Prion protein monoclonal antibody (PRN100) therapy for Creutzfeldt–Jakob disease: evaluation of a first-in-human treatment programme

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Summary

Background Human prion diseases, including Creutzfeldt–Jakob disease (CJD), are rapidly progressive, invariably fatal neurodegenerative conditions with no effective therapies. Their pathogenesis involves the obligate recruitment of cellular prion protein (PrP^C) into self-propagating multimeric assemblies or prions. Preclinical studies have firmly validated the targeting of PrP^C as a therapeutic strategy. We aimed to evaluate a first-in-human treatment programme using an anti-PrP^C monoclonal antibody under a Specials Licence.

Methods We generated a fully humanised anti-PrP^C monoclonal antibody (an $IgG_4\kappa$ isotype; PRN100) for human use. We offered treatment with PRN100 to six patients with a clinical diagnosis of probable CJD who were not in the terminal disease stages at the point of first assessment and who were able to readily travel to the University College London Hospital (UCLH) Clinical Research Facility, London, UK, for treatment. After titration (1 mg/kg and 10 mg/kg at 48-h intervals), patients were treated with 80–120 mg/kg of intravenous PRN100 every 2 weeks until death or withdrawal from the programme, or until the supply of PRN100 was exhausted, and closely monitored for evidence of adverse effects. Disease progression was assessed by use of the Medical Research Council (MRC) Prion Disease Rating Scale, Motor Scale, and Cognitive Scale, and compared with that of untreated natural history controls (matched for disease severity, subtype, and *PRNP* codon 129 genotype) recruited between Oct 1, 2008, and July 31, 2018, from the National Prion Monitoring Cohort study. Autopsies were done in two patients and findings were compared with those from untreated natural history controls.

Findings We treated six patients (two men; four women) with CJD for 7–260 days at UCLH between Oct 9, 2018, and July 31, 2019. Repeated intravenous dosing of PRN100 was well tolerated and reached the target CSF drug concentration (50 nM) in four patients after 22–70 days; no clinically significant adverse reactions were seen. All patients showed progressive neurological decline on serial assessments with the MRC Scales. Neuropathological examination was done in two patients (patients 2 and 3) and showed no evidence of cytotoxicity. Patient 2, who was treated for 140 days, had the longest clinical duration we have yet documented for iatrogenic CJD and showed patterns of disease-associated PrP that differed from untreated patients with CJD, consistent with drug effects. Patient 3, who had sporadic CJD and only received one therapeutic dose of 80 mg/kg, had weak PrP synaptic labelling in the periventricular regions, which was not a feature of untreated patients with sporadic CJD. Brain tissue-bound drug concentrations across multiple regions in patient 2 ranged from 9·9 µg per g of tissue (SD 0·3) in the thalamus to 27·4 µg per g of tissue (1·5) in the basal ganglia (equivalent to 66–182 nM).

Interpretation Our academic-led programme delivered what is, to our knowledge, the first rationally designed experimental treatment for human prion disease to a small number of patients with CJD. The treatment appeared to be safe and reached encouraging CSF and brain tissue concentrations. These findings justify the need for formal efficacy trials in patients with CJD at the earliest possible clinical stages and as prophylaxis in those at risk of prion disease due to *PRNP* mutations or prion exposure.

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Introduction

Prions are lethal pathogens that cause neurodegenerative diseases, including Creutzfeldt–Jakob disease (CJD) in humans, scrapie in sheep, bovine spongiform encephalopathy in cattle, and chronic wasting disease in cervids.[1] Prions are composed of polymeric assemblies of misfolded, host-encoded cellular prion protein (PrP^C), a cell-surface sialoglycoprotein. Prions are devoid of nucleic acid and consist of paired double helical fibrils that act as templates or seeds and propagate by

Research in context

Evidence before this study

We systematically searched PubMed in English for articles published between database inception and June 30, 2021, using the term "Creutzfeldt-Jakob disease" and checking the "clinical trial" article type filter, and additionally using the terms "prion protein" and "antibody therapeutic". For Creutzfeldt–Jakob disease (CJD), only clinical trials of repurposed compounds, quinacrine, doxycycline, pentosan polysulphate, and flupirtine, and no antibody treatments, were found. CJD and other prion diseases are invariably fatal neurodegenerative conditions caused by prions—assemblies of misfolded host-encoded cellular prion protein (PrP^C). No disease-modifying treatments are available. Although rare conditions, prion diseases are considered to be the paradigm for more common neurodegenerative dementias, notably Alzheimer's disease, in which similar seeded propagation and spread of assemblies of misfolded proteins (so-called prion-like mechanisms) are increasingly recognised as being key to pathogenesis. In prion disease, PrP^C has been firmly validated as a therapeutic target because it is the obligate substrate for the generation of all propagating and toxic disease-related PrP assemblies. Monoclonal antibodies targeting PrP^C can eradicate prion infection from cells in culture (with a half maximal effective concentration as low as 1 nM) and passive immunisation has shown powerful therapeutic effects in animal models.

Added value of this study

In an academic-led project, we generated a fully humanised anti-PrP^C monoclonal antibody (PRN100) and oversaw its manufacture to industry standard for human use. With the support of the University College London Hospital National Health Service Foundation Trust, which provided appropriate governance oversight, we treated six patients with CJD under a Specials Licence. Patients were treated with increasing doses of PRN100 by intravenous infusion and closely monitored. Intravenous administration was safe and able to target the brain compartment; no clinically significant adverse reactions were seen. Although disease progression was not halted or reversed in any patient, Medical Research Council Prion Disease Rating Scale scores did appear to stabilise in three patients for periods when CSF drug concentrations reached the target concentration, but the small number of patients precluded meaningful statistical analysis. Neuropathological examination of a patient who had the longest clinical duration we have yet documented for their subtype of iatrogenic CJD showed no evidence of cytotoxicity but did show marked drug effects, with modification of the deposition of disease-associated PrP and brain tissue-bound drug concentrations across multiple regions ranging from 9·9 µg per g of tissue in the thalamus to 27·4 µg per g of tissue in the basal ganglia.

