Ann Ist Super Sanità 2011 | Vol. 47, No. 1: 55-59
DOI: 10.4415/ANN_11_01_12

Need to improve clinical trials in rare neurodegenerative disorders

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Summary. Rare neurodegenerative diseases are fatal and no therapy is available to cure or slow down the progression of disease. We report possibly weaknesses in the management of clinical studies in these diseases, ranging from poor preclinical studies, difficulties in the recruitment of patients, delay in the onset of treatment because of lack in early disease-specific biomarkers, and suboptimal design of Phase II clinical trials. The adoption of innovative statistical approaches in early Phase II trials might improve the screening of drugs in rare neurodegenerative disorders, but this implicates efforts from clinical researchers, statisticians, and regulatory people to the development of new strategies that should maintain rigorous scientific integrity together with a more ethical approach to human experimentations.

Key words: clinical trials, neurodegenerative diseases.

Riassunto *(Necessità di migliorare le sperimentazioni cliniche nelle malattie neurodegenerative rare).* Le malattie neurodegenerative rare sono patologie ad esito infausto e gli interventi terapeutici per la loro cura o anche solo per rallentare il decorso clinico sono praticamente inesistenti. In questo articolo si riportano le possibili cause che rendono difficili la gestione degli studi clinici nelle patologie neuro degenerative rare: studi preclinici non sufficientemente robusti, difficoltà nel reclutare i pazienti, ritardo nell'inizio dei trattamenti per mancanza di biomarcatori specifici precoci e disegni sperimetali non ottimali negli studi clinici di Fase II. L'impiego di approcci statistici innovativi nei trial iniziali di Fase II potrebbe migliorare la selezione di farmaci efficaci per le malattie neurodegenerative rare, ma ciò richiede lo sforzo congiunto dei ricercatori clinici, degli statistici e dei responsabili delle agenzie regolatorie, al fine di sviluppare nuove strategie che da una parte mantengano l'integrità del rigore scientifico e dall'altra adottino un approccio sempre più etico alle sperimentazioni nell'uomo.

Parole chiave: sperimentazione clinica, malattie neurodegenerative.

INTRODUCTION

Rare neurodegenerative disorders, such as amyotrophic lateral sclerosis (ALS), Huntington disease (HD), and transmissible spongiform encephalopathy (TSE) or prion diseases, have a fatal outcome within months (TSE) or years (ALS, HD) from clinical onset without any real possibility of treatment. Patients and their relatives are soon well aware that there is virtually no hope for stopping the progression of disease and are therefore desperately looking for any possible, though labile, hope that research might offer them. Patient's associations are very active in sustain the need of patients and their families, in pressing the public opinion to help and devote resources for patients with rare diseases, and in recent years to harvest important amount of money for funding research aimed to improve the life of patients and their families. In doing that, however, they run the risk to over-push patients and their families to look for alternative therapies every time that basic researchers present preliminary data on the effect of novel compounds on often questionable experimental disease models. In this respect patients are often quickly moving from one therapy to another with the hope to find a labile possibility to survive the disease. While this is understandable for the single person with untreatable diseases, it is not useful for the community of patients because it reduces the number of patients enrolled in each study and further delays the recognition of therapeutic substance that might give small, but sometimes significant improvement in the survival and possibly quality of life of patients with such devastating diseases.

The traditional drug development is an orderly process where each stage builds upon the information obtained in the previous stage(s): from preclinical studies (to test toxicity, dose levels, and, with the recent development of disease-specific animal models, efficacy of novel compounds) to Phase I trials (to assess safety and pharmacokinetic in man), to Phase II trials (to define biological activity, optimal dose and regimen, magnitude of any treatment effect and evaluate endpoint for subsequent Phase III trial) and finally Phase III trials (to provide substan-

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tial evidence of efficacy and safety). Data from each of the previous steps is crucial to optimal design of pivotal Phase III studies.

