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Drugs and clinical trials in neurodegenerative diseases

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Summary. Neurodegenerative diseases are disabling conditions continuously increasing due to aging of population. A disease modifying therapy that slows or stops disease progression is therefore a major unmet medical need. Unfortunately, research for effective treatments is hampered by lack of knowledge on the pathologic processes underpinning these diseases and of reliable biomarkers. Clinical trials are difficult, as they require large populations that need to be followed for very long periods to capture possible effects on disease progression. These difficulties produce frequent failures and waste of human and economic resources. Since research has to continue in this area, until comprehensive knowledge of basic pathologic processes is obtained, alternative study designs can be considered to identify disease modifiers and to reduce costs of clinical studies.

Key words: neurodegenerative diseases, disease modifier, delayed start design, randomized withdrawal design, futility study.

Riassunto *(Farmaci e studi clinici nelle malattie neurodegenerative)*. Le malattie neurodegenerative sono condizioni che conducono a disabilità, destinate ad aumentare a causa dell'invecchiamento della popolazione. Per tale motivo, una terapia in grado di alterare il corso della malattia *(disease modifier)* costituisce una necessità primaria. Sfortunatamente la ricerca di trattamenti efficaci è resa difficoltosa a causa della mancata conoscenza dei processi patologici alla base di queste condizioni e di *biomarkers* di malattia. Gli studi clinici sono difficili in quanto necessitano di grandi popolazioni che devono essere seguite per lunghi periodi di tempo in modo da indentificare potenziali effetti sulla progressione della malattia. Questo è causa di frequenti fallimenti e spreco di risorse umane ed economiche. Dal momento in cui la ricerca in questo ambito deve continuare, fino a che non si sia ottenuta una esaustiva conoscenza dei processi patologici di base, si potrebbero prendere in considerazione studi clinici con disegni alternativi per individuare farmaci *disease modifier* e per ridurre i costi.

Parole chiave: malattie neurodegenerative, *disease modifier, delayed start design, randomized withdrawal design*, studio di futilità.

INTRODUCTION

Neurodegenerative diseases such as Parkinson's disease (PD) and dementia of Alzheimer type (AD) are conditions whose incidence increases with age thus, in the near future they will cause a significant burden on the populations that, like ours, are aging. Neurodegenerative diseases represent a scientific challenge as for most of them aetiology and pathogenesis are not known. Developing effective treatments for conditions whose causes are still unclear is a difficult but necessary task. Clinical trials for neurodegenerative diseases require great number of patients to be followed for very long time, making those studies very difficult to be carried forward and causing inflation of the costs. Moreover, the rate of success is very low so that only few symptomatic treatments are available, whereas therapeutic agents able to affect disease progression have not been developed until now. Since research must progress, while awaiting that the processes underpinning neurodegeneration are revealed, alternative study designs may prove to be useful to detect disease modifying treatments.

TREATMENT OF NEURODEGENERATIVE DISEASES: AN UNMET NEED

In neurodegenerative diseases a progressive neural loss leads to a number of different clinical entities ranging from relatively common conditions, such as dementia of Alzheimer type or Parkinson's disease, to less frequent ones like amyotrophic lateral sclerosis (ALS), progressive spinal muscular atrophies or hereditary sensorymotor neuropathies. Despite many years of research and advancements in basic and clinical research, aetiology and pathogenesis of most of those conditions are still obscure. Dementia of Alzheimer type and Parkinson's disease are the most represented within the group in terms of prevalence

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and socio-economic burden. This is especially true for high-income countries with longer life expectancy, since PD and AD incidence increases with aging. Epidemiologic studies show that PD has an estimated prevalence between 65.6 (age under 65 years old) and 12 500 (age above 85 years old) per 100 000 and an estimated incidence between 5 (age under 65 years old) and 346 (age above 85 years old) per 100 000/year in Europe [1] and AD has an estimated incidence of ~ 300 to 5600 per 100 000/year in USA, significantly increasing with age groups (from 65-69 to 90+ year) [2]. Similar figures are found in Europe for AD with incidence of 240 to 7020 per 100 000/year [3].