Implications of all the available evidence

This Specials Licence treatment programme, utilising a single batch of drug product, could be offered to only a small number of patients. Our cautious dose escalation meant that it took a highly clinically significant amount of time to reach the target drug CSF concentration. The encouraging safety profile and CSF and brain tissue concentrations of PRN100 following intravenous administration and preliminary clinical data justify conducting a formal efficacy trial in patients at the earliest possible clinical stage, before extensive neuronal loss is present and irreversible secondary neurodegenerative processes are established. Further studies to determine whether the onset of disease can be prevented or delayed in healthy individuals iatrogenically infected with prions or harbouring pathogenic *PRNP* mutations might also be justified. This approach to the development and evaluation of a rational treatment for CJD might be of wider interest in the assessment of therapeutics for other rare fatal diseases for which there might be a clear therapeutic target but no traditional business case for a pharmaceutical industry-led programme.

recruitment of PrP^C with fibre elongation and subsequent fission.[1] The commonest human prion disease, sporadic CJD, has a relatively uniform annual incidence of 1–2 cases per million people and a lifetime risk of approximately 1 in 5000. Generally, sporadic CJD is a rapidly progressive illness with a typical clinical duration of 6 months. The inherited prion diseases are caused by one of more than 40 distinct genetic mutations in the prion protein gene (*PRNP*) and account for a considerable fraction of early-onset familial dementias.[2] Iatrogenic CJD can arise from accidental exposure to prions from cadaver-derived pituitary hormones, dura mater, and corneal grafts and contaminated neurosurgical instruments, and variant CJD can arise from dietary exposure to bovine spongiform encephalopathy prions.[1] The incubation periods of human prions are prolonged and can exceed 50 years.[3]

Several repurposed agents have been experimentally used to treat CJD, but none have shown effects on disease progression or mortality.[4–9] There remains a crucial unmet clinical need for an effective therapy to treat prion disease and to prevent onset in those who are infected or at genetic risk. No specific, rationally designed treatment has yet been used in human prion disease.

PrP^C is a uniquely attractive therapeutic target because it is the obligate substrate for the generation of all propagating and toxic disease-related PrP assemblies; constitutive PrP knockout mice are completely resistant to prion infection and disease.[10] Importantly, the conditional knockout of neuronal PrP^C in adult mice excluded PrP^C loss of function as a sufficient cause of neurodegeneration,[11] and targeting neuronal PrP^C expression during established neuroinvasive prion disease in mice prevented progression to clinical disease

and led to the reversal of early spongiform neuropathology and behavioural deficits.[12,13]

An advantage of studying prion diseases compared with other neurodegenerative conditions is that prion diseases occur also in other mammals and are transmissible between species with conserved clinical and pathological features. Consequently, mouse models of prion disease are not disease models in the usual sense. PrP^C, which has a predominantly α-helical fold, needs to largely unfold to adopt the β-sheet rich structure of its infectious amyloid form; therefore, binding of a ligand to the folded domain of PrP^C will reduce the availability of unfolded PrP for prion propagation by acting as a pharmacological chaperone.[14,15] Prions exist in multiple strain types. The strains themselves are not a molecular clone but exist as a cloud or ensemble of sub-species.[16] Therefore, agents binding to disease-related PrP risk the development of drug resistance by strain selection, which has indeed already been shown.[17] Conversely, agents binding to PrP^C should be effective against all prion strains. Monoclonal antibodies targeting PrP^C should therefore be effective therapeutics; proof of principle has been shown by their ability to eradicate prion infection in cell cultures chronically infected by prions[18,19] and by their powerful therapeutic effects after passive immunisation.[20,21] Following the development and characterisation of an extensive series of mouse monoclonal antibodies raised against human PrP,[22] we developed a fully humanised monoclonal antibody (an $IgG_4κ$ isotype; PRN100) as a clinical candidate designed to bind and stabilise PrP^C (appendix p 4).

See Online for appendix

With the support of the University College London Hospital (UCLH) National Health Service (NHS) Foundation Trust, treatment was offered in accordance with guidance note 14 of the Medicines and Healthcare products Regulatory Agency (*The supply of unlicensed medicinal products ["specials"]*)[23] and the product was released under a Specials Licence rather than as part of a regulated clinical trial. Here, we report the results of what is, to our knowledge, the first administration of a humanised monoclonal antibody as a treatment for patients with rapidly progressive CJD. Our objective was for individual patients to benefit by slowing or halting the rapid progression of the symptoms and signs of CJD, and, conceivably, by inducing some symptomatic reversal, without adverse events.

Methods

Treatment programme design and patients

In the UK, since 2004, the referral, assessment, and monitoring of patients suspected to have prion disease has been coordinated via a national agreement between specialist units at the NHS National Prion Clinic at UCLH in London and the National CJD Research and Surveillance Unit in Edinburgh. In this first-in-human treatment programme, we offered treatment with PRN100 to six patients with a clinical diagnosis of probable CJD[24] who were not in the terminal stages at the point of first assessment and who were able to readily travel to the National Institute for Health Research (NIHR) UCLH Clinical Research Facility, London, for treatment. Patients with inherited forms of the condition were identified by *PRNP* sequencing and excluded from our treatment programme. For more details on patient selection, please see the appendix (pp 10–11).

Following the experience of the Medical Research Council (MRC) PRION-1 trial,[4] we developed a large-scale observational cohort, the National Prion Monitoring Cohort (NPMC) study, to establish the natural history of prion disease and provide written consent for the use of historical control data in future interventional studies by enrolling symptomatic patients with prion disease in the UK.[25] In parallel with the development and preclinical testing of PRN100, we developed bespoke clinical rating scales and investigated biomarkers to facilitate clinical studies.[25,26] Patient trajectories of MRC Scales and survival were compared with untreated natural history controls from the NPMC study recruited between Oct 1, 2008, and July 31, 2018, matched for baseline MRC Prion Disease Rating Scale score (±1 point) and polymorphic *PRNP* codon 129 genotype and disease subtype, a known modifier of rates of clinical progression.[27] Neuropathology of the PRN100-treated patients was compared with that of 28 controls with sporadic CJD and four controls with iatrogenic CJD from the NPMC study.

The PRN100 drug product was released to UCLH under a Specials Licence and administered as an NHS treatment to a series of patients according to a prespecified treatment plan. An Oversight Committee was established at UCLH to oversee the development of the treatment plan and its legal, safe, and effective delivery, and met on an ad hoc basis as required. The Oversight Committee comprised senior physicians, pharmacists, academics, and lawyers, who independently confirmed a clear clinical need for administering the treatment per patient, and its realistic and reasonable scientific basis. The Oversight Committee approved the treatment plan and arrangements for consent. In English law, if patients do not have the capacity to consent to a serious medical treatment outside of an ethically approved clinical trial, then its legality can be determined by judgement of the Court of Protection. An Oversight Committee Clinical Subgroup, comprised of two senior physicians and the Head of Pharmacy at UCLH, reviewed the treatment team's conclusions about capacity to consent and safety data, and gave approval to start and escalate PRN100 treatment on an individual patient basis following a review of safety data after each dose administration. Three patients were assessed to have the capacity to provide written consent to the treatment; the legality of treatment for the other three patients was individually determined by the Court of Protection.[28] The Court of Protection also received regular reports on individual patients' progress from the Chair of the Oversight

Committee Clinical Subgroup (BW). Ethical approval for the NPMC study was obtained from the Scotland A Research Ethics Committee, but was not needed for the PRN100 treatment as it was given as an NHS treatment and not as part of a research study.

