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REVIEW ARTICLE

Treatment of Prion Disease: Is it possible? A Review

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Abstract

Just when scientists believed they had a stronghold on human micro-organisms, up come a new group of disease called prion disease. This new category of disease is fatal in both infected humans and animals. First detected as scrapie in sheep and goats in as early as 1730s, it has evolved and possibly mutated to now infect humans who consume meats of sheep, goats and cows, among others. This review article attempts to look at existing and potential treatment for this currently incurable disease. It is hoped that this article will give scientists hope to continue their tireless struggle to find a cure for this illness.

Keywords: Prion disease, virus, Creutzfeldt Jacob Disease, animals, humans, therapy.

INTRODUCTION

Prion disease is a new kid on the block. A rather new but a fatal cause of various infectious disease, prion diseases known as transmissible spongiform encephalopathies (TSEs), features as misfolding of a self-protein (PrPC) into a pathological, but deadly infectious conformation (PrPSc) [1].

Sigurdsson first described the concept of slow viruses while researching neurodegenerative disease in sheep, and was later aknowledged in a hypothesis by a veterinary pathologist that kuru and this new neurodegenerative disease were related disorders. At this time, the hypothesis about the similarity between kuru and another human neurodegenerative disease called Creutzfeldt-Jacob disease was made [2, 3]. Ultimately work by Gajdusek et al showed that a transmissible agent was responsible for the disease [4, 5].

This neurodegenerative disorders group of diseases comprises of Gerstmann Straussler syndrome (GSS), kuru, Creutzfeldt-Jakob disease (CJD) and fatal familial insomnia (FFI) in human beings, as well as scrapie in goats and sheep, bovine spongiform encephalopathy (BSE) in cattle, and encephalopathies in mink, mule deer, cats and elk [6-8]. Prion disease attracts a great deal of attention due to the impact on both human and animal health and the almost

certain death of its sufferers.

Three different manifestations of prion diseases are recognized: familial, infectious, and sporadic [9]. Prion diseases are hard to detect and treat because they can arise on a genetic basis as well as by infection [9]. About 10% of all CJD cases and all GSS and FFI cases are linked to mutations in the PrP gene on chromosome 20 [9, 10].

This review article will look at past and current treatment for fatal causes of infection. Even though treatment is postulated as mainly supportive, it will be interesting to investigate any treatment options, both allopathic and alternative [6].

METHODS

Available journal published articles including case reports, randomized controlled trials, systematic review and review articles were searched from inception till December 2019. Data was extracted including the name of drug/compound, mechanism of action, dosage and whether the drug/compound is still in animal trials or has already progressed to human trials.

RESULTS

Table 1 shows the list of drugs used as treatment of prion diseases.

Table 1. List of drugs used as treatment of prion diseases

Name of drug	Mechanism of action	Dose	Clinical trials (animal trials unless stated) [16-18]
Acridines (antimalarial drug), Quinacrine [14]	Inhibits the conversion of normal host prion protein (PrP^{C}) to PrP^{Sc} at a half-maximal concentration of 300 nM	Oral quinacrine at doses of 37.5 mg/kg/D and 75 mg/kg/D was administered for 4 consecutive weeks.	Human trials
MC [11]	A molecular chaperone that binds to PrPC to prevent its aberrant conformational change might efficiently treat the disease, independently of the TSE-causing agent.	Weekly intraperitoneal injection of MC increased survival time by about 3 weeks compared with saline treatment acting as placebo.	
5 µl of a 0.01% RML-Chandler strain scrapie brain homogenate [12]	Inhibits PrPres production formation.	Intracerebrally inoculated with 5 µl of a 0.01% RML-Chandler strain scrapie brain homogenate (obtained from mice with symptomatic scrapie infection) diluted in PBS containing 2% fetal calf serum, plus 45ul of either HaPrP (0.7mg/ml) for high dose treatment, HaPrP (0.35 mg/ml) for low dose treatment, or 45 ul of vehicle only (10 mM sodium acetate, pH 5) for mock-treated mice	
Antisense oligonucleotides (ASOs) [13]	Lowering PrP expression as a therapeutic strategy.	Stereotactic intracerebroventricular (ICV) injection of 300 µg of either ASO versus saline treatment (placebo).	
Bis-acridine derivatives [16]	Binds to unknown receptor?		