AD and PD are very highly disabling conditions (AD is listed among the top 20 leading disabling conditions worldwide by WHO [4]) for the affected subjects but also have a strong impact on their caregivers and to the local health system. Parkinson's disease and AD can therefore be considered as paradigmatic of all neurodegenerative diseases.

Developing a medicinal product able to cure neurodegenerative diseases is such a huge commitment that long time and hard work are still required for its achievement. There are many open questions that need to be answered, such as identification of plausible drug candidates, of reliable animal models with good predictive value to establish neuroprotection, identification of sensitive clinical endpoints and measurement tools, validation of biomarkers and design and execution of trials *(Table 1)*. Discussing all those issues is out of the scope of this paper. Therefore, only some aspects will be addressed thereafter regarding the requirements of an effective treatment and on clinical trial designs.

SYMPTOMATIC TREATMENT *VS* DISEASE MODIFICATION

Long time has passed since in 1817 James Parkinson published his famous *An essay on the shaking palsy* [5], and since in the early 1900's Aloysius Alzheimer described both clinical presentation and histopathology of the condition that later was named after him. Nevertheless, to date no cure has been found for those conditions and for all remaining neurodegenerative diseases. Indeed, thus far only *symptomatic* treatments are available, *i.e.* treatments able to ameliorate symptoms of the disease without slowing or stopping its progression. Symptomatic drugs for the treatment of PD show an effect on the key motor features of the disease as they reduce or normalize rigidity, bradikinesia (slowing of movements) and tremor. A good effectiveness is obtained during the first months or years but afterwards, when progression ensues, drugs effect decreases and almost invariably long-term treatment complications appear making the quality of life of those patients very poor. Symptomatic treatment of mild or moderate AD has a mild efficacy in restoring memory and other cognitive functions. Unfortunately the effect is transient and the effect size quite unremarkable. For the other neurodegenerative diseases no specific treatments have been approved on the market so far, and as a result they are all undertreated. An exception is represented by ALS, for which riluzole (an anticonvulsant) has been demonstrated "to extend life or the time to mechanical ventilation for patients with amyotrophic lateral sclerosis". Clinical trials have demonstrated that riluzole extends survival for patients with ALS. The median survival time approached 16.5 months versus 13.5 months for riluzole 100 mg/day and placebo, respectively [6]. Although a 3-month survival difference was considered as statistically significant in this rapidly evolving disease, the clinical significance of this result is not impressive.

Another limitation of symptomatic drugs is that they often control only one symptom of diseases that often present multiple symptoms, reflecting degeneration of different neurotransmitter systems and different areas of the central nervous system. For instance, in PD – for which only dopaminergic drugs are available – not only dopamine producing cells of *substantia nigra pars compacta* die. Many signs and symptoms possibly result from loss of other cells and neurotransmitter systems [7] that are unresponsive to dopamine replacement therapy.

Complexity of neurodegenerative diseases causes them to be very difficult to treat, and it is clear that symptomatic treatment only is not sufficient. Therefore, a *disease modifying* treatment able to remarkably slow, or better to halt disease progression would be the goal. A disease modification process implies that a permanent effect on the underlying disease process should be demonstrated. *Neuroprotection*, *i.e.* a mechanism able to prevent pathological neural loss is part of the disease modifying process, and not synonym of it. Transient effects, such as those related to symptomatic drugs, are not consistent with a disease modification that instead should reflect permanent changes in the pathologic process.