Procedures

For details on the production of PRN100 and preclinical studies, see the appendix (pp 4–5). Candidate patients were transferred to UCLH for diagnostic and baseline blood tests, MRI imaging, CSF analysis (including RT-QuIC, 14-3-3 protein concentration, total tau concentration, protein concentration, cell count, and glucose concentration), and neurophysiological investigations, as per usual clinical care. We proposed treating patients with rapidly progressive CJD by intravenous infusion of PRN100 on a dosing schedule estimated from testing in cynomolgus macaques (appendix p 13). On the basis of mouse and cellular data (half maximal effective concentration for curing prion-infected cells in vitro is around 1 nM),[29] we aimed for a target drug concentration in CSF of 50 nM. If reaching this CSF concentration by intravenous administration was not possible, the treatment plan allowed progression to intracerebroventricular infusion.

PRN100 treatment was administered by 4-h intravenous infusion at the NIHR UCLH Clinical Research Facility to facilitate close monitoring for safety purposes. As the treatment plan represented the first-in-human use of a novel monoclonal antibody, the initial dosing schedule was cautious: patients would start on a dose of 1 mg/kg, which would escalate to 10 mg/kg and then 80 mg/kg at intervals of between 2 days and 6 days if no adverse effects were recorded. The dose of 80 mg/kg was to be repeated every 2 weeks until patient death or withdrawal, whichever occurred first, and patients would be closely monitored for evidence of adverse events.

There were no unexpected clinical symptoms or signs, other than infection related to an intravenous cannula in patient 4, which promptly resolved on removal of the cannula and antibiotic treatment. Given the absence of adverse effects, permission was given by the Oversight Committee after the first four patients had received the 80 mg/kg dose to omit the intermediate 10 mg/kg dose and to increase the maximum dose from 80 mg/kg to 120 mg/kg.

Vital signs and electrocardiograms were closely monitored before, during, and for 24 h after all infusions. The morning following treatment, after a systematic neurological and general medical assessment, a safety-monitoring blood profile was drawn for measuring drug concentrations and conducting haematological, biochemical, hepatic, renal, clotting function and immunological tests, and a lumbar puncture was done for CSF analysis on follow-up, for which protein, cell count, glucose, Qalb, total tau, and PRN100 concentrations were measured. Following 80 mg/kg or 120 mg/kg intravenous treatments, patients were discharged home at least 24 h after the end of the infusion. CSF analysis was omitted at the patients' or families' requests on several occasions. As treatment was authorised via a Specials Licence rather than through a regulated approved clinical trial, measurements were limited to those deemed necessary for patient monitoring and safety. All patients and their families were offered a research autopsy. Autopsies were performed for PRN100-treated patients for whom consent was obtained and for controls recruited to the NPMC by use of full CJD precautions,[30] and brain tissues were removed for neuropathology and drug assay with consent of relatives. Molecular strain typing on brain tissue from patients 2 and 3 showed protease-resistant disease-associated PrP^{Sc} type 3 in patient 2 and type 2 in patient 3 (using the London classification; appendix p 34).[31]

Through item-response modelling with NPMC data, we developed bedside outcome measures for patient assessment: the MRC Prion Disease Rating Scale (a functionally oriented composite scale of disease severity; 0 equates to a comatose state and 20 equates to independence for activities of daily living)[25] and scales designed to measure disease progression on the basis of neurological examination (MRC Motor Scale) and bedside neuropsychological assessment (MRC Cognitive Scale).[32] These bedside assessments were supplemented by repeat MRI imaging or neurophysiological assessments, or a detailed neuropsychological assessment, at approximately 6-week intervals or when prompted by specific symptoms or signs. Patients were assessed (with at minimum a face-to-face consultation) at baseline, daily in hospital when treated, at least once per week between 80 mg or 120 mg treatments, and at least once every 2 weeks until death once treatment had stopped.

PRN100 concentrations were measured by ELISA (appendix pp 5–7) in the serum before and 24-h after dosing and in the CSF 24-h after dosing. A similar ELISA was applied to measure PRN100 concentrations in one post-mortem brain by use of grey matter homogenates from different regions, with a wash protocol to remove blood-borne PRN100 before the assay (appendix pp 7–8).

Statistical analysis

The single batch of PRN100 available determined the number of patients we could treat, but this number could not be prespecified because treatment durations were expected to be highly variable due to different rates of disease progression. Kaplan–Meier survival analysis and linear mixed modelling (for comparison in MRC Prion Disease Rating Scale slopes) were done by use of Stata, version 15.0.[27] The linear mixed model with an unstructured correlation matrix including 1586 MRC Prion Disease Rating Scale measurements from 305 patients was developed by Mead and colleagues,[27] and is described in detail in the appendix (pp 8–11). Descriptive statistics used means, SDs, and ranges.

Role of the funding source
The funders of the treatment programme had no role in programme design, data collection, data analysis, data interpretation, or writing of the report.

Results
Between Oct 9, 2018, and July 31, 2019, we started treatment in two men and four women aged 45–72 years at initial assessment (appendix p 14); five patients had a diagnosis of probable sporadic CJD and one had a diagnosis of probable iatrogenic CJD related to the use of cadaveric human growth hormone in childhood (table 1; appendix p 12). MRI features and the CSF real-time quaking-induced conversion assay were positive for CJD in all cases, implying near certainty of diagnosis. *PRNP* analysis excluded inherited prion disease. MRC Prion Disease Rating Scale scores ranged from 11 to 18 at the clinical assessment immediately before treatment. Three patients died while on the treatment plan and one patient withdrew due to disease progression. For two patients, treatment was eventually discontinued due to exhaustion of the available batch of drug product.

