Chapter 16
Overview on Treatment of Prion Diseases and Decontamination of Prions

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Abstract Currently, there are no prophylactic or disease-modifying therapies for prion diseases with proven, significant efficacy. The discovery of treatments by design is hampered by incomplete understanding of prion disease pathogenesis. However, therapeutic considerations have broadly centered on a loss of function of the normal prion protein or possible toxicity of abnormal prion proteins. Potential treatments have been assessed by in vitro cell-free studies, cell-culture studies, in vivo animal experiments, and in human clinical trials. The last of these poses several problems including the rarity of prion diseases, variations in the rates of clinical progression, difficulties in measuring this clinical progress, and in the difficulty of early diagnosis at a time before significant neurological damage has already occurred. Given the transmissibility of prion diseases, one aspect of their prevention involves decontamination of potentially contaminated medical instruments. Unfortunately, prion infectivity is particularly difficult to remove or inactivate, with variations between different prion agent strains and methodological problems in the assessment of the effectiveness of any proposed method. The general principles underpinning prion disease treatment and decontamination are reviewed with reference to past research and current knowledge.

Keywords Efficacy • Diagnosis • Prion decontamination • Prion protein • Treatment of prion diseases

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W.-Q. Zou and P. Gambetti (eds.), *Prions and Diseases: Volume 2, Animals, Humans and the Environment,* DOI 10.1007/978-1-4614-5338-3_16,

16.1 Introduction

The prevention of prion disease depends on the type of disease concerned. In acquired forms, protecting human diet from infection, avoiding the use of potentially contaminated materials (including blood), and the satisfactory decontamination of materials or medical instruments are important. Specific therapies could either prevent disease in those at particular risk of it (by exposure to infection or by virtue of inheritance) or treat clinically ill individuals. Prevention is particularly important in the absence of any effective disease treatment. This is an overview of the key concerns in the areas of therapy and decontamination.

16.2 Treatment

16.2.1 Treatment: General Principles

Medical treatment may be preventative, symptomatic, and disease modifying. Given the rarity of prion diseases, preventative measures would be considered for only those at particular risk of illness: known carriers of pathogenic *PRNP* mutations and those known to have been exposed to a relevant risk (such as cadaveric-derived human growth hormone or recipients of blood from a vCJD donor). Various manifestations of human prion disease may be considered for symptomatic treatment (such as agitation or myoclonus), but such symptomatic treatment is not specific to prion diseases and follows general principles. This overview will address mainly prophylactic and disease-modifying treatments. The rational treatment of disease requires diagnosis and, in general, the earlier a disease is diagnosed, the more efficacious treatment is to likely be; unfortunately, early diagnosis is often problematic in prion diseases. Potential treatments need to be discovered and then assessed (for efficacy and potential toxicity).

16.2.2 Diagnosis

Diagnosis is an important and (in prion diseases) difficult precursor to treatment. There are situations where individuals are known to be at risk of such disease and therefore can, at least in principle, be monitored in order to recognize disease at an early clinical stage. However, in most cases, the diagnosis is generally made relatively late in the illness. This is particularly so in sCJD, where the diagnosis is made typically when there is severe neurological impairment, often only shortly before death. As a general principle, even very effective treatments may not be of much benefit if given late in a disease process. Moreover, even if a treatment halted the progression of prion disease, it would not necessarily undo existing

neurological damage; this might not be advantageous (and might even be regarded as disadvantageous) if it simply left the patient in a severely disabled state. In the case of sCJD, the presentation is typically neurological and indicates a serious, progressive encephalopathy. However, there are other common causes of, say, dementia with ataxia, than sCJD. The process of exclusion of other diagnoses necessarily takes time and sCJD is rapidly progressive with a median duration from first symptom to death of only around 4 months (in most countries). The EEG, CSF protein tests, and the cerebral MRI are helpful, but these tests are not absolutely specific, generally playing a supportive role (Chap. 13). There are, currently, no noninvasive, clinical diagnostic tests completely validated for sCJD. In vCJD, the illness progression is typically slower, with a median illness duration of around 14 months and there is a potentially useful, disease-specific (albeit somewhat invasive), test in the form of tonsil biopsy (Chap. 13). However, the presentation of vCJD is very nonspecific, typically consisting of psychiatric features without specifically neurological symptoms or signs for several months (Spencer et al. 2002). Early diagnosis is potentially very difficult, but it is often made at a stage of lesser neurological disability than in the case of sCJD.

The development of disease-specific tests might allow accurate diagnosis at earlier, lesser, stages of neurological impairment; recent reports of a blood test for vCJD and a CSF test for sCJD may prove useful (Edgeworth et al. 2011a, b; Atarashi et al. 2011; McGuire et al. 2012) (the current status of diagnostic test development is reviewed in Chap. 13).