Table 1 | *Neurodegenerative diseases: open questions*

Lack of knowledge of biology of neurodegenerative diseases
Unknown aetiology and pathophysiology
Diagnosis uncertain (especially in early stages)
Difficult selection of patients for clinical trials
Lack of reliable animal models
Lack of biomarkers
Diagnostic; predictive of progression; safety
Lack of candidate drugs
Need to improve clinical trials methodology
Study design (necessity of alternative designs)
Study population (degree of severity, subpopulations, etc.)
Duration
Sensitive measurement tools
Clinical endpoints of interest
Surrogate endpoints
Statistical analysis (slope analysis, survival analysis, missing data, drop-outs)

ALTERNATIVE TRIAL DESIGNS

To date, all attempts made to identify disease modifying agents have been unsuccessful. All the compounds that demonstrated promising effects in preclinical models did not replicate the same effects in humans. To further highlight the difficulties of research in this ground, it has to be noted that the rate of failure is also very high when developing symptomatic drugs. Another unresolved issue is the difficulty to distinguish between a symptomatic and a disease modifying effect. In 2008 the European Medicine Agency (EMA) released two guidelines for the development of medicinal products for PD and AD wherein indications to discriminate symptomatic effect from an effect on disease progression are given from a regulatory perspective [8, 9]. A disease modifying effect will be considered when the pharmacologic treatment delays the underlying pathological or pathophysiological disease processes and when this is accompanied by an improvement of clinical signs and symptoms. Consequently a true disease modifying effect cannot be established conclusively based on clinical outcome data alone, such a clinical effect must be accompanied by strong supportive evidence from a biomarker programme. The demonstration of clinical improvement alone will be sufficient for the claim of a symptomatic effect. These recommendations seem reasonable; however, since there are no validated biomarkers yet, the full claim of disease modifier is unlikely to be achieved soon based on these criteria.

With regard to the type of study to be used, there is no universal trial design specifically recommended. The usual placebo-controlled single-period studies – where patients are randomized to one or more dosages of active medication or to placebo, and changes in certain functional scales from baseline to last visit are compared between the groups – have great limits in distinguishing effects of study medication due to relief of symptoms from true effect on disease progression. For this reason, alternative designs have been proposed. Delayed start or randomized withdrawal designs are examples of the so called two-period designs, in which some or all patients switch treatment during the course of the study. In delayed start design (or staggered start design) subjects are randomized to active treatment followed by active treatment (A/A, early start group) vs placebo followed by active treatment (P/A, delayed start group) *(Figure 1)*. In the first period a group is on active treatment and the control on placebo; if a difference between groups is observed at the end of this period it is difficult to establish whether it is related to effects on symptoms, disease-modifying effects, or both. In the second period, both groups receive the active treatment. If at the end of this period constant differences between the two groups are detected the possibility of a disease-modifying effect could be argued. Similarly, in randomized withdrawal design subjects are randomised to active treatment followed by placebo (A/P), and in the other arm are randomized to placebo followed by placebo (P/P). Differences in period 1 should reflect total treatment effect and period 2 should estimate symptomatic and disease modifying components.

Nevertheless, several potential problems make these designs difficult to be applied (need for large sample size, requirement of long time of observation to capture disease modifying effects or to ensure that symptomatic effects disappear before switch of period, risks of unblinding due to treatment switch, etc.). Interpretation of results can also be puzzling.

A recent example of two-period design is the so called ADAGIO study [10]. The objective of the study was to test if rasagiline, an inhibitor of monoamine oxidase type B (MAO-B) had a disease modifying effect on motor impairment of PD over an observation period of 18 months. A delayed start design was applied, and three hierarchical end points had to be met. The trial was methodologically rigorous; the sample size large (1176 subjects randomized)