Patient trajectories on the MRC Prion Disease Rating Scale (figure 1) and patient survival (figure 2) were compared with those of natural history controls derived from the NPMC study (see the appendix [pp 8–12] for an overview of this study and details of matching, baseline characteristics). Given the small number of patients who could be treated with the available drug product and the known variability of disease progression, clear clinical evidence of efficacy would have been likely only if the decline in MRC Prion Disease Rating Scale score was

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age at first recruitment to the NPMC study, years	47	45	72	50	67	50
Sex	Male	Female	Male	Female	Female	Female
Diagnosis	Sporadic CJD	Iatrogenic CJD (human growth hormone)	Sporadic CJD	Sporadic CJD	Sporadic CJD	Sporadic CJD
Ethnicity	White British	White British	White British	South Asian	White British	Mixed (White British and Jamaican)
Date of onset of clinically significant neurological features	April 2018	January 2018	November 2018	August 2018	February 2019	December 2018
Main symptom or symptoms at presentation	Balance problems; behavioural changes	Balance problems	Unable to write	Behavioural changes; abnormal gait	Visual disturbance	Mood disorder
MRC Prion Disease Rating Scale score at recruitment to the NPMC study	16	20	14	18	19	15
Main signs at presentation, ordered by severity	Ataxia; myoclonus; cognitive impairment	Ataxia	Hemianopia; dyspraxia; cognitive impairment	Visual processing defects; cognitive impairment; mild ataxia	Visual processing defects; cognitive impairment; myoclonus; mild ataxia	Ataxia; cognitive impairment
Comorbidities	Steatohepatitis	None	Ischaemic heart disease	None	None	None
Brain MRI finding	High signal on DWI in striatum, thalamus, and cortex	High signal on DWI in striatum, thalamus, and cortex	Extensive cortical ribbon on DWI	High signal on DWI in striatum, thalamus, and cortex	Cortical ribbon on DWI	High signal on DWI in striatum, thalamus, and cortex
CSF 14-3-3 protein finding	Positive	Positive	Positive	Positive	Positive	Negative
CSF real-time quaking-induced conversion assay finding	Positive	Positive	Positive	Positive	Positive	Positive
EEG finding	Normal	Normal	Periodic sharp wave complexes	Intermittent slow	Periodic sharp wave complexes	Slow
PRNP codon 129 allele	MV	MV	MM	MV	MM	MV
Capacity to consent	No	Yes	No	No	Yes	Yes
Date of PRN100 treatment initiation	October 2018	December 2018	December 2018	January 2019	March 2019	July 2019

CJD=Creutzfeldt–Jakob disease. DWI=diffusion-weighted imaging. MRC=Medical Research Council. NPMC=National Prion Monitoring Cohort.