16.2.3 Disease-Modifying Treatment

A systematic review has summarized the published data concerning prion disease therapy in humans over the period 1971–2007 (Stewart et al. 2008). It found reports of a total of 149 patients treated with 14 drugs. However, most publications concerned single case reports of a few patients, only four were comparative studies with only one of these being a randomized controlled trial (RCT). The reported drugs included Interferon, Acyclovir, Vidarabine, Amphoteracin, Clomipramine, Venlafaxine, Anti-oxidants, Amantadine, Topiramate, Phenytoin, Levetiracetam, Flupirtine, Quinacrine, and Pentosan Polysulphate; the therapeutic choices reflecting various ideas including possible viral causation, effects on protein aggregation, and possibilities of neuro-protection. In most, there was no convincing evidence of efficacy but, given the small numbers treated and the poor methodology (including lack of controls), it was often not possible to form an absolutely definitive opinion. The single RCT showed some improvement in the group treated with Flupirtine, compared with placebo. However, this was only a small study (13 patients with active treatment; 15 controls) with the same overall survival in both groups; whether this reflected a symptomatic or a partial disease-modifying effect is uncertain (Otto et al. 2004).

16.2.4 Preventative Treatment

Given the often fulminating disease course (for example in sCJD) and the established neurological damage by the time of diagnosis, the greatest likelihood for effective treatment might well be in preventing disease in those at significant risk of developing it. Unfortunately, the commonest form of disease (sCJD) is not a reasonable candidate for prophylactic therapy. The two main areas for this consideration are carriers of known pathogenic *PRNP* mutations and those at risk of disease through known exposure to infection. In both instances, treatment would be given to healthy individuals and, therefore, lack of toxicity is a more important consideration than in the treatment of clinically ill individuals. The assessment of efficacy is potentially problematic: those at risk via exposure may never develop disease or only after possibly very long incubation periods; with genetic mutations, disease penetrance and age at disease onset may be variable. A study of potentially preventative therapy (using doxycycline) in *PRNP*-D178N mutation carriers is planned in Italy (reference to Chap. 7 (2)).

16.2.5 Treatment: Discovering Potential Treatments

The discovery of disease therapies can be fortuitous or by design. In the latter case, one needs a reasonable understanding of disease mechanism. Unfortunately, while much is known about the molecular underpinning of prion disease, its precise pathogenesis (what actually leads to neuronal dysfunction and death) is not well understood. Theories of pathogenesis have, very broadly, involved the possible effects of loss of function of the normal cellular protein PrP^{C} (due to its conversion to PrP^{Sc}), possible toxicity of aggregated deposits of the abnormal, disease-related PrP^{Sc}, and possible toxicity of intermediate forms between PrP^{C} and PrP^{Sc}, with a current tendency to favor the last of these (Weissmann and Aguzzi 2005; Zanusso and Monaco 2005).

The selection of potential treatments has been based on their potential effects on PrP^{C}, the conversion of PrP^{C} to PrP^{Sc} (the abnormal disease-related prion protein), or the aggregation and accumulation of PrP^{Sc} in tissues. Experimental work has shown that PrP^{C} is required for successful transmission of prion disease and, while the normal role of PrP^{C} is uncertain, its acquired absence may not be significantly deleterious to animal health (Mallucci et al. 2002). In one study, depleting PrP^{C} in an animal infection model prevented progression to clinical disease and even reversal of early neuropathological changes (Mallucci et al. 2003). As a result, one therapeutic approach is based on removal of PrP^{C} by using antibodies against PrP^{C}. Immunomodulatory approaches to treatment are reviewed in Chap. 7(3). Another set of approaches is to identify molecules that could stabilize PrP^{C}, prevent its conversion to PrP^{Sc}, destabilize PrP^{Sc}, or to break up aggregations of PrP^{Sc}. The last of these is reasonable if aggregated deposits are harmful and/or it aids the breakdown

of PrP^{Sc}, but could be useless or potentially harmful if the aggregates are not intrinsically toxic and if more toxic prion protein forms were released. A useful review of therapeutic approaches to prion diseases was published in 2005 (Weissmann and Aguzzi 2005).

Three general steps can be taken to identify possible treatments: in vitro cell-free studies, cell culture studies, and in vivo animal experiments. These entirely reasonable, desirable steps have potential limitations: success in a chemical or cell-line setting is not success in a whole organism and treatment results in animals (even transgenically modified ones) may not be directly transferable to humans. A particular difficulty with animal experiments is that typically treatment is given relatively close in time to the inoculation of infection with efficacy often expressed in terms of the number of animals which either fail to become ill or do so with prolonged incubation periods. This is not the same situation as treating clinically ill individuals. Quite aside from these irreducible facts, laboratory experiments have to use selected strains of prion disease and treatments may have prion strain specificity. There is a useful systematic review (up to 2006) of experimental models in prion disease therapeutics (Trevitt and Collinge 2006). Cell-based assays at least allow for relatively rapid, high-throughput searches for anti-prion disease compounds (Kocisko and Caughey 2006).