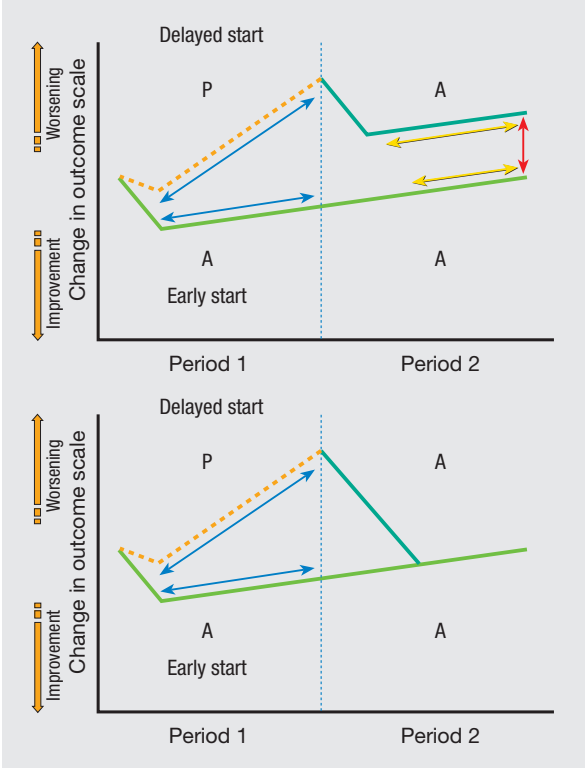

Fig. 1 | *Delayed start design. During Period 1, the early start group is on active treatment (A, solid green lines), while the delayed start group is on placebo (P, dashed orange lines). The blue arrows are not parallel, indicating efficacy of treatment with respect to placebo. At the end of this period it is not possible to establish if the effect is transient (symptomatic) or disease modifying. In Period 2, early start group keeps on active treatment and delayed start group is switched to active treatment. The yellow arrows are parallel, indicating that after the delayed start group takes the active treatment an effect is seen consistent with that one observed in the early start group. However a constant difference observed between the two groups at the end of Period 2 (upper panel, red arrow) may suggest a disease modifying effect of the treatment (differently from what shown in the lower panel where the two lines intersect).*

and the observation period of 18 months considered as adequate by regulatory bodies. The three primary endpoints were met so that a possible disease modifying effect for the study drug at the dose of 1 mg (but not 2 mg) was claimed. Nevertheless, it has to be noticed that at the end of the observation period only a difference of 1.68 points was detected for a main motor feature between study arms on the outcome scale (total UPDRS score) over a baseline total score of 20.6, corresponding to about 8% improvement with the study drug. In presence of a disease modifying agent, hopefully a more sound difference would have been expected after an 18-month period. Despite the positive result of the trial (in terms of statistical significance), the clinical relevance is still not fully convincing.

Another similar study assessing pramipexole (a dopamine-agonist drug) as possible disease modifier in PD, PROUD study, did not achieve positive results [11].

CUTTING THE COSTS: FUTILITY STUDIES

The invariable failure in the development of a breakthrough treatment for neurodegenerative diseases is frustrating and expensive. The large majority of the compounds that are in research, after a long and costly development process rarely reach registration. Of the 509 compounds listed in a paper by Myoung-Ok Kwon and Paul Herrling [12] that were under any stage of development until June 2006, no one has reached the market yet. It is very likely that all products that were in Phase II or III at that time have been dropped due to inefficacy. As a consequence all human and economic resources invested have been wasted. It is estimated that the expenditure for clinical trials necessary to bring a new drug to market is on average $ 1 billion [13, 14]. Pharmaceutical firms might be reluctant to invest in this field because of the high costs and risks of unsuccessful outcomes.

Recently, an innovative model of study design has been put forward [15, 16], the so called *adaptive design* that is thought might improve trials outcome and significantly reduce their costs. The originality consists in the fact that planned modifications of one or more specified aspects of the study design and hypotheses are allowed based on analysis of interim data. In this context, a pragmatic strategy would be to "kill" the therapeutic agents that during early clinical stages do not show promise before they enter more expensive phases in the development. Eliminating inefficacious drugs would improve the safety of patients due to reduced exposure to ineffective treatments, reduce the duration of the studies, and eventually significantly cut the costs. Nevertheless, deciding what is futile and what is not is crucial, the risk being that agents erroneously considered futile might be irreversibly discarded. Differently to the usual efficacy studies – that test the null hypothesis that treatments are equivalent and reject the null hypothesis if one treatment is likely to be more effective than the other – the so called *futility studies* are not efficacy studies but are instead designed to test if a treatment shows promise and will therefore produce results exceeding a meaningful threshold. The threshold is the key point of these studies. If the futility threshold is accurately set, the drugs overcoming that threshold can be considered as "non-futile drugs" and they should proceed to confirmatory trials while ineffective treatments should not be studied further. Futility studies have been successfully used in oncology research for years, but recently have been taken into consideration in the neurodegenerative area. They are Phase II studies usually comparing a single treated arm to a predefined threshold value representing a consistent clinical measure, over a reasonably short period of time.