Table 1: **Baseline characteristics**

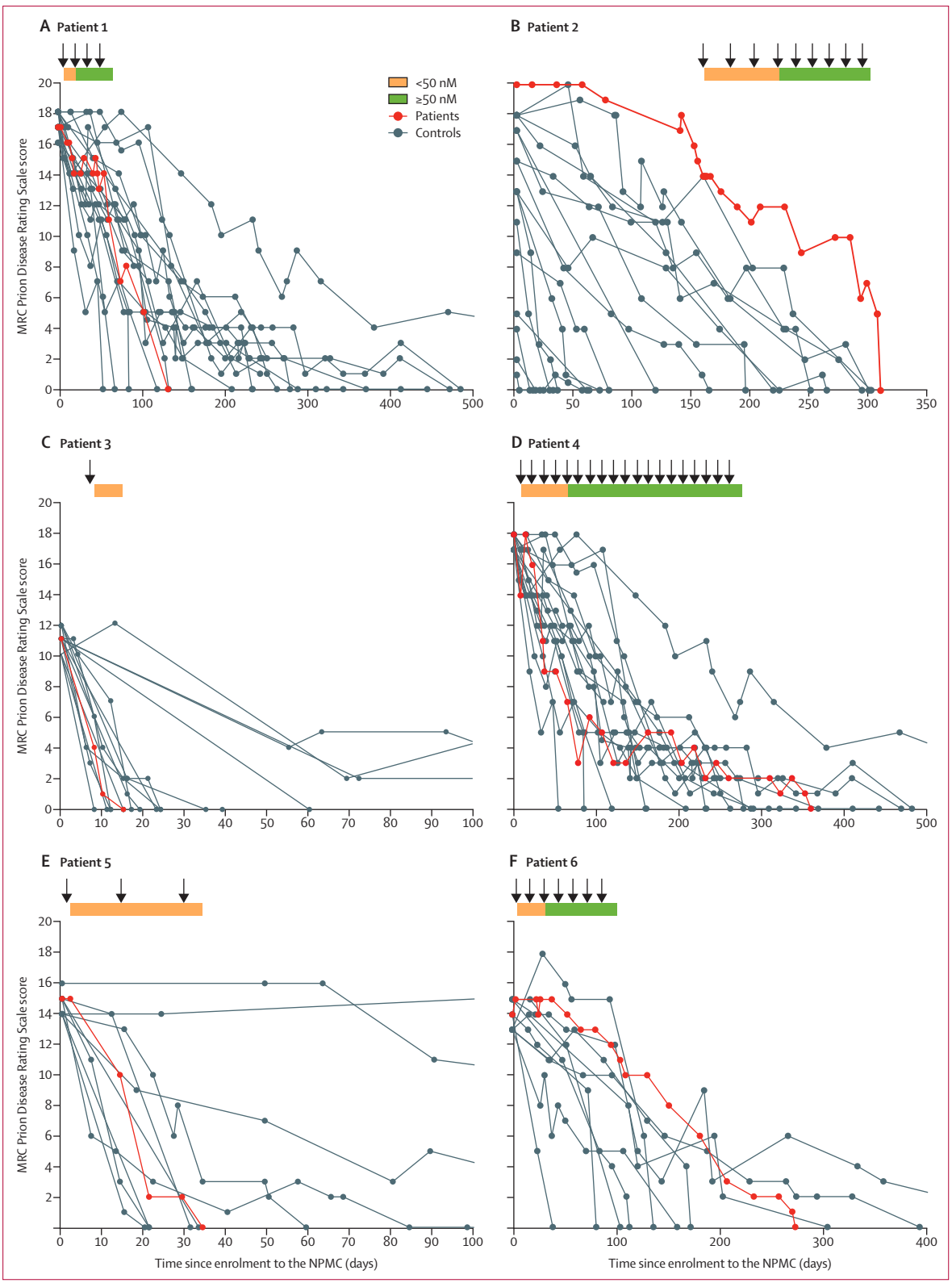

Figure 1: **Trajectories on the MRC Prion Disease Rating Scale for six patients versus 72 natural history controls**
(A) Patient 1 versus 18 controls with sporadic CJD, a score of 16–18 on the MRC Prion Disease Rating Scale, and a heterozygous genotype at codon 129 in the *PRNP* gene. (B) Patient 2 versus 17 controls with iatrogenic CJD, any score on the MRC Prion Disease Rating Scale, and any *PRNP* codon 129 genotype. Note that all patients with iatrogenic CJD recruited to the NPMC were included because this subtype of CJD is very rare and matching was not possible. (C) Patient 3 versus 17 controls with sporadic CJD, a score of 10–12 on the MRC Prion Disease Rating Scale, and a genotype at codon 129 in the *PRNP* gene. (D) Patient 4 versus 18 controls with sporadic CJD, a score of 16–18 on the MRC Prion Disease Rating Scale, and a heterozygous genotype at codon 129 in the *PRNP* gene. (E) Patient 5 versus ten controls with sporadic CJD, a score of 14–16 on the MRC Prion Disease Rating Scale, and a methionine homozygous genotype at codon 129 in the *PRNP* gene. (F) Patient 6 versus ten controls with sporadic CJD, a score of 13–15 on the MRC Prion Disease Rating Scale, and heterozygous *PRNP* codon 129 genotype. Arrows indicate treatment with 40–120 mg/kg of PRN100. The orange and green bar indicates the measured concentration of PRN100 in patients' CSF, extended until the next CSF measurement or 2 weeks after treatment cessation (or to the day of death); orange represents concentrations of less than 50 nM and green represents concentrations of 50 nM or more. For PRN100 CSF concentrations over time, see the appendix (p 35). CJD=Creutzfeldt–Jakob disease. MRC=Medical Research Council. NPMC=National Prion Monitoring Cohort.

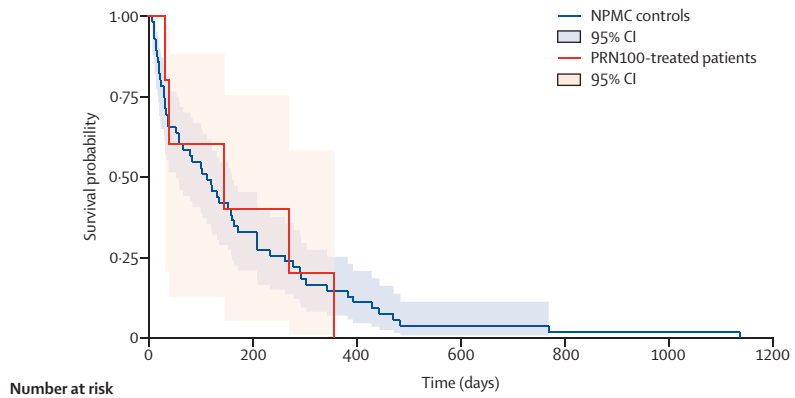

Figure 2: **Kaplan–Meier survival estimates of five PRN100-treated patients with sporadic CJD versus all matched controls**
Patient 2, who had iatrogenic CJD, and the 17 controls with iatrogenic CJD were excluded from this plot. CJD=Creutzfeldt–Jakob disease. NPMC=National Prion Monitoring Cohort.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Time on treatment, days	50	140	7	260	30	85
Number of all doses received	6	11	3	21	4	8
Maximum dose of PRN100, mg/kg	80	120	80	120	120	120
Total dose of PRN100 received, mg/kg	291	811	91	2131	321	886
Peak serum PRN100 concentration, μM	13	32	14	35	18	26
Peak CSF PRN100 concentration, nM	63	121	16	76	27	132
MRC Prion Disease Rating Scale score						
Before treatment start	16	14	11	18	15	14
Last score (on treatment)	11	7	1	3	2	10
Slope (genotype centile rank)*	60	77	37	59	37	68
Clinical duration from symptom onset until death, months	10	16	2	17	3	16
Post-mortem examination done	No	Yes	Yes	No	No	No

MRC=Medical Research Council. NPMC=National Prion Monitoring Cohort. *Calculates the linear rate of decline in the MRC Prion Disease Rating Scale from before treatment start to the end of treatment in patients compared with natural history controls for genotype from the NPMC (zeroth centile represents the fastest rate of decline; 100th centile represents the slowest rate of decline).

Table 2: **Disease progression in patients on treatment**

halted for a prolonged period or reversed in one or more patients. Formal comparison of the decline in MRC Prion Disease Rating Scale score between treated patients and matched historical controls by linear mixed modelling did not show a statistically significant difference.[27]

Detailed patient vignettes are given in the appendix (pp 15–32). In brief, patient 1 had a stable MRC Prion Disease Rating Scale score on treatment (once the PRN100 CSF concentration target of 50 nM was reached) but did not return for further treatment after six doses after a clinical decline associated with a urinary tract infection and while off treatment during the Christmas period. Patient 2, who had iatrogenic CJD, had relatively stable scores during the treatment window when the target PRN100 CSF concentration was reached, but then developed a pneumonia and died while on treatment. Her duration of illness was the longest we have encountered in the historical NPMC group of patients with iatrogenic CJD (she had clinically significant symptoms for 11 months before treatment); consent for autopsy was given. Unfortunately, patient 3 had a very rapidly progressive course and their MRC Prion Disease Rating Scale score declined from 11 to 4 during dose escalation. Treatment with the 80 mg/kg dose went ahead despite his advanced clinical stage as the patient and his family had expressed a strong wish in that regard. The patient died of the disease 5 days later and consent to autopsy was given. The MRC Prion Disease Rating Scale of patient 4 declined sharply during the first six doses, but this decline levelled off for 6 months, albeit at an advanced clinical stage, during which time PRN100 CSF concentrations remained at 50 nM or more. The patient died of the disease following cessation of treatment when supply of the drug product was exhausted. Patient 5 also had a very rapidly progressive disease course and died of disease progression before the target CSF drug concentration was reached. Patient 6 had a more slowly progressive course of disease but all her MRC Scale scores declined while on treatment. Treatment was discontinued when supply of the drug product was exhausted and the patient died of disease progression several months later.

Follow-up MRI brain imaging in four patients showed stable CJD-related signal changes (eg, high signal on diffusion weighted imaging in the cortex, striaum and thalamus) in three and brain volume loss in three (appendix pp 17, 20, 26, 31); there were no unexpected imaging findings. CSF analysis showed unexpected and consistent findings on treatment that were detectable following the first doses (table 2). Routine CSF white blood cell count and protein concentrations are usually unremarkable in patients with CJD; however, we saw consistent abnormalities in CSF protein concentrations, CSF white blood cell count, and CSF/serum albumin quotients, consistent with leakage of the blood–brain barrier (table 3). These abnormalities were treatment-related and persistent (but not progressive), and there were no symptoms or signs of meningism or neuropathy.