It is however distressing that only about 8% of compounds tested for neurological disorders between 1991 and 2000 from first-in-man clinical studies reached drug registration. Analysis of causes of high failure rates indicated that i) animal models do not appear to be predictive of efficacy; ii) efficacy endpoints are often subjective and highly variable; and iii) trials are affected by high attrition rates [1]. In rare neurodegenerative diseases, the success of clinical research is even lower than that reported for other neurological disorders. In prion diseases, no drugs are still available and the only positive results for the treatment of ALS comes from the double-blind, placebo-controlled trial of the anti-glutamate agent riluzole [2], which showed only 2-3 months delay in the survival of treated patients [3]. Despite initial positive results in preclinical and early clinical studies, clinical trials with all potential therapeutic agents have, for several reasons, failed to show robust therapeutic effects in ALS. This lack of benefit might reflect inappropriate approaches to treatment or the use of invalid or flawed trial designs [4].

There are several points of weakness in the nowadays management of clinical studies in the rare neurodegenerative diseases, which are discussed in this short review.

Preclinical studies

Animal models for testing possible therapeutics in neurodegenerative disorders are scanty, except maybe for prion diseases, and pre-clinical data obtained with these experimental models are often of limited value for their translations into clinical practice or over-interpreted by researchers, media, and often by association of patients that, with the reasonable intention to promote knowledge among their affiliates, run the risk to give false hopes to patients and their families.

In prion diseases, decades of experimental work have produced excellent models in non-human primates, small ruminants, felines, and a variety of wild type and transgenic (tg) rodents. In these laboratory animals, the disease is induced after incubation periods of months or years, depending on the models, after the injection of tissue preparation containing prion infectivity [5]. The long incubation period mimics that observed in variant Creutzfeldt-Jakob diseases (CJD) where patients acquire the disease either by the oral route through food contaminated with the bovine spongiform encephalopathy (BSE) agent [6, 7] or by blood transfusion (as occurred in four recognized human-to-human transmission of disease) [8], or iatrogenic CJD, where patients get infected through medical (cadaveric human pituitary hormones) or surgical (implants of cadaveric dura mater, corneal transplantation, etc.) procedures [9]. The weakness of prion models, however, is that both wild type and tg humanized mice expressing polymorphisms or mutations of the prion protein (PrP) gene *(PRNP)* do not develop any spontaneous prion diseases (as likely occurs in sporadic or genetic CJDs) and therefore are not comparable to what occurs in humans [10]. Tg humanized mice, however, are more susceptible to disease than wild-type mice when injected with brain tissues from sporadic or genetic CJD patients [10, 11] suggesting a possible role of unidentified exogenous factors in the development of disease.

In other neurodegenerative diseases, animal models are almost exclusively based upon damaging particular brain areas with specific chemicals (as in models for HD, PD, and Alzheimer disease) or, in more recent years, on the development of tg mice carrying one or more mutations in genes that have been correlated with the genetic forms of diseases [12].

Though these models are of great importance for understanding specific pathogenic pathway of disease, their use to predict the efficacy of therapeutics have been relatively poor with some exceptions. Jucker [12] and van der Worp [13] have recently outlined pros and contras in the use of preclinical studies to predict the outcome of a therapy. The major pitfalls in preclinical studies are the over-interpretation of results, often based on badly designed studies (*e.g.*, no randomization, disparity in gender or genetic background, no blinded evaluation, poor sample size), the overestimation of available animal models, which often do not reflect the full complexity of diseases in man, and the misinterpretation of experimental treatment, which often is started before the development of clinical signs, a condition that is unlikely to occur in most neurodegenerative disorders where preclinical biomarkers are unavailable or poorly predictive. These biases lead to major overstatement of efficacy that might result in the failure of clinical trials. A correct use of animal models and a proper interpretation of results would improve this trend.