Selection of the threshold is the key aspect for the sensibility of the trial as it may produce an erroneous discharge of potentially therapeutic compounds or, on the contrary, too many useless drugs further investigated with waste of resources. It can be selected upon best clinical judgement or consensus between experts, but normally it is derived from historical data (data from previous trials), or on estimated results from a control group, which may be included as a calibration arm in the trial. For example *(Figure 2)*, the primary outcome of a futility study in a neurodegenerative condition could be the reduction in the decline of a meaningful clinical parameter from baseline to the end of the observation period. Changes of a motor or a cognitive scale could be used in PD or AD respectively. The expected proportion of decline (Exp) is obtained from historical data from previous studies. The reduction of decline (Δ) considered as clinically meaningful is predetermined before the start of the study. The futility threshold is the difference between the expected proportion of decline and the predetermined accepted significant reduction of decline (Exp - Δ). If the observed decline is greater than the threshold the treatment should be considered futile. The reliability of historical data, in terms of homogeneity of the previously examined population in comparison the population selected for the "futility trial", are crucial. However, it is not always possible to have historical data of a population matched with that under investigation. On the other hand, the clinical characteristic of the population accounts for the degree of clinical decline historically observed, which may differ from the decline in a different population with different clinical characteristics. Therefore experts' opinion must be taken into account while deciding the threshold.

The futility design has been applied in the Neuroprotection Exploratory Trials in Parkinson's Disease study sponsored by the National Institute of Neurologic Disorders and Stroke (NINDS NET-PD study [17]), a 12-month randomized, double-blind, futility clinical trial of creatine and minocycline, in parallel, in early PD. A placebo group was also included

as calibration arm. The threshold for futility used was a 30% reduction in PD progression measured by total UPDRS score and was obtained from historical data of a previous large study on early PD, the DATATOP study [18]. Neither drug could be considered futile at the end of the study with creatine performing better than minocycline in affecting progression of disease. The authors suggest that further aspects will need to be explored before conclusively choosing these two drugs for Phase III studies, including safety, tolerability, activity, cost, and availability. However, the core aspect that has to be highlighted is that only 200 subjects were necessary to obtain sufficient evidences, while it is calculated that a usual Phase II study would have required 850 to 1080 patients.

DISCUSSION

If prevention is not possible, the best way to cure a disease is to identify its cause and possibly remove it. Unfortunately, for neurodegenerative disease we still seem far from this. Aetiology and pathophysiology of these conditions are complex and most likely multifactorial. As a consequence of this lack of knowledge, it is difficult to infer other factors necessary for the development of therapeutic agents such as clear diagnostic criteria to select homogeneous study population, reliable animal models, validation of biomarkers, and sensitive study designs. The result is that clinical trials for neurodegenerative diseases require very large population followed for long time with a consequent inflation of human and economic resources. Nonetheless, the rate of failure is very high.

In the research of therapeutic agents for neurodegenerative diseases, a distinction between symptomatic and disease modifying activity is necessary. Symptomatic agents affect symptoms without altering disease progression; on the contrary, disease modifiers should halt or significantly slow neurodegeneration. Finding a disease modifier would be a better achievement; nevertheless distinction of a symptomatic vs. disease modifying effect can be puzzling and somehow arbitrary. For the time being, the indications given by the EMA, appear reasonable. A disease modifying effect can be claimed when the treatmentt delays the underlying pathological or pathophysiological disease processes and when this is accompanied by an improvement of clinical signs and symptoms. Since the clinical outcome data alone are not sufficient, such a clinical effect must be accompanied by strong supportive evidence from a biomarker programme. One limitation of this definition is that there are no validated biomarkers available to date, and developing a biomarker programme along with the development of a drug can be too demanding.