Regular blood testing for biochemical, haematological, hepatic, renal, and clotting functions showed no notable changes compared with baseline on treatment. At baseline, CSF total tau was elevated beyond the normal laboratory range in all patients and continued to increase on treatment, as has been observed in untreated patients.[33]

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Reason for stopping treatment	Urinary sepsis; patient too unwell to travel to treatment centre	Patient died of pneumonia	Patient died due to disease progression	Treatment supply exhausted	Patient died due to disease progression	Treatment supply exhausted
Dose before stopping, mg/kg	80	80	120	120	120	120
Adverse events	Urinary tract infections partly related to catheterisation	Respiratory tract infection	None	Line infections on three occasions that responded promptly to line removal and intravenous antibiotics	None	None
Notable blood test results	Abnormal LFT	Minor increase in CRP; mildly abnormal LFT	None	Increase in CRP	None	None
Timing of blood test results*	Predating treatment; did not worsen on treatment	CRP abnormality was persistent throughout treatment with no clear cause, but we suspected chest infection; mildly abnormal LFTs predated treatment and persisted without changes	NA	Timing of abnormalities suggested they were related to cannula infections	NA	NA
CSF findings (maximum abnormality)	†White cell count (17 cells per µL); †protein (2·68 g/L); †Qalb (46)	†White cell count (18 cells per µL); †protein (2·47 g/L); †Qalb (42)	White cell count (2 cells per µL); †protein (1·24 g/L); Qalb not recorded	White cell count (5 cells per µL); †protein (1·56 g/L); †Qalb (27)	White cell count (3 cells per µL); †protein (1·60 g/L); †Qalb (21)	†White cell count (21 cells per µL); †protein (2·71 g/L); †Qalb (41)
Timing of CSF test results*	24 h after the second dose of 80 mg/kg; on later repeat testing, white cell count was 8 cells per µL and protein concentration was 2·51 g/L	24 h after the first dose of 80 mg/kg; on later repeat testing, white cell count was <1 cell per µL and protein concentration was 1·03 g/L	24 h after a single (and only) dose of 80 mg/kg	White cell count abnormality was recorded after seven doses of PRN100. White cell count returned to normal at six repeats; protein concentration remained persistently elevated	24 h after first dose of 120 mg/kg, CSF findings remained similar when repeated twice	24 h after first dose of 80 mg/kg, white cell count decreased to 7 cells per µL at last CSF test; protein concentration was 2·71 g/L at last check

CRP=C-reactive protein. LFT=liver function test. Qalb=CSF/serum albumin quotient. *See the patient vignettes in the appendix (pp 15–32) for more details. †Outside normal range.

Table 3: **Safety measure and adverse effects**

PRN100 concentrations were measured in serum before and 24-h after dosing on 91 occasions, and in the CSF 24-h after dosing on 32 occasions. PRN100 was detectable in all post-dose samples, with a roughly dose-proportional increase in systemic exposure to free PRN100; there was little accumulation of PRN100 after repeated dosing at any one dose level. Serum PRN100 concentrations did not vary much between patients (post-dose coefficient of variation 22%). The maximum serum concentration of free PRN100 was 35 µM in patient 4 (range across all patients 13–35 µM; table 3). In FVB/N mice and cynomolgus macaques, the pharmacokinetics of PRN100 were characterised by target-mediated drug disposition, with very rapid loss of exposure at free serum PRN100 concentrations of less than 1·3 µM (data not shown). In keeping with predictions, the clinical dosing regimen did appear to saturate target-mediated drug disposition. The concentration of free post-dose PRN100 in CSF increased with time (appendix p 35), reaching 50 nM after a mean of 47 days (SD 24; range 22–70) in four patients. Two patients died before reaching the target CSF drug concentration of 50 nM. The concentration of free PRN100 in the CSF reached a maximum of 0·11–0·61% of the corresponding serum concentration (n=6). In patients 2, 4, and 6, who had 3 months of data after the start of treatment, maximum free PRN100 concentrations in CSF 24 h after a 120 mg/kg dose were 121 nM (18·1 µg/mL), 76 nM (11·4 µg/mL), and 132 nM (19·8 µg/mL), respectively. In patient 4, for whom serial serum samples were available after the last dose, the terminal half-life of free PRN100 was around 12 days, consistent with the expected half-life of an IgG in humans.

Tissue-bound PRN100 IgG was measured in multiple brain regions obtained at autopsy from patient 2 (appendix p 7). Mean concentrations of tissue-bound PRN100 IgG were 9·9 µg per g of tissue (SD 0·3) in the thalamus, 15·2 µg per g of tissue (1·5) in the cerebellum, 17·7 µg per g of tissue (0·4) in the parietal cortex, 18·2 µg