Quinacrine was suggested as a treatment on the basis of in vitro work (Korth et al. 2001). Subsequently, it has been used in animal experiments and humans, with no significant efficacy (Collins et al. 2002; Collinge et al. 2009). Animal experiments involving intra-cerebro-ventricular administration of Pentosan Polysulphate (PPS) showed promising results (Doh-Ura et al. 2004). Subsequent treatment of human prion disease has suggested some slowing of disease progression in some cases (most convincingly in vCJD) but without effects in most cases, without consistent effects on brain disease-related PrP and without halting progression (Tsuboi et al. 2009; Honda et al. 2012; Bone et al. 2008).

16.2.6 Treatment: Assessing the Efficacy of Potential Treatments in Humans

Since prion diseases are uniformly fatal with a relatively predictable course, it might be thought that assessing treatment efficacy would be much more straightforward than in diseases with a highly variable course and prognosis, such as multiple sclerosis. However, there are significant, interacting, methodological problems:

(a) Dramatic or curative efficacy would not be difficult to demonstrate. However, initial therapies may be only partially beneficial; a relatively minor effect may be more difficult to confirm, especially in the light of other factors, detailed below. While minor efficacy may not be immediately valuable, it may be an important lead in the development of more effective drugs.

(b) How is efficacy to be measured? At present, any measures probably need to be clinical ones as there are no established para-clinical tests or disease markers of progression. Clinical improvement may not be expected even if disease progression is halted, due to the typically established neurological damage at diagnosis. Slowing of disease progression or even clinical stability may be difficult to confirm if there is already severe neurological impairment. Total illness duration is a simple measure but one that may be affected by a number of factors as discussed in (c) below. If significant impairment "milestones" (such as inability to walk, mutism, requirement for tube feeding, etc.) have not already been reached, then the time taken to reach them could be used (Bone et al. 2008; Mead et al. 2011).

(c) Concerning clinical measures, there is variation within the prion diseases. For example, vCJD has a slower progression and longer duration than sCJD. Even within one form of prion disease, there can be significant variation in simple clinical measures such as total illness duration. Within sCJD, a variety of factors are known to influence survival: age at onset, sex of the patient, *PRNP*-129 genotype, and disease-associated prion protein type. There are, therefore, good arguments for dividing patients into appropriate subgroups before treatment. Naturally, aside from these essentially biological factors, different disease management approaches (such as the use of feeding tubes and the treatment of intercurrent chest infections) may also affect disease duration.

(d) These are rare diseases, with annual mortality rates of around 1–2 per million population. While international collaboration in treatment trials could at least partially overcome this problem, the need for subgrouping (including within sCJD) exacerbates the numerical problem.

16.2.7 Treatment: Assessing the Toxicity of Potential Treatments in Humans

Given the severe, progressive, and ultimately fatal nature of these diseases, one might be prepared to consider relatively toxic treatments if there was a chance of benefit. While this is an arguable position for the treatment of clinical illness, it is certainly not so for prophylactic therapy. For example, if one were considering treating currently healthy *PRNP* mutation carriers, especially with uncertainties about disease penetrance or age of illness onset, then treatment toxicity would be an important consideration. There is the additional problem of assessing neurotoxicity in ill patients when the illness itself is so neurologically devastating. There is always the theoretical possibility that treatments aimed at disease mechanisms may exacerbate the disease process and the detection of this is subject to the same considerations as those listed above for assessing efficacy.

16.2.8 Ethical Considerations

The possibility of slowing or halting progression of a disease that has already caused serious and potentially irreversible brain damage is something that doctors, patients, and families need at least to reflect upon. In addition, with an inevitably progressive and fatal disease, is it right and/or possible to run a control group for comparison? There are sound arguments for having a control group: treatment requires time-consuming interventions (medical supervision with assessments); treatment may be toxic; clinical measures (including simple disease duration) are subject to individual variations as outlined above. The acceptability of a control arm to prion disease patients or families trials is uncertain. The UK Prion-1 Trial did not manage to recruit significantly into a control arm (Collinge et al. 2009). However, the Flupirtine trials succeeded in this (Otto et al. 2004).

16.3 Decontamination

16.3.1 The Background to Decontamination Concerns

The existence of iatrogenic CJD justifies the development of decontamination procedures for prion disease (ref to appropriate chapter section).

