Title
Doxycycline for Creutzfeldt-Jakob disease: A failure, but a step in the right direction

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No treatment trials so far have stopped or slowed the progression of prion diseases—the most rapidly progressive forms of neurodegenerative disease.\textsuperscript{1,2} The most common form of prion disease—sporadic Creutzfeldt-Jakob disease—typically progresses rapidly, with most patients dying in less than a year from onset, often in less than 6 months.\textsuperscript{4,5} Results of the trial reported in \textit{The Lancet Neurology} by Stéphane Haïk and colleagues\textsuperscript{6} that used oral doxycycline to treat Creutzfeldt-Jakob disease are no exception to previous study outcomes, with the drug showing no survival benefit. Nonetheless, it is an important study because it showed that multinational collaborations, rapid enrolment, and rigorous study methods can be achieved for treatment of a rare, rapidly progressive dementia.

Several aspects of this study deserve commendation. That two countries with different medical systems were able to combine forces in a treatment trial is remarkable. Despite major differences in how patients were enrolled, such as exclusion on the basis of disease duration in Italy and involvement of many local study sites in France, the trials were sufficiently similar to allow data to be combined for primary and secondary analyses. Additionally, the way in which the French cohort was enrolled—with rapid administrative procedures to enable local referring centres to become study sites—could serve as a model for future trials, because this method enabled a greater number of patients to be enrolled in a fairly short timeframe. Furthermore, in Italy, the investigators were able to use rapid genetic analyses to stratify patients for randomisation.

The investigators also showed that patients with Creutzfeldt-Jakob disease can be enrolled in a randomised, placebo-controlled trial without offering the possibility that all patients might eventually receive active drug. In our sporadic Creutzfeldt-Jakob disease trial of quinacrine,\textsuperscript{7} we offered open-label treatment to patients returning for their 2 month study visit because we were concerned that patients would not enrol if they were not eventually offered active treatment. This turned out to be a weakness of our trial design, because the 2 month randomised phase might have been too short.\textsuperscript{2} The results of this doxycycline randomised trial strongly contradict observational data from Italy and Germany suggesting that doxycycline prolonged survival in patients with Creutzfeldt-Jakob disease.\textsuperscript{8} An important lesson from the trial, as the investigators allude, is that observational or historical series data should not be relied upon to determine whether treatments are efficacious; all too often, the biases of observational studies become apparent when their findings are tested with appropriate scientific methods in randomised controlled trials.

Although this trial offers much to emulate for future trials, it also had shortcomings, including the use of a drug without compelling preclinical efficacy. Many complex factors need to be considered when choosing drugs for prion trials. Many compounds, including doxycycline, are effective in vitro or in in-vivo animal models when given before, with, or immediately after prion inoculation, but are ineffective when given later in the disease course.\textsuperscript{9–11} This observation is not analogous to Creutzfeldt-Jakob disease, in which patients are already symptomatic. Two compounds have shown significant efficacy in animal models when given at midpoint of incubation or at or around symptom onset,\textsuperscript{12,13} but these drugs were either too toxic or failed even in observational studies.\textsuperscript{13–16} Also, the route of administration might be important. The only doxycycline animal study that showed even minimal benefit once animals had begun to show symptoms used intraventricular liposomal delivery,\textsuperscript{17} not oral delivery, which was used in this trial. Additionally, drugs reported to be effective against one prion strain or in one animal genetic background are often ineffective against other strains or in other animal backgrounds.\textsuperscript{9,15,19} Many drugs, including doxycycline, are tested against only one or a few strains of prion and in animals from one or a small number of genetic backgrounds.\textsuperscript{10,17} Recent research also suggests the development of drug-resistant prion strains with monotherapy.\textsuperscript{18} Because of drug resistance and the number of human prion strains, some have suggested that future treatment might require multidrug therapy.\textsuperscript{18} Testing of compounds at a more meaningful point, such as midway through the incubation period
or at symptom onset, against several prion strains and in different animal backgrounds, makes better sense for modelling treatment of Creutzfeldt-Jakob disease. An exception to the testing of compounds in animals later in the disease course would be the identification of compounds to treat people at risk for prion disease, such as through known exposure (iatrogenic) or those carrying a prion gene (PRNP) mutation; as the investigators note, doxycycline is currently being tested in a trial for presymptomatic fatal familial insomnia in a single extended Italian family.