With regard to the study designs to be used, recently some innovative models have been proposed that show promise in unveiling compounds that alter the course of neurodegenerative diseases. Differently from the usual placebo-controlled single-period studies, in delayed start or randomised withdrawal designs patients switch treatment during a two-period study (from active treatment to placebo, or *vice versa*). Analysis of slopes and differences at the end of the periods may discriminate if the progression of the disease has been altered. A large delayed start study has been done studying the effects of rasagiline on disease progression in early PD patients. The outcome was in favour of a disease modifying action of the study drug, although the clinical relevance was not extremely notable. A similar study testing the effects of pramipexole, a dopamine-agonist, on PD progression on the contrary gave negative results. Maybe we are not in front of convincing data yet, however the studies performed helped to increase the sensitivity of the test that will be hopefully better applied in future trials.

Another major issue in drug development is represented by the increasing costs in front of very high rates of failure. Considering that million dollars are

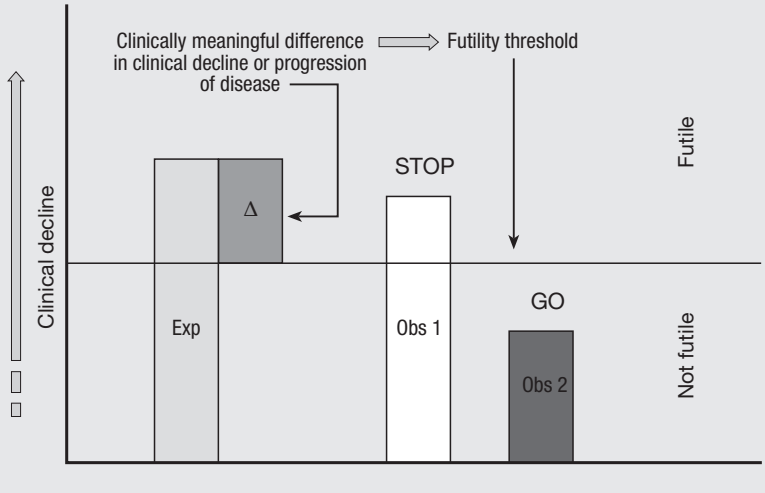

Fig. 2 | *Futility study. Two preliminary data are required before the start of the study; the expected proportion of decline (Exp) obtained from historical data, and a predetermined accepted reduction of decline (Δ) considered as clinically meaningful by the investigators. The futility threshold is the difference between Exp - Δ. If the observed decline (Obs 1) is greater than the threshold, the treatment should be considered futile and discarded. If the observed decline is below the futility threshold (Obs 2), the treatment should be considered for confirmatory studies.*

necessary to bring a drug on the market, trying to reduce costs would encourage pharmaceutical industries to invest more in this field. Since clinical trials in humans account for most of the expenses, a valuable strategy would be to select the promising therapeutic agents and reject all those that do not show potential efficacy. Futility studies, although relatively new in the neurodegenerative arena, seem to be a good tool to select drugs that deserve to go through the confirmatory phases of development. Another great advantage of futility studies is that they need much less subjects to be enrolled as compared to classical Phase II studies, thus improving global safety by reducing exposure of patient to possible inefficacious drugs.

The possible shortcomings of futility studies originate from their most remarkable benefits. For instance, reducing sample size and duration as compared to a usual Phase II study may cause feeble but significant safety signals not to be detected. Moreover, given the slow degenerative process underlying neurodegenerative diseases, effects of drugs with delayed effects might not be noticed. Finally, setting an appropriate futility threshold is not always a simple exercise in absence of reliable historical data.

CONCLUSIONS

A disease modifying therapy that slows or stops disease progression is the major unmet medical need in neurodegenerative diseases. Although aetiology and pathogenesis of such disorders are not fully elucidated, attempts to develop treatments able to affect disease progression must continue.

In the setting of human clinical trials, use of innovative study designs such as the delayed start and randomised withdrawal designs could help disentangle between symptomatic and disease modifying effects of a therapeutic agent. Futility studies represent another viable strategy to foster research in the neurodegenerative field by cutting the costs of drug development programs.

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.

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