Cell Therapy:

Stem cell therapy has been investigated as a potential method for repairing neurons damaged by misfolded prion proteins. Research by Hoang et al. (2022) emphasized that mesenchymal stem cells (MSCs) have features such as self-renewal, differentiation capabilities, immunomodulation, and the ability to migrate to injured tissues, making them suitable for addressing prion diseases. The main types of stem cells used in therapeutic applications include embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and adult MSCs [27]. While stem cell therapy holds potential for neuroprotection and repair, it remains experimental, and there is no established stem cell therapy specifically approved for prion diseases. Further research is needed to understand the safety, efficacy, and practical application of these treatments.



*Courtesy: *Ling Liu et al., 2024*

FIGURE-2: Stem cell therapy holds promise for repairing injured brain tissue and treating neurodegenerative diseases. Among the most promising approaches are the use of embryonic stem cells (ESC), mesenchymal stem cells (MSC), induced pluripotent stem cells (iPSC), and neural stem cells (NSC) [5].

Clinical Trial Case Studies on Vaccines Against Prion Diseases in Humans:

Clinical trials have tested the efficacy of anti-prion antibodies in preventing the spread of PrPSc in prion diseases. In 2022, Mead et al. conducted the first clinical trial for prion disease in humans. The study involved six CJD patients (two men and four women) treated at University College London Hospitals (UCLH) between October 2018 and July 2019. The treatment involved repeated intravenous dosing of PRN100 over 7 to 260 days. The drug was well tolerated and achieved the target cerebrospinal fluid (CSF) concentration of 50 nM in four patients. Over 22 to 70 days, no significant adverse reactions were reported. However, all six patients showed progressive neurological decline, as measured by the Medical Research Council (MRC) Scales. Neuropathological examination of two patients revealed no evidence of cytotoxicity. Notably, Patient 2, who received treatment for 140 days, exhibited patterns of disease-associated PrP that differed from untreated patients, suggesting potential drug effects. Patient 3, who received a single dose, showed weak PrP synaptic labeling not observed in untreated patients. Drug concentrations in patient 2's brain tissue varied by region, ranging from 9.9 µg/g in the thalamus to 27.4 µg/g in the basal ganglia, translating to concentrations of 66-182 nM. The study concluded that the experimental vaccine treatment was safe and achieved promising CSF and brain tissue concentrations, indicating the need for further efficacy trials in early-stage CJD patients and as prophylaxis for those at risk due to PRNP mutations or prion exposure [28].

Conclusion:

Prion diseases are among the most rapidly progressive neurodegenerative disorders, and currently, no effective treatment exists. This review has explored various emerging technologies and treatment strategies for prion diseases, including immunotherapy, gene therapy, targeted protein degradation therapies, and stem cell technology. Clinical study effects have also been outlined, emphasizing the ongoing need for effective therapies.

Despite decades of research, no approach has yet proven successful in halting or reversing prion diseases. Researchers face significant challenges, such as effectively targeting and clearing misfolded prion proteins, dealing with the rapid progression and complex pathology of these diseases, and managing potential complications from experimental therapies. The rarity of prion diseases and the lack of reliable predictors for disease onset complicate the design of randomized controlled trials. Previous studies have been limited by small sample sizes, highlighting the need for multicentric, long-term research efforts. Continued research is essential to develop viable therapies, improve understanding of prion pathology, and discover innovative treatment methods to enhance clinical outcomes for affected individuals.

Conflicts of Interest

There are no conflicts of interest between authors.

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References:

1. Imran, M., Mahmood, (2011) S. An overview of human prion diseases. Virol J 8, 559 .

2. Creutzfeldt HG. On a particular focal disease of the central nervous system (preliminary communication), (1920). Alzheimer Dis Assoc Disord journal. 1989 Spring-Summer;3(1-2):3-25.

3. Geschwind MD. (2015) A article on Prion Diseases, Continuum (Minneap Minn) journal (6 Neuroinfectious Disease):1612-38.

4. Reinhold Nafe, Christophe T. Arendt, and Elke Hattingen, (2023) Human prion diseases and the prion protein. Transl Neurosci journal. 14(1): 20220315.

5. Simone Baiardi , Marcello Rossi , Sabina Capellari , Piero Parchi (2019) Recent advances in the histo-molecular pathology of human prion disease Brain Pathol journal. 29(2): 278–300.

6. Fangzhou Liu Wenqi Lü Ling Liu, (2024) New implications for prion diseases therapy and prophylaxis Front. Mol. Neurosci journal., Volume 17 – 2024.

