Human drug studies: update

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There is a wide scope of clinical phenomenology in human prion disease, regarding the age of onset, presenting features, rate of progression and appearance of other clinical manifestation. Because of clinical heterogeneity, the diagnosis at early stages might be difficult. However, recent advances in clinical diagnostic techniques such as cerebrospinal fluid tests and magnetic resonance imaging, allow to recognize the disease at earlier disease stages, but better tests are needed to identify patients as early as possible, at best at pre-clinical stage. This might allow the physicians to think about therapy in patients with prion diseases, which is reflected in the increasing number of publications on this subject. On the other hand, clinical studies in patients with prion diseases are hampered by various clinical presentations and variability in the disease course, which are influenced by several factors such as age at onset, gender, molecular disease subtype and PRNP codon 129 genotype and those specific problems have to be addressed.

So far, only a few case reports on administration of some specific drugs in CJD patients are available (for Review, (Stewart et al., 2008; Trevitt and Collinge, 2006)). Several compounds have been tested for their potential as an anti-prion drug in humans. They belonged to distinct classes such as analgesic, anti-depressant, anti-psychotic, anti-microbial and anti-coagulant drugs. Most of them were tested in observational trials only on a small number of individuals and mainly case reports for these patients are published. Controlled therapeutic trials in humans are limited.

Flupirtine

A controlled clinical trial using a prospective double blinded approach was performed for flupiritine only. Flupiritine trial was conducted in 26 sCJD patients and 2 patients with iatrogenic
prion diseases (Otto et al., 2004). 13 patients were treated with 100 mg (300-400 mg) flupiritine daily, 15 controls received placebo. There was no difference on the survival time, being 107 days for the treatment group and 106 for the controls. One of the parameters used to monitor the disease progression was the change in cognitive functions as measured by the Alzheimer’s disease assessment Scale Cognitive Subscale (ADAScog). Patients treated with flupiritine showed significantly less deterioration in the dementia tests than patients treated with placebo. The mean change in ADAS-Cog (baseline to best) was +8.4 (+/-15.3) in the flupiritine group and +20.6 (+/-15.1) in the placebo group (p = 0.02, one-sided t-test).

According to cell culture experiments and animal experiments, doxycyclin may directly bind PrP\textsuperscript{Sc} thus preventing further conformational changes. In animal experiments, doxycycline administration prolonged survival time in infected hamster when given intramuscularly, intravenously, intraperitoneally and subcutaneously. Even when treatment was started at advanced stages, an effect was observed. A number of patients with sCJD were treated with doxycycline and an increased survival in these patients compared with historical sCJD cases was reported (F. Tagliavini, personal communication)

On this ground, a small series of CJD patients in Italy and Germany received treatment with doxycycline at a daily oral dose of 100 mg with the same study protocol. The clinical progress of the disease is observed by follow up examinations in an outpatient setting including standardized questionnaires, physical examination and neuropsychological testing.

Between June 2006 and May 2008, 51 patients have been included in the observational trial (44 patients with sporadic CJD and 7 patients with genetic CJD) in Germany. They received doxycycline at a daily dose of 100 mg. First analysis of survival data suggests a delay in disease progression and a significant (p=0.005) prolongation in survival time from onset in patients treated with doxycycline (median: 292d, range: 162d-635d, treated group) compared to historical data in untreated patients (median: 167d, range: 33d-1448d).
Even though the treatment does not cure CJD, a deceleration in disease progression seems possible, which is especially interesting for patients diagnosed at early stages of disease. These data have to be confirmed in a randomized, double blinded, placebo controlled study, which are currently underway in Italy and Germany. Whether doxycycline might represent a potential option for prophylactic treatment in healthy mutation carriers, has to be carefully considered in future. Many questions have to be addressed with this respect, such as potential side effects and risks (which seem to be low as known for long-term treatment with doxycycline for various other chronic diseases or for prophylaxis), but also the duration of the treatment and the best possible time point for initiation of drug administration (E. Mitrova, personal communication).

