Italian trial with doxycycline in Creutzfeldt-Jakob disease: background, study protocol and update on study population

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The prion diseases are fatal neurodegenerative disorders for which no effective treatment is available. Previous studies from our group led to recognize that some tetracyclic compounds, such as iododoxorubicin and tetracyclines, are able to (i) interact with and revert the protease-resistance of PrPSc extracted from brain tissue of patients with all forms of CJD, cattle with BSE and rodents with experimental scrapie, (ii) reduce the infectivity titer in prion-contaminated material, and (iii) prolong survival of prion-infected animals. On this ground, a series of CJD patients observed at "Carlo Besta" Institute received compassionate treatment with doxycycline at a daily oral dose of 100 mg from the time of diagnosis to death. The choice of this drug among others tetracyclic compounds effective in experimental models was based on the observation that doxycycline has favorable kinetics, relatively good capacity to cross the blood-brain barrier, low toxicity and good tolerability even for prolonged administration. Indeed, no CJD patient chronically treated with this drug showed adverse secondary effects. The retrospective analysis revealed that the subjects treated with doxycycline (n=21) survived significantly longer than untreated patients (n=78); in particular, the survival time (median ± SE) was 13.0 ± 4 months in the former and 6.0 ± 0.7 months in the latter (Log Rank test: p<0.001). A significant difference was still present when the doxycycline-treated group was compared to an untreated group equivalent for sex, age at onset and codon 129 PRNP polymorphism (treated: 13.9 ± 3.8 months, untreated: 6.1 ± 0.5 months, p<0.01), which are major predictors of survival of CJD patients. This result, prompted us to set up a randomized, double-blind study of doxycycline versus placebo that has been approved by the Italian Agency of Drug (AIFA) and the ethical committees of the five participating clinical centers. The study started on April 2007 and, at the time of writing, 28 CJD patients entered into the trial. We will illustrate the study design, efficacy evaluation criteria and the electronic CRF developed for data collection, and will report the number and characteristics of patients recruited into study. A positive outcome of this trial would activate similar studies in other neurodegenerative disorders due to protein misfolding such as
Alzheimer’s disease, since the effects of doxycycline seem to be dependent upon a direct interaction with abnormal protein conformers with an extensive beta-sheet conformation rather than with a specific amino acid sequence. (Supported by AIFA, project FARM573ME8, and NoE NeuroPrion).