Recruitment of patients

The recruitment of patients is a difficult task in rare neurodegenerative diseases because of the paucity of available patients who fulfilled the sometimes stringent criteria of selection, the quite heterogeneity of clinical presentation, and finally because patients or their families are in continuous search for better and more promising treatments. In ALS, for example, it has been estimated that only about 8% of patients were enrolled in clinical trials and even worst figures are available in patients with prion diseases (quinacrine trial) [14]. Thus, understanding the barriers responsible for the participation and retention of patients with rare diseases in studies and then eliminating these limiting factors is of paramount importance. In trials conducted by the Northeast ALS Consortium (NEALS), particularly in those of long duration or associated to significant toxicity, the dropout rate was high mostly because of

patient's choice for an early discontinuation, rather than for adverse events, disease progression, or difficulty in travelling to the clinical centre [15].

The only published clinical trial in prion disease (the PRION-1 study [14] where the patient or his family had the possibility to choose among three options − no treatment, experimental treatment and being randomized − showed that one patient opted for being randomized and 70% of them for receiving no treatment.

Delay of treatment

One of the greatest problem in treating neurodegenerative disorders is that a relatively confident diagnosis is usually made several weeks or months after clinical onset, often because of poor specific biomarkers of disease. Delay in therapy is often fatal to any hope of success and make most beneficial effects found in experimental models where animals have been treated before clinical onset or at very early stage of disease probably useless. Moreover, to improve efficiency, clinical trials often require a "lead-in" period before patients are randomised to the experimental drug or placebo further delaying the beginning of intervention [16]. The development of disease-specific early biomarkers will anticipate any therapeutic attempts and likely increase the success of trials.

Trial designs

In recent years, the design of trials in neurodegenerative disorders, such as ALS, has been disputed and it has been suggested that the design of such trials might in part be responsible of their failure [17, 18]. A more efficient approach to early phase clinical trials is needed to accelerate the identification of useful agents for rare neurodegenerative disorders. Focused, early Phase II studies defining dosage, pharmacodynamics, and drug interactions will likely improve the likelihood of success for Phase III trials [15, 19]. The ultimate purpose of Phase II screening trial is to inform decision about whether and how to proceed to Phase III, rather than providing definitive efficacy data on the experimental treatment [20].

In this respect, *non-superiority trial designs* (or *futility studies*) are mainly focused to test whether a novel drug is worth bringing forward to Phase III in a relatively short period of time and small number of patients. Futility designs remain within the testing hypothesis framework and have recently been employed in PD, Huntington's disease, and ALS primarily to eliminate drugs that are not worthy of proceeding to Phase III trials. Futility designs are especially useful when there are several candidate compounds to test and limited resources, as in case of rare neurodegenerative disorders (they should however assure appropriate sample sizes to guard against type 2 errors). The critical point of these studies is the *a priori* definition of what is futile: a large definition of superiority (> 30-40%) would quickly pick up likely high effective compounds but, on the other hand, would discard drugs that might have low effect in a field, such as rare neurodegenerative disorders, where there is no therapy at all or the available therapy is extremely limited (*e.g.*, riluzole, the only authorized drug for ALS, only prolongs survival of about 2-3 months) [3].

The use of historical controls rather than placebo treated patients may represent a strategy particularly relevant to neurodegenerative diseases where the delay of any potential therapy, even only for a few weeks or months, results in a permanent loss of vital functions. However, studies involving historical controls may distort the outcome of the trial by introducing possible biases. For example, the placebo effect on the control arm of the study would be missed giving a false positive efficacy of the experimental treatment. To avoid this possible bias, the NEALS group has initiated in 2003 a program to store all placebo data in a control database at the National Institute of Neurological Disorders and Stroke (NINDS) [21]. Observed differences between control arms of various trials may be due to eligibility criteria, variations in the methods to define time from onset or time from diagnosis, or geographical and temporal trends. Thus, thought the use of historical controls might contribute to increase the recruitment of patients and decrease the number of early discontinuations because patients would rightly feel more reassured by this type of study, the inclusion of a placebo arm remains the gold standard. In some cases, using a small concurrent randomized placebo control group may be a valid compromise to detect any major deviations in the assumption of the validity of the historical controls to avoid biases in favour of the intervention under study.