Name of drug	Mechanism of action	Dose	Clinical trials (animal trials unless stated) [16-18]
6H4B [16]	Impedes PrPC-PrPSc interaction		
Quinolines: 2,2'-biquinoline [16]	Unsure mechanism		
Congo red [16]	Inhibits conversion, stabilizes PrPSc		
SAF93 [16]	Impedes PrP^{C}-PrP^{Sc} interaction		
Filipin [16]	Disrupts lipid rafts, reduces endocytosis, causes release of PrP^{C} from cell surface		
Polysulfonated small-molecular weight compounds, Suramin [16]	Plasma membrane endocytosis, intracellular retention and degradation		
Cyclic tetrapyrrols PcTS,TMPP-Fe^{3+} [16]	Unknown		
β-sheet breaker iPrP13c[16]	Disassembles PrP^{Sc}		
Peptides PrP106-128,PrP113–141 [16]	Impede conversion by binding to PrP^{C} or PrP^{Sc}		
Polyamines polypropyleneimine (PPI) [16]	Destabilizes PrP^{Sc}		
Polyanions (heparan mimetics/anticoagulants) Pentosan polysulfate (PPS) [16,18]	Interferes with PrP-glucosaminoglycans interaction; stimulates PrP^{C} endocytosis	Treatment for 5 months before actual fatality	Human trials
Dextransulfate, HM2602 [16]	Interferes with PrP-glucosaminoglycans interaction		
Polyene antibiotics, Amphotericin B [16,18]	Unknown. However ineffective in human	Amphotericin at 0.25–1.0 mg/day for 4-8 months	Established drug in humans, but potentially toxic
MS8209 [16]	Prevents uptake of prions in periphery?		
ICSM18[16]	Impedes PrP^{C}-PrP^{Sc} interaction		
Aptamers DP7 [16]	Impedes PrPC-PrPSc interaction		
SAF93 [16]	Impedes PrPC-PrPSc interaction		
Anthracyclins 4'-iodo-4'-deoxy- doxorubicin [16]	Binds to PrP^{Sc}?		
Anti-PrP antibodies Fab D18 [16]	Impedes PrPC-PrPSc interaction		
6H4 [16]	Impedes PrPC-PrPSc interaction		
Analgesics, Flupirtine [17-18]	Largely unknown, but documented in vitro activity		Human trials

Name of drug	Mechanism of action	Dose	Clinical trials (animal trials unless stated) [16-18]
Statins, Lovastatin and squalestatin [17]	Largely unknown, but documented in vitro activity		Human drugs
Antidepressant drugs, Clomipramine and venlafaxine [18]		Clomipramine at 125mg/day for 3 weeks followed by venlafaxine at 200 mg/day for 7 weeks	
Anticonvulsant drugs, Levetiracetam [18]		1,000–2,000mg/day for myoclonus control (symptomatic control only)	
Anticonvulsant drugs, Topiramate/phenytoin [18]		phenytoin at a dose of 300 mg/ day then topiramate at 100–200 mg/day for 7 months -improvement in myoclonic jerks and rigidity	
Biologic response modifiers, Interferon [18]		Treatment for 7-21 months before fatality at 7th and 21st months in the 2 reported case.	
Antiviral drugs, Acyclovir [18]		30 mg/kg/day and 1,500 mg/day for 4 weeks before fatality in 2 reported cases	
Antiviral drugs, Amantadine [18]		Fatality after 6-7 months of treatment	
Antiviral drugs, Vidarabine [18]		15 mg/kg/day for 9 months before fatality	

As seen in the above table, a variety of drugs are used from anti-infectives, anti-inflammatory, immune modifiers, anticonvulsants, antidepressants, and even anticoagulants. There are many postulated mechanisms of action ranging from impeding PrPC-PrPSc interaction, destabilizing the culprit protein to largely unknown mechanisms. Out of these 34 drugs or compound suggested, many are still in animal trials or status unknown with only 3 known to be currently researched as clinical trial in humans and two used off label (statins and amphotericin B).

DISCUSSION

Effective treatment is still a dream too far for prion disease. The fatalities as proven by the absolute number of 100% certain death are still substantial. Incidence has been reported as ~0.6–1.2 × 10−6 per year [15]. There are two issues facing this illness. First incidence is low, so is research validated for this cause that can involve a large sum of scarce economic resources. Secondly, the high fatality rate of 100%, so treatment is definitely needed.

As seen in table 1, there are many drugs/ compounds that have been tried for prion diseases. Most of the drugs used above are off-label meaning that they were not primarily aimed for treating prion diseases. As most drugs are still in trial phases (mainly in animals), it is not yet possible to determine the effectiveness of these drugs [18].

More studies are needed in the future before these drugs are deemed safe for treating patients infected with prion diseases. However, treatment will be needed to relieve the patients of this disease who sometimes suffer for years before the actual diagnosis is made (up to 11 years), which is unfortunately often when it is too late most of the time [18].

This is one area of research that both general and clinical scientists need to work together to seek a cure for this currently uncurable disease. At the physician level, collaboration is needed between both medical

and veterinary doctors to find the missing link of this ambiguous jigsaw puzzle.

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Conflict of Interest

The author has no declared conflicts of interest.

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علاج مرض البريون: هل من الممكن؟ مراجعة

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الملخص

الخلفية والاهداف: بمجرد أن تمكن العلماء من السيطرة على الكائنات الحية الدقيقة البشرية، ظهرت مجموعة جديدة من الأمراض تسمى مرض البريون.

منهجية الدراسة: هذه الفئة الجديدة من المرض قاتلة لكل من البشر والحيوانات المصابة. تم اكتشافه لأول مرة على أنه سكرابي في الأغنام والماعز في وقت مبكر من ثلاثينيات القرن الثامن عشر، وقد تطور وربما تحور ليصيب الآن البشر الذين يستهلكون لحوم الأغنام والماعز والأبقار وغيرها.

النتائج: تحاول مقالة المراجعة هذه إلقاء نظرة على العلاج الذي تم استخدامه أو من المحتمل استخدامه لهذا المرض غير القابل للشفاء حاليًا.

الكلمات الدالة: مرض البريون، الفيروس، مرض كروتزفيلد جاكوب، الحيوانات، الإنسان، العلاج.