New paradigms of clinical trial design for genetic prion diseases

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New paradigms of clinical trial design for genetic prion diseases

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We declare no competing interests.

Diagnosis of a genetic, incurable disease is devastating for the affected individuals and their families. In the case of genetic prion disease, a rare disease of the CNS caused by mutations of the human prion protein gene *PRNP*, mutation carriers usually do not exhibit symptoms until late adulthood. Genetic prion diseases comprise a relatively small fraction (10–15%) of all prion diseases, the most common being sporadic Creutzfeldt-Jakob Disease[1]. Since no therapy exists except palliation, individuals with a family history of genetic prion disease are facing the dilemmatic decision whether to undergo genetic testing.

Due to the phenotypic variability of genetic prion diseases and the lack of biomarkers that predict clinical onset, sufficiently powered clinical trials would require several hundreds of individuals — an unrealistic scenario given the rarity of these diseases. Three unsuccessful randomised controlled trials were conducted in patients with human prion disease using the analgesic flupirtine, the antiprotozoal quinacrine, and the antibiotic doxycycline. In addition to the weak rationale for employing these drugs, participants were already symptomatic at the time of enrollment and most likely beyond any therapeutic windows[1]. In *The Lancet Neurology*, Sonia Vallabh and colleagues provide a roadmap for a therapeutic trial against genetic prion diseases using *PRNP*-targeting antisense oligonucleotides (ASOs)[2]. ASOs are short single-stranded synthetic oligodeoxynucleotides that bind to pre-messenger ribonucleic acid (mRNA) by Watson-Crick pairing. The resulting RNA-DNA complexes are then degraded via RNases[3]. ASOs have gained attention as potential therapies for CNS diseases since the approval of nusinersen for the treatment of spinal muscular atrophy by the US Food and Drug administration (FDA) in 2016.

A hallmark of prion diseases is the seeded aggregation of a partially protease-resistant isoform of the prion protein PrP^{Sc} onto the cellular isoform PrP^{C}. Mice devoid of *Prnp*, the gene encoding PrP^{C}, are resistant to prion diseases, and crucially hemizygosity for *Prnp* conspicuously prolongs the latency time of disease[4]. To lower PrP^{C} levels in brains of *PRNP* mutation carriers, Vallabh and co-workers propose a prophylactic treatment regimen using ASOs against *PRNP* in the framework of an Accelerated Approval procedure by the FDA.

Vallabh and colleagues had previously provided proof-of-concept evidence that prophylactically administered ASOs against *Prnp* reduce prion pathology, vacuolation, and PrP^{Sc} deposits of prion-infected mice, and most importantly extend their life-span[5]. In the trial laid out by Vallabh and co-workers, PrP^{C} levels in CSF, which provide a robust surrogate marker for PrP^{C} levels in brain, can be easily measured by conventional ELISA, thereby providing a means to monitor the pharmacodynamic on-target effectiveness of the therapy.

Lowering PrP^{C} levels in the brain reduces prion disease susceptibility, but this strategy is not without risks. Whereas certain phenotypes of *Prnp* knock-out mice were shown to be genetic artifacts, peripheral demyelinating polyneuropathy was a consistent feature due to the action of PrP^{C} onto its receptor Adgrg6[6]. *Prnp* heterozygous mice, however, did not show demyelination, suggesting that PrP^{C} levels might not limit Schwann-cell health[6].

Which treatments may compete with ASOs for treatment of prion diseases? Anti-PrP^{C} antibodies delay disease onset in animal experiments[7], but the blood-brain barrier is still a formidable obstacle despite promising inroads[8]. As of October 2019, PRN100, a humanized monoclonal antibody against the C-terminal domain of PrP^{C}, was given to six patients diagnosed with sporadic Creutzfeldt-Jakob Disease; the outcome is still undisclosed. Polythiophenes are anionic compounds that act as prion hyperstabilizers[9]. Although rational design of luminescent conjugated polymers, anti-prion compounds based on polythiophenes, prolonged survival of prion-infected mice[9], a therapeutic window has not been established yet. Meanwhile, ASOs are increasingly successful in diseases as disparate as spinal muscular atrophy (nusinersen), Duchenne muscular dystrophy (eteplirsen), and familial hypercholesterolemia (mipomersen).

Most individuals affected by genetic prion diseases are aware of their mutation years or even decades prior to symptom onset. This makes them ideally suited for the prophylactic trial proposed by Vallabh and co-workers. Likewise, carriers of autosomal-dominant mutations in the *PSEN1* gene, manifesting as Alzheimer's disease, are part of a preventive placebo-controlled trial involving the anti-β-amyloid antibody crenezumab[10]. However, *PSEN1* mutations are more prevalent than *PRNP* mutations and have a more predictable clinical course[10].

Lastly, this trial is also personal: Sonia Vallabh, the first author of the paper, is a *PRNP* mutation carrier herself and has been at the forefront of innovative clinical trials in genetic prion disease. Those who have had the opportunity to experience Ms Vallabh's courage and gallantry will most likely agree that this trial will bring a significant advance towards the therapy of genetic prion diseases.

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