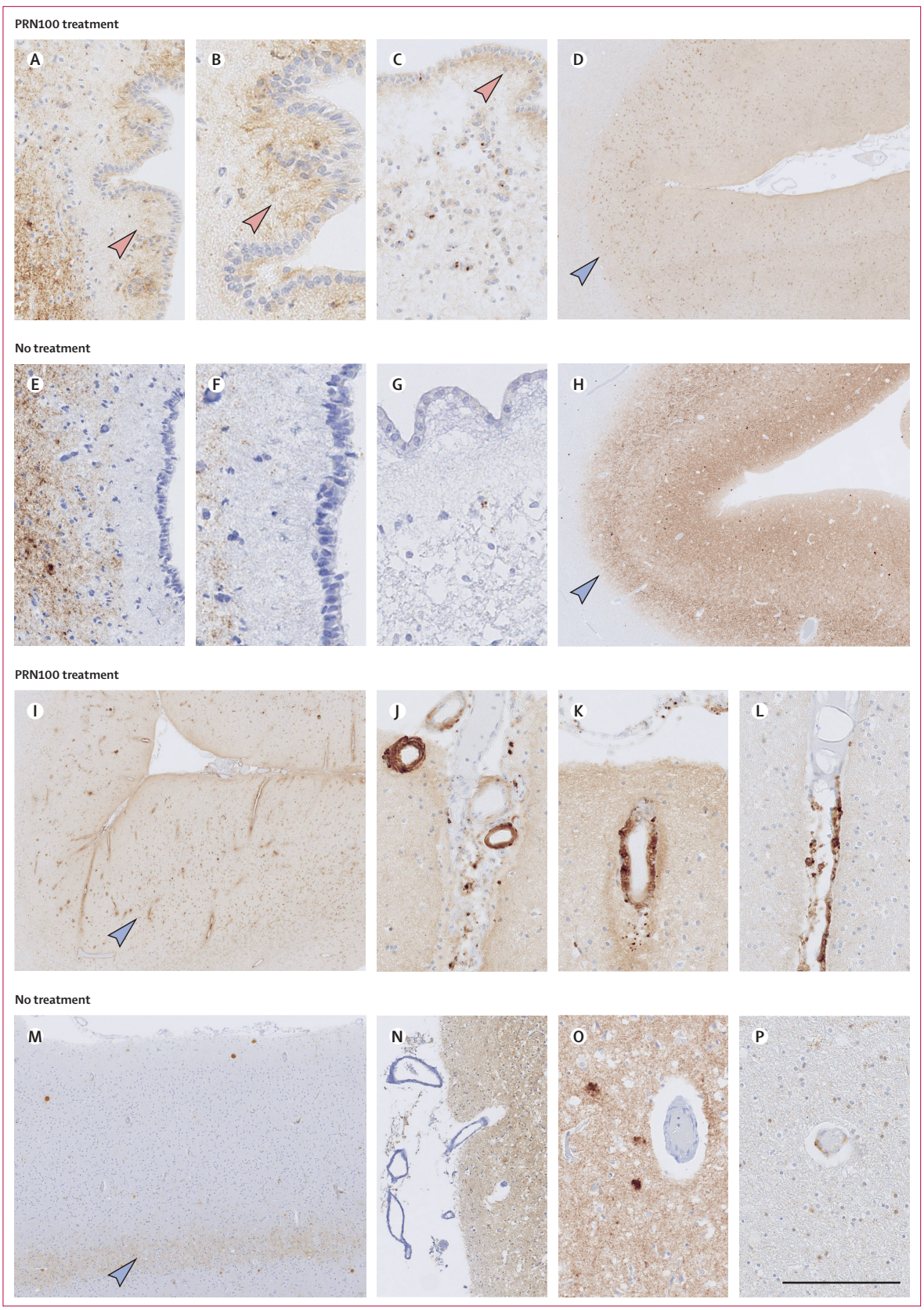

Figure 3: **Effect of PRN100 treatment on clearance of disease-associated PrP from the brain**

PrP labelling in the brain of PRN100-treated patient 2 (iatrogenic CJD; A–D) and in the brain of an untreated patient with iatrogenic CJD (E–H). In the treated patient, there is a diffuse PrP deposition in the subependymal region around the aqueduct (A, B; red arrowheads) and the lateral ventricle (C), which is not seen in the non-treated patient with iatrogenic CJD (E–G). Perinuclear dot-like deposits beneath the lateral ventricle near the caudate nucleus are variably present in treated (C) and non-treated (G) patients with iatrogenic CJD. The parietal cortex in the treated patient shows weak synaptic labelling, giving the impression of a washed-out appearance (D; blue arrowhead), and in the untreated patient there is diffuse and dense pan-cortical synaptic labelling with occasional microplaques (H; blue arrowhead). The two lower rows show further brain areas of the PRN100-treated patient 2 (I–L) and, for comparison, untreated patients with iatrogenic CJD (M–P). In the PRN100-treated patient, PrP labelling in the occipital cortex has a washed-out appearance (I), compared with crisp, laminar labelling in the deep cortical layers, with occasional pan-cortical microplaques, in an untreated patient with iatrogenic CJD (M; blue arrowhead). Vascular PrP amyloid (PrP cerebral amyloid angiopathy) in leptomeninges (J), cortex (K), and subcortical white matter (L) in the treated patient. No vascular PrP amyloid deposition is seen in the leptomeninges (N), cortex (O), or white matter (P) in the brains of untreated patients. Occasional perivascular granular deposits (P) are a feature of all forms of prion disease. The scale bar represents 2 mm for panels D, H, I, and M; 200 μm for panels A, C, E, and G; 150 μm for panels J–L and N–P; and 100 μm for panels B and F. CJD=Creutzfeldt–Jakob disease. PrP=prion protein.

per g of tissue (0·2) in the hippocampus, 18·9 µg per g of tissue (0·7) in the occipital cortex, 19·9 µg per g of tissue (1·8) in the frontal cortex, and 27·4 µg per g of tissue (1·5) in the basal ganglia.

Neuropathological examination was done on patients 2 (iatrogenic CJD) and 3 (sporadic CJD). The most notable findings in the PRN100-treated patient with iatrogenic CJD (in comparison with four untreated patients with iatrogenic CJD from the NPMC) were, first, considerably attenuated labelling, with loss of the crisp, granular structure of PrP in the parietal and occipital cortex, giving the impression of a washed-out staining (figure 3). Second, there was an absence of abnormal PrP labelling in subventricular areas surrounding the aqueduct and the lateral ventricles in non-treated patients, but these regions showed synaptic labelling in the PRN100-treated patient with iatrogenic CJD. Finally, in the brain of patient 2, there was striking and widespread deposition of PrP in the walls of the leptomeningeal, cortical, and, occasionally, subcortical white matter blood vessels, with appearances corresponding to PrP cerebral amyloid angiopathy (figure 3J–L). Such PrP cerebral amyloid angiopathy was not seen in the four brains from patients with untreated iatrogenic CJD or in the 28 brains from patients with sporadic CJD that we examined for comparison.

The abnormal PrP labelling pattern in the cortical regions and deep grey nuclei in patient 3, who had sporadic CJD and only a single 80 mg/kg dose of PRN100, and in whom the target CSF drug concentration was not reached (peak CSF drug concentration 16 nM), did not differ from that in the brains of 28 untreated patients with sporadic CJD; however, patient 3 did have weak synaptic labelling in the periventricular regions, which was not a feature of untreated patients. There was no PrP cerebral amyloid angiopathy in the brain of patient 3.

Most importantly, in neither treated patient was there evidence of cytotoxicity, such as neuronophagia, microglial nodules, any apparent lymphocytic inflammation, or increased formation of vacuoles (see the appendix [pp 32–33] for details on the quantification of microglial density, amyloid β cerebral amyloid angiopathy, and tau pathology).

Discussion

We report our experience of the first-in-human treatment of six patients with CJD with PRN100. We show that PRN100 was safe and able to access the brain (CSF data in four patients and autopsy data in one patient) in target concentrations after intravenous dosing. Limited brain autopsy evidence from two patients showed that PRN100 treatment did not induce neurotoxicity and suggests that PRN100 might help to clear disease-related PrP from the brain. At this stage, the number of treated patients is too small to determine whether PRN100 altered the course of the disease. Based on these safety data and demonstration of brain accessibility to PRN100 following intravenous administration, a larger study, ideally at the earliest possible intervention, is now warranted.