**Problems to address in future**

Single prospective double-blinded trials in CJD were carried out, thus giving the proof-of-concept that such trials are possible even in a rare disorder. Nevertheless, the clinicians face several difficulties with the design, which are discussed below:

*Early diagnosis*

Because of rapid disease progression, the clinical diagnosis of CJD is frequently made at middle and late disease stages. Substantial advances have been made in last decade in terms of improvement of the clinical diagnosis. Some brain-derived proteins such as 14-3-3 and tau have been shown to increase in the cerebrospinal fluid already at early disease stages. Highly sensitive techniques such as diffusion-weighted (DWI) and fluid-attenuated inversion recovery imaging (FLAIR) magnetic resonance imaging displays early alterations of cortical and subcortical areas. However, the time between onset of first symptoms and disease specific diagnostic tests might typically span from several weeks to month. At the time suspicion is raised and appropriate tests are done, many patients might already suffer from a severe neurological deficit.
Disease incidence and prevalence

sCJD represents the most common human prion disease form. The annual incidence of sCJD ranges between one and two cases per million per year worldwide. The disease is rare in young people and the incidence increases with age, but then occurs less frequently in patients aged over 70. The median age at onset is 65 years. Thus, CJD is still a rare condition. A potential benefit, which might be achieved by the compound, has to be proven on a large number of patients in order to increase the power of the study. This can require a long time period in single countries, thus, the powerful analysis can only be achieved in a reasonable time period by pooling data from different centers, preferably by the same study design.

Monitoring of disease progression

Dementia syndrome in CJD differs from other more common neurodegenerative dementia such as Alzheimer’s disease, but has been poorly characterized and neuropsychological assessment data are limited. Commonly used dementia scales were designed to monitor disease progression in Alzheimers disease and scales for vascular dementia and frontotemporal dementia are available too. However, these scales and scores might not be suitable to monitor cognitive decline in CJD patients, therefore, disease specific scores have to be developed. In addition, scores for monitoring other neurological abnormalities such as ataxia, rigidity or myoclonus have also to be applied in clinical trials. Because of the variability in clinical syndromes and survival times across molecular CJD subtypes, scales might be weighted for single subtypes: Ataxia is more prominent in VV2 subtype and an ataxia scale might be more useful to monitor the disease progression in this subtype, whereas a score which involves neuropsychiatric assessment might reflect disease progression for the MM1 subtype.

Specific problems
A serious problem is the rapid disease progression. Given a short survival time in most patients, an early case identification is crucial to start the treatment.

A specific problem has to be addressed when a clinical trial has to be carried out in patients with dementia, which might be severe at the time when the CJD diagnosis is made. Ethical issues concerning the trials, which will be carried out on patient unable to give an informed consent have to be solved.

**Access of the compound to the brain**

Pharmacokinetic properties of the compounds, which might be chosen to treat humans with CJD, have to be carefully addressed. Ideally, such a drug will be administered via oral or subcutaneous route. The intravenous administration might be challenging in terms of practical reasons (might require hospitalization or special assistance). Many of the drugs tested in animal experiments were given by intracerebral or intraventricular route in order to reach high brain concentrations. However, unlike in inflammatory diseases, the blood brain barrier is not disrupted in patients with CJD. This limits the access of the compound to the brain. Even in effective drugs, major limitations result from the intact blood brain barrier. If the drug has to be delivered by a continuous or repeated intraventricular administration, this might cause severe side effects such as intracranial haemorrhage, risk of inflammation, intracranial injury. Neurosurgery might be required for administration of intraventricular pumps. The high risk of contamination of the instruments via contact with infectious brain material has not been eliminated and the problems of decontamination of surgical instruments are not solved yet.

**Animal models**

The results of studies, which use animal disease models of prion infection, can only to a limited extent be transferred for human application. In most animal trials, the time point of treatment was set closely to prion infection in order to achieve a standard study design. Transferring this
theoretically to the application in humans, this would mean by definition a “prophylactic”
treatment, when a drug is given to prevent the infection or cure early stages of infection. In
patients, who already develop first symptoms of the disease, the response to the drug might be
completely different for various reasons, such as neuronal damage, which already has taken
place at disease onset and potential mechanisms of degeneration and repair, which might
subsequently lead to distinct treatment response.

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