Selection paradigm design is another proposed randomized, parallel-group, and multi-arm Phase II trial for rare neurodegenerative disorders [20]. This study would simultaneously compare two or more compounds with the aim to select the best one to move forwards to Phase III trial. In this context, the "winner" drug is that given to the group of patients where the best response was observed. In other words, selection design studies provide ranking candidate agents with a relatively small sample size. Moreover, recruitment and retention of patients are facilitated because each subject would receive an active agent during the trial. The disadvantage of these studies is that it provides little information about the potential efficacy of the selected "winner" agent. Moreover the "looser" drugs would not necessarily be ineffective. In ALS, selection paradigm studies have been already used and the "winner" drugs further investigated by futility analysis, either in comparison with placebo [22] or with historical controls [23].

Recently, the need to use historical controls for phase II studies in rare neurodegenerative disorders has encouraged the use of a *Bayesian approach* to decide whether drugs with proved efficacy in pre-

clinical experiments would have therapeutic effect in patients [24]. The Bayesian approach to decision-making considers the *prior* probability that a drug will be effective and then, depending upon the clinical data produced during the trial, the *prior* belief might be modified, following defined models, in new belief, *i.e.*, the *posterior* probability. The formalization of the decision-making process is advantageous when decisions to test novel therapeutic compounds need be made when there is still limited information. The adoption of Bayesian methodologies, however, requires specific and advanced statistical knowledge − still uncommon in the trial community − and a novel theoretical approach to inferential reasoning that are not yet well accepted (or maybe fully understood) by most scientists in the field of clinical trials.

The multi-stage adaptive designs (also called adaptive seamless trial designs) are becoming used in trials of rare neurodegenerative disorders [25]. The aim of these approaches is to address within a single trial both the learning (Phase IIb) and the confirmatory (Phase III) stages through "adaptive" modifications of trial procedures (eligibility criteria, dose and duration of treatment, study endpoints, laboratory testing procedures, diagnostic procedures, criteria for evaluation and assessment of clinical responses), statistical procedures (randomization, study design, study hypothesis, sample size, data monitoring and interim analysis, statistical analysis plan and/or methods for data analysis), or both, during the conduct of the study. The modifications and adaptations to the trial need to be pre-planned and based on the data collected during the study and should be accomplished without spoiling the validity and integrity of the trial [26, 27]. Compared with more traditional trial designs, adaptive approaches require more work and additional effort during planning, implementation, execution, and reporting [28].

A trial design, which might be particularly interesting for patients and bioethicians, is the response adaptive randomization design, where "adaptation" is implemented by modifying the treatment assignment ratio (*i.e.*, the ratio of the number of patients between the treatment group and the placebo group) according to the observed outcomes of the ongoing study [29, 30]. In these studies, the probability that a patient is randomly assigned to the most promising treatment constantly increases during the trial. The goal is to minimize expected treatment failures (worst response) while preserving statistical power and randomization. This design seems particularly useful for the very rare (about 1-2 cases per million people per year) prion diseases with a short clinical duration (usually about 6 months) and an inevitably fatal outcome [31]. The reluctance of patients to be randomized in classical placebo-controlled trials would likely be reduced by adopting the adaptive randomization rules where the probability of receiving placebo is less than that of being treated with a likely active anti-prion substance. It is likely that by adopting this design patients and their families will likely be more favourable to accept randomization so that these studies would fulfil blinding and random allocation together with a more ethical approach to human experimentation.

CONCLUSIONS

Taking a drug from "bench-to-bedside" is a complex and expensive process. New initiatives are necessary to improve preclinical studies and optimize Phase II clinical trials in rare neurodegenerative disorders where the number of patients is limited and there is the need to minimize resources on drugs that might fail during later stages of development. Statistical modifications in early Phase II trials can also help the screening of drugs more efficiently and with more humanity [32]. Finally, we have to learn about the current use and future directions of adaptive trial designs in drug development, and learn about prior successes and failures in the use of these designs [33].

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

Submitted on invitation.
Accepted on 20 September 2010.

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