A number of factors are relevant: the type of prion disease, the tissue spatial distribution of infectivity (which varies with disease type), the temporal tissue distribution of infectivity (which may be different at different disease stages), the amount of infectivity likely to be found on any relevant material or instrument and the difficulties of removal or inactivation of prion infectivity. In relation to the last point, prion infectivity is notoriously resistant to routinely employed sterilizing methods: germicidal light, glutaraldehyde, formaldehyde, alcohol, and certain autoclaving settings are all of negligible effect (McDonnell and Burke 2003). Resistance to very high temperatures has also been demonstrated (Brown et al. 2000). Certain methods such as exposure to 2M sodium hydroxide are effective but not practical in routine practice (ACDP REF). Various autoclaving protocols involving 134–137 C reduce infectivity but cannot be relied upon for its complete removal (ACDP ref). In addition to these biological considerations, there are epidemiological and practical factors to take into account. In terms of the former, it is a question of the risk of infection being present in the population and this varies with disease and country. For example, studies have suggested the existence of a significant number of individuals with potential vCJD infection in the UK (Hilton et al. 2004; de Marco et al. 2010). In terms of the latter, quite aside from any theoretical considerations and laboratory demonstrations of decontamination efficacy, there are important practical and logistic considerations. Success on the laboratory small scale does not automatically lead to the adoption of a method into real-

life clinical practice. Any decontamination method of practical merit needs to be one that can be used on a large scale, in routine clinical settings, on instruments or materials as they are currently employed, without possible corrosive or destructive effects on the items being treated. In addition, the actual costs and opportunity costs of any general decontamination protocols need to be taken into account.

Decontamination may be considered in two intertwined but separable parts: cleaning and inactivation of infection. Cleaning is an important aspect as obvious remnants of tissue or bodily secretions may contain infectious material and make inactivation of infection more difficult. However, even with rigorous macroscopic cleaning, protein residues that may remain are particularly important in prion disease (Murdoch et al. 2006). The precise nature of the prion (the infectious agent) is still uncertain, but the current view is that it is entirely, or largely, composed of PrP^{Sc}, the disease-related, abnormally folded prion protein. There is evidence that prion protein is firmly adsorbed to steel surfaces, with associated infectivity (Zobeley et al. 1999). There is another factor of importance, namely the effect of drying of items prior to decontamination processes, with drying making decontamination more difficult (Secker et al. 2011; Lipscomb et al. 2006).

There are two broad decontamination situations: decontamination of items with known exposure and general decontamination methods of universal application. In either case, an alternative to decontamination is disposal of the item. In considering a single item (for example, a specific surgical instrument used in someone with a prion disease or at known increased risk of prion disease), the risk of reuse needs to be balanced against the cost of disposal and replacement of the item. In considering universal measures, the particular circumstances of a country may be relevant. For example, in the UK, because of estimates of vCJD subclinical infection prevalence in the population, with the potential involvement of reticulo-endothelial tissues, disposable instruments for various procedures have been considered; however, the general use of disposable instruments is not without possible problems. For example, in England, when disposable instruments were introduced for tonsillectomy (because of the possibility of vCJD transmission), there was a consequent rise in surgical morbidity (Maheshwar et al. 2003; Nix 2003). In the case of brain biopsy for a non-focal cerebral illness, especially a dementing one, it is possible to quarantine the instruments until the biopsy pathological report confirms or excludes prion disease.

16.3.2 Methods of Decontamination

There are various decontamination methods. A review in 2006 detailed the methods recommended by the WHO and the UK ACDP (Advisory Committee on Dangerous Pathogens); the USA CDC recommends following the WHO guidelines. Updated UK ACDP guidelines can be found on the relevant website (refs below and Sutton et al. 2006).

In recent years, a variety of new approaches have been developed including radio-frequency gas-plasma treatment, hydrogen peroxide gas plasma treatment, and an enzyme-detergent method (Baxter et al. 2005; Rogez-Kreuz et al. 2009; Jackson et al. 2005).

16.3.3 Assessment of Decontamination Methods

As the ultimate nature of prion infectivity remains uncertain, determination of infectivity and the effectiveness of decontamination processes has been by protein detection methods, cell-based assays, or by bioassay of infectivity. Protein detection methods have included western blotting, fluorescent microscopy, scanning electron microscopy, energy-dispersive spectroscopic analysis, and quantitative total amino acid analysis (following acid stripping and hydrolysis) (Howlin et al. 2010; Baxter et al. 2005, 2006). A cell-based assay has been described and employed in a comparative assessment of commercially available prion decontamination reagents (Edgeworth et al. 2009, 2011a, b). Bioassay methods involve attempted transmission to experimental animals and are, therefore, a more direct assessment of infectivity. However, they are expensive and time-consuming.

Steel wires have often been used in the experimental assessment of decontamination processes, but concerns have been expressed as to whether this is an entirely valid method (Lipscomb et al. 2006).

One potential problem with the assessment of decontamination methods is the evidence that inactivation of infection varies between different strains of prions (Taylor et al. 2002; Somerville et al. 2002). Therefore, general extrapolation of any specific experimental determination of decontamination is not necessarily valid.

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