A second major issue with the trial by Haik and colleagues was the inclusion of patients with very advanced disease. Essentially no exclusion requirements were stipulated for disease severity in the French cohort, and the Italian investigators used time from symptom onset for exclusion as a surrogate for disease severity. As a result, a large proportion of the enrolled patients were already at the end stage of disease, with akinetic mutism or dependence on feeding, at randomisation. Patients with very advanced disease would have been highly unlikely to respond to any treatment. The inclusion of only patients who had symptoms for up to 6 months does not make sense for several reasons. Survival in Creutzfeldt-Jakob disease is variable: although most patients have a rapid course, Creutzfeldt-Jakob disease is variable: although most patients who were most likely to have the disease. In France, where patients were referred from doctors all over the country, there was probably less prescreening before patients were referred to the national Creutzfeldt-Jakob disease surveillance centre in Paris. Investigation into what types of physicians made misdiagnoses and why would be helpful, so that education on Creutzfeldt-Jakob disease diagnosis can be appropriately targeted.

Although this study was not without flaws, the investigators should be commended for their accomplishments. One of the most exciting aspects of this trial is that it provides an example for future multinational Creutzfeldt-Jakob disease treatment trials. Despite this study failing to show a benefit, much was learned. More consideration of factors for optimisation of preclinical models could result in more promising therapeutic candidates. Furthermore, identification of drugs for treatment of Creutzfeldt-Jakob disease could have implications far beyond prion disease and perhaps for more common neurodegenerative proteinopathies, which have been shown to display prion-like properties and thus might respond to treatments for prion diseases.

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The development of robots to help with rehabilitation of paretic arms and legs after stroke is based on translational research. The exoskeleton robot ARMIn has seven actuated axes (ie, degrees of freedom), making it the most advanced commercially available robot offering antigravity support for a paretic arm. The efficient gears and sensors in the exoskeleton control the position and interaction force between robot and user, allowing patients with severe impairment to safely practise daily tasks and play games in a virtual environment.

In The Lancet Neurology, Verena Klamroth-Marganska and colleagues report findings from their multicentre, parallel-group randomised trial of the ARMIn robot in patients with moderate-to-severe arm paresis after a stroke and who had had motor impairment for more than 6 months.1-77 Eligible individuals were randomly assigned to receive 24 sessions (each lasting at least 45 min) of either robotic or conventional therapy. Patients assigned to robotic therapy had significantly greater increases in score on the arm section of the Fugl-Meyer assessment (FMA-UE) than did those assigned to conventional therapy (mean difference in score 0.78 points, 95% CI 0.03–1.53; p=0.041).1 Additionally, robotic therapy was shown to be safe. The investigators do acknowledge that the difference between the groups was small, which could well be a result of the minor flaws that are inherent in rehabilitation trials, such as increased enthusiasm for novel therapies in unmasked patients and therapists. Indeed, similar numbers of patients in both groups achieved the clinically meaningful change in FMA-UE score: 13 (34%) of the 38 patients assigned to robotic therapy and nine (26%) of the 35 assigned to conventional therapy included in analyses improved by at least 5 points.1

The results of this well done Swiss trial agree with the available evidence: training with an arm robot is safe2-4 and improves body functions, activities, and participation (ie, social functioning) equally as well as the same amount of conventional therapy offered by a therapist.2-4 Klamroth-Marganska and colleagues’ findings1 support previous findings suggesting that intensity of practice is associated with improvement in function, and that this important principle also applies to robotic therapy after stroke.2-3,8 Additionally, robots do not get tired, can generate more repetitions than can a therapist in the same time, offer accurate feedback about patients’ performance, and can be fun to use.

As would be expected, Klamroth-Marganska and colleagues’ proof-of-concept trial1 raises several questions for bioengineers and clinicians who design and test rehabilitation robots. First, little is known about what patients actually learn when showing improvement in motor performance after stroke. Longitudinal studies with intensive, repeated three-dimensional kinematics1-4 have shown that patients learn to adapt to, or compensate for, their motor deficits by using their trunk and affected arm muscles differently. However, the synergy-dependent intra-limb couplings (ie, functionally related, stereotyped patterns of muscle