All prion diseases are relentlessly progressive, invariably fatal conditions. However, our understanding of their requirement for PrP^C for pathogenesis and unequivocal preclinical validation[10,12,13] of the effect of targeting PrP^C provide a strong expectation that passive immunotherapy with anti-PrP^C monoclonal antibodies should be an effective therapeutic strategy, assuming adequate concentrations reach brain tissue without dose-limiting toxicity and that treatment is initiated before major neuronal loss and irreversible secondary neurodegenerative processes are underway. Such a treatment strategy is expected to be particularly promising as secondary prophylaxis in asymptomatic individuals known to be infected with prions or harbouring a pathogenic *PRNP* mutation. By targeting the obligate substrate for prion propagation and neurotoxicity, rather than prions themselves, the treatment should also be effective against all prion strains and avoid the development of drug resistance by strain adaptation and selection.[34]

On this firm scientific foundation, we have treated six patients with CJD with PRN100 under a Specials Licence, proceeding with great caution and independent oversight. The nature of the recruitment process for this first-in-human treatment programme meant that most patients were rapidly progressing and at the mid-stages of the disease at onset of therapy. In addition, our cautious intravenous dose-escalation protocol meant that it took a mean of 47 days to reach the target CSF concentration of 50 nM and clinically significant further neurological decline occurred during this period (for context, in the NPMC study [544 individuals with sporadic CJD], median survival from enrolment was 25 days (Q1–Q3 10–97).[27] Our interpretations are necessarily limited by the small number of patients who could be treated with our single available batch of drug product, their rapid clinical progression and well established neurodegeneration at the outset of treatment, and the fact that we evaluated an NHS treatment and did not do a clinical trial with prespecified outcomes, analyses, and research biomarkers. This approach meant that clear evidence of efficacy could be concluded only if one or more patients ceased to decline neurologically or showed sustained improvement on treatment, an outcome we have not seen in our natural history study.[25]

Encouragingly, intravenous administration did reach our target CSF drug concentration of 50 nM in four patients and direct intracerebroventricular infusion was unnecessary. Indeed, CSF analysis indicated that PRN100 itself might have resulted in increased permeability of the blood–brain barrier, compared with baseline and controls, perhaps via interaction with PrP^C on the surface of endothelial cells,[35] facilitating its own entry. Most importantly, we saw no clinical evidence of toxicity and there was no evidence of cytotoxicity related to therapy in the two patients in whom autopsy examination was done. Intravenous infusion of PRN100

was well tolerated and there were no acute or chronic adverse events for up to 8 months of treatment.

Although disease progression was not halted or reversed in any patient, MRC Prion Disease Rating Scale scores did appear to stabilise in three patients for periods when CSF drug concentrations reached the target concentration, but the small number of patients precluded meaningful statistical analysis. However, neuropathological examination of patient 2 provided strong evidence of target engagement and drug effect, with striking attenuation of abnormal PrP immunoreactivity in the parietal cortex and occipital cortex, markedly altered distribution of disease-related PrP in subventricular areas, and PrP cerebral amyloid angiopathy, which was not seen in untreated patients. We note that amyloid β cerebral amyloid angiopathy has been observed as a consequence of amyloid β monoclonal antibody therapy, but we did not detect amyloid-related imaging abnormalities in any patient. The second patient on whom autopsy was done only received a single dose of 80 mg/kg but also showed altered PrP labelling in periventricular regions. Compared with untreated historical controls, concentrations of tissue-bound drug estimated in post-mortem brain tissue were similar to those in CSF, well in excess of concentrations shown to cure cells of prion infection.

We are therefore encouraged by these findings, which, taken together, suggest that intravenous administration of PRN100 treatment is safe and can attain, and sustain in the long term, brain tissue concentrations in the range expected to be therapeutically active without detectable toxicity. It will be important to now evaluate PRN100 in a regulated phase 2 study in which we would seek to enrol patients at the earliest clinical stages and perform much more rapid dose escalation to achieve target CSF drug concentrations within 48–72 h. Modelling studies based on the NPMC dataset with genetic stratification by *PRNP* codon 129 genotype estimate that a suitably powered trial can be conducted with 50 patients.[27] The availability of this large natural history dataset of a rare disease allows innovative trial designs to assess efficacy with minimal or no randomisation to placebo, which is understandably challenging for this patient population to accept.[4]

Subject to satisfactory safety data, further studies to evaluate PRN100 for secondary prophylaxis to prevent the clinical onset of disease could be undertaken in carriers of *PRNP* mutations and those exposed to prions via medical or surgical procedures or laboratory incidents, which includes a large number of individuals treated with human cadaveric growth hormone potentially contaminated by prions (around 1800 people in the UK; around 5000 people in the USA). Possible blood biomarkers of proximity to clinical onset in people at risk could be important components of preventive studies.[26] Dietary exposure to prions resulted in the historical epidemic of kuru, transmitted by ingestion of human tissues at mortuary feasts in Papua New Guinea, and variant CJD from exposure to bovine spongiform encephalopathy prions in the UK and some other countries. Although variant CJD is now very rare, screening of anonymised archived tissue has suggested that around one in 2000 people in the UK population could be silently infected following exposure to bovine spongiform encephalopathy in the 1980s and 1990s.[36] Variant CJD prion infection has also been iatrogenically transmitted by blood transfusion or blood products and several thousand UK individuals have been notified that they are at risk of developing prion disease as a result of such exposure.

In addition to meeting the unmet clinical need to treat and prevent prion disease, it is anticipated that much will be learned in the course of these future clinical studies about the capacity for cognitive and neurological recovery upon halting a neurodegenerative process in humans. Such knowledge could be extremely valuable in the development and evaluation of therapies for the more common dementias. Furthermore, a growing body of data supports a role for PrP^C in Alzheimer's disease in its binding of synaptotoxic amyloid β assemblies.[37] The interaction between PrP^C and synaptotoxic amyloid β assemblies can be efficiently blocked by PRN100, suggesting a possible future role for anti-PrP antibodies in treating Alzheimer's disease[38] and, possibly, other common neurodegenerative diseases.[39]

Contributors

JC led the development of PRN100 with SM, AK-S, CP, NM, NE, PH, and MW. Patient assessment and treatment and review of investigations was done by JC, SM, PR, TM, AN, and HH. PRN100 assays and other laboratory investigations were designed, conducted, or designed and conducted by AK-S, SC, CS, TC, and LD. Neuropathology was done by ZJ, JL, and SB. VL and BW provided clinical advice and coordinated and liaised with the Oversight Committee. The underlying data have been verified by JC, SM, HH, AK-S, and SB. The manuscript was drafted by JC and SM, with contributions from all authors. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

JC is a director and shareholder of D-Gen, an academic spinout in the field of prion disease diagnosis and therapeutics; D-Gen owns intellectual property relating to PRN100. All other authors declare no competing interests.

Data sharing

Individual-level data from all patients are given or illustrated in the Article and its appendix. Any data shown are available from the corresponding author on reasonable request (jc@prion.ucl.ac.uk).

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