ALS: ARE PRECLINICAL ANIMAL STUDIES PREDICTIVE AND NECESSARY FOR DRUG DEVELOPMENT?

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Amyotrophic lateral sclerosis (ALS) remains a dreadful disease with a relentless evolution leading to death in a median survival time of 3 to 4 years. Until now, no drug is able to stop this evolution. Only one drug, riluzole, proved to slow down the rate of evolution but this clinical effect remains modest. To find out a more active drug is mandatory for the patients.

However, during the process of selection of any compound, one of the major steps is the phase of preclinical animal studies. During this phase, it is claimed that it is possible to answer important questions as the mechanism of action, the pharmacokinetic, the active drug concentration etc…

In ALS, the major preclinical animal model remains the SOD1 transgenic rodent (mainly mice) model. This animal model was engineered after the identification of Cu/Zn SOD1 as the mutated protein in approximately 20% of familial amyotrophic lateral sclerosis (FALS) cases in the mid 1990's. This finding led to the generation of transgenic rodent models of autosomal dominant SOD1 FALS. Of the more than 100 mutations in humans, 3 (SOD1G85R, SOD1G37R, and SOD1G93A) have been extensively characterized in transgenic mouse models of ALS. In these mice, the mutant human protein is ubiquitously expressed (under control of the human or mouse SOD1 gene promoter) at levels several fold higher than the level of endogenous SOD1. Only one model, the transgenic mice with a G86R mutation in the mouse superoxide dismutase (SOD-1) gene, which corresponds to a mutation that has been observed in familial amyotrophic lateral sclerosis (ALS), has been developed and display progressive loss of motor function providing a valuable model of ALS with a normal level of endogenous SOD1. Through extensive studies of these mice models, we know that they develop a disease which broadly recapitulates the human disease. Some pathological features are very similar to the human disease, particularly the sporadic form, such as microgliosis and astrocytosis, but some neuropathological changes are not seen in ALS patients. It is the case for the vacuolar degeneration that is seen in at least some of the mice and which is not seen in ALS patients. The vacuolar or neuropril degeneration often reflects a dramatic ballooning of mitochondria. Recently it was observed in ALS cases a mislocalization of the TAR-DNA binding protein (TDP-43) from the nucleus to the cytoplasm of diseased motor neurons. It was also shown an association with intraneuronal ubiquitinated inclusions. Robertson et al., (Neurosci. Lett. 2007; 420: 128) investigated TDP-43 immunoreactivity in G93A, G37R and G85R and compared with labelling in one sporadic ALS case and two familial ALS cases carrying mutations in SOD1, A4T and I113T. They found that there is no mislocalization of TDP-43 to the cytoplasm in motor neurons of mutant SOD1 transgenic mice, nor association of TDP-43 with ubiquitinated inclusions, in contrast to what is observed in both FALS and SALS. This result raises the question of a different disease process of motor neuron degeneration in mutant SOD1 transgenic mice as compared to humans.

Even if we have strong reasons proposing the SOD1 mutated mice model as the most valuable model to analyze the disease processes at the moment, we have also strong reasons to modulate this assumption and to wait for further models, such as a transgenic TDP-43 rodent model. Another strong reason for modulating this assumption remains the major differences between anatomical pathways in rodent and in human, an important fact in view of the concomitant involvement of both upper and lower motor neurons in the human disease.

The most confusing results, which shed major interrogations to validate the SOD1 mutated mice model as a model for preclinical studies in the development of potential therapeutic targets, is the lack of correlation between the results of preclinical studies in rodents and the results of the clinical trials in humans for at least five different compounds.

Gabapentin, an antiglutamate drug with a pharmacological profile very close to riluzole, was shown by Gurney et al. (Ann. Neurol., 1996) to be active on survival in at least one G93A mice line (L) and not in another one (H). In humans, Miller et al., (Neurology, 2001) were unable to detect any positive effect on survival. However, in a meta-analysis of both the phase II and III trials, they observed a significant negative, harmful, effect of the drug. This negative effect was not detected in the preclinical model.

Topiramate, another antiglutamate drug, with also a pharmacological profile very close to riluzole, was tested in preclinical studies by Maragakis et al. (Neurosci. Lett., 2003). They concluded that the drug had no effect on survival in the D93A transgenic mice model of the Jackson Laboratory. In humans, Cudkowicz et al. (Neurology, 2003) observed at 800 mg/day during 12 months a significant negative, harmful, effect of the drug on the functional endpoint (MVIC) and no effect on survival. Once again this negative effect was not detected by the preclinical studies.

Three other drugs had similar discrepancies between preclinical and clinical studies: creatine, active on survival in D93A mice model (Klyvenyi et al., Nature med. 1999), a result not confirmed in human (Groeneveld GJ, et al. Ann Neurol 2003); Celecoxib, active on survival in D93A (Drachman et al., Ann. Neurol., 2002) but not active in huma n (Cudkowicz et al., Ann. Neurol., 2006); more recently, Copaxone active in preclinical models (Angelov et al., PNAS, 2003; Habisch et al., Exp. Neurol., 2007) has no detectable clinical efficacy in humans (Meininger et al., to be submitted).

In only one case, it was possible to be more or less predictable. Gurney et al. (Ann. Neurol., 1996), when using tocopherol in the D93A mice model, observed a delay in disease onset and no effect on survival. This absence of activity was confirmed by two trials in humans at low (Desnuelle et al., ALS J., 2001) and high doses (Graf et al., J. Neural. Transm., 2005).

Even if we need preclinical studies, it remains to be firmly demonstrated that the transgenic models are the most accurate and useful models, at least in ALS. Major improvements have also to be made to ensure a valuable translation between the models and humans. Without these prerequisite, it remains at the present time unacceptable to use these models as useful preclinical models in therapeutic research.