7. Paweł P. Liberski, Agata Gajos, Beata Sikorska, Shirley Lindenbaum (2019) Kuru, the First Human Prion Disease Viruses journal. (3): 232

8. Prusiner, S. B., Scott, M., Foster, D., Pan, K. M., Groth, D., Mirenda, C., et al. (1990). Transgenetic studies implicate interactions between homologous PrP isoforms in scrapie prion replication. Cell press journal Volume 63, Issue 4 p 673-686 .

9. Baiardi, S., Mammana, A., Capellari, S., & Parchi, P. et.al., (2023). Human prion disease: molecular pathogenesis, and possible therapeutic targets and strategies. Expert Opinion on Therapeutic Targets journal, 27(12), 1271–1284.

10. Michael D Geschwind (2009)Clinical trials for prion disease: difficult challenges, but hope for the future Lancet Neurol. (4): 304–306.

11. Sanders WL., (1979) Creutzfeldt-Jakob disease treated with amantadine. Neurol Neurosurg Psychiatry Journal 42:960–961.

12. Braham J. (1971) Jakob-Creutzfeldt disease: treatment by amantadine. Br Med Journal. 1971; 4:212–213. 29.

13. M Otto , L Cepek, P Ratzka, S Doehlinger, I Boekhoff, J et.al., (2004) Efficacy of flupirtine on cognitive function in patients with CJD: A double-blind study Neurology journal 62(5):714-8

14. Tsbuoi Y, Doh-Ura K, Yamada T. (2009) Continuous intraventricular infusion of pentosan polysulfate: clinical trial against prion diseases. Neuropathology Journal 29:632–636.

15. I Bone , L Belton, A S Walker, J Darbyshire (2008)Intraventricular pentosan polysulphate in human prion diseases: an observational study in the UK .Eur J Neurol (5):458-64.

16. M. Nakajima, Tatsuo Yamada, T. Kusuhara, H. Furukawa, Mitsuo Takahashi, A. Yamauchi, Y. Kataoka (2004) Results of quinacrine administration to patients with Creutzfeldt-Jakob disease. Dement Geriatric Cognit Disorder J. 17:158–163.

17. John Collinge, Michele Gorham, Fleur Hudson, Angus Kennedy, Geraldine Keogh, et.al.,(2009) Safety and efficacy of quinacrine in human prion disease (PRION-1 study): a patient-preference trial. Lancet Neurol J. 8:334–344. 55

18. Geschwind MD, Kuo AL, Wong KS, Haman A, Devereux et.al., (2013) BL Quinacrine treatment trial for sporadic Creutzfeldt-Jakob disease. Neurology j. 3;81(23):2015-23.

19. Haïk S, Marcon G, Mallet A, Tettamanti M, Welaratne A, Giaccone G, Azimi et.al., (2014) Doxycycline in Creutzfeldt-Jakob disease: a phase 2, randomised, double-blind, placebo-controlled trial. Lancet Neurol. (2):150-158.

20. Varges D, Manthey H, Heinemann U, Ponto C, Schmitz M et.al., (2014) Doxycycline in early CJD: a double-blinded randomised phase II and observational study. J Neurol Neurosurg Psychiatry. 88(2):119-125.

21. Brandner S, Jaunmuktane Z (2017) Prion disease: experimental models and reality. Acta Neuropathol. 133(2):197-222.

22. Gail A. Van Norman (2019) Limitations of Animal Studies for Predicting Toxicity in Clinical Trials JACC Basic Transl Sci. 4(7): 845–854.

23. Inga Zerr, MD and Matthias Schmitz, MD Genetic Prion Disease (2021). National library of Medicine.

24. Napper S, Schatzl HM. (2023) "Vaccines for prion diseases: a realistic goal?" Cell Tissue Res. 392(1):367-392.

25. Ma, Y., & Ma, J. (2020) "Immunotherapy against Prion Disease." Pathogens, 9(3),216.

26. Vallabh SM, Minikel EV, Schreiber SL, Lander ES (2020) Towards a treatment for genetic prion disease: trials and biomarkers. The Lancet Neurology, 19(4), 361368.

27. Zayed M, Kook SH, Jeong BH (2023) Potential Therapeutic Use of Stem Cells for Prion Diseases. Cells. 12(19):2413.

28. Mead S, Khalili-Shirazi A, Potter C, Mok T, Nihat A et.al., (2022) Prion protein monoclonal antibody (PRN100) therapy for Creutzfeldt-Jakob disease: evaluation of a first-in-human treatment program." Lancet Neurol. 21(4):342-354.