Reducing the number of patients needed in disease modifying trials for parkinsonian disorders.

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Planning and improving the design of trials to evaluate the potential of candidate disease modifying interventions for Parkinson's (PD) and related disorders, is perhaps just as important as being able to select the right drug. We have yet to prove that any intervention has a meaningful impact on the rate of PD progression.

The perfect design also has to be pragmatic. Large numbers of patients followed up for many years would certainly be the optimal way of confidently reporting whether a drug was disease modifying or not, but with limited financial and patient resources we must allocate these resources across a range of different putative interventions to maximise chances of identifying agents with meaningful beneficial effects. Furthermore, patient motivation to participate in these types of trials is greatly reduced if there's a high likelihood of being allocated a placebo intervention for many years.

There are two papers in this issue of Brain which have both explored means of reducing the sample size required to detect beneficial effects of a disease modifying intervention. The first by Joza et al. [1] explored how many people would be required if recruitment targeted those at the very earliest stages of the neurodegenerative process by studying the natural history of a population meeting Movement Disorder Society criteria for prodromal "synucleinopathy" (i.e. idiopathic REM sleep behaviour disorder and sufficient additional risk markers to meet the threshold of >80% certainty for prodromal PD) [2]. It is well documented that polysomnography confirmed REM sleep disorder is a major risk factor for neurodegeneration with >75% of those affected ultimately developing PD, multiple system atrophy (MSA) or dementia with Lewy bodies (DLB), all characterised by alpha synuclein pathology. For the purposes of this longitudinal evaluation, the team combined progression outcomes irrespective of whether an individual deteriorated in terms of motor or cognitive manifestations (i.e. towards PD or DLB).

This may sound a bit like combining apples with pears, but in fact aligns with a recent shift in thinking based on confirmation of the sensitivity and specificity of the alpha synuclein seed amplification assay as an objective means of quantifying the initiation of the pathological process of synuclein associated neurodegeneration[3]. Building on this, a newly proposed staging system proposes that PD and DLB can be essentially considered as the same pathophysiological process, but involving different brain regions hence causing a different motor/ cognitive phenotype [4].

Joza et al. found that the best way of measuring progression towards an ultimate diagnosis of PD, is to track the motor signs of the disease ,i.e. the MDS UPDRS part 3 scores, whereas the best way to measure progression to "any Lewy body alpha synucleinopathy" is instead to measure a composite of both motor and cognitive scores. This may not be a surprise, but

the data can be used to calculate the sample sizes required for trials of putative disease modifying interventions to prevent progression of "Lewy body alpha synucleinopathy" from its very first stages, conceptually a different approach than attempting to delay progression of either established PD or DLB alone.

Supporting this shift in thinking is also the fact that fairly similar motor and autonomic trajectories were observed among patients irrespective of whether they ultimately converted to a PD or DLB phenotype. It begs the question regarding why such different motor or cognitive presentations emerge, perhaps due to different environmental exposures / routes of exposure triggering the process, the role of epistatic / genetic factors, or even reflecting coexisting amyloid or tau co-pathologies. Despite this and other uncertainties, the good news is that a two-year trial featuring 117 people per arm with a composite outcome of motor and cognitive progression (i.e., without necessarily progressing to overt PD or DLB) is an entirely feasible sample size.

The second paper by Street et al.[5] also reports a natural history study, not in PD patients but among people with atypical parkinsonism participating in the PROSPECT study and looked at the relative merits of measuring progression using the traditional clinical scales in comparison to structural neuroimaging, as a means of reducing the necessary sample sizes for trials. This study recruited patients with MSA, progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS) and carefully phenotyped them into subgroups to explore progression rates with longitudinal follow up.

In this report, in contrast to the prodromal cohort, the phenotyping detail becomes particularly important, but nevertheless common themes emerged across these different atypical parkinsonism groups. While the standard clinical scales evaluating motor severity (PSPRS, UMSARS etc) were quite good at measuring progression within the phenotypic subgroups, the use of volumetric structural MRI, e.g. pontine measurements for MSA and ventricular measurements for PSP, reduced the necessary sample sizes for disease modifying trials to less than fifty participants for a 2 arm, 1 year trial of an intervention with an effect size of 50%.

Structural imaging is therefore confirmed as a valuable tool for measuring progression in patients with atypical parkinsonism whether MSA, PSP or CBS for clinical trial purposes. This is not yet proven to be the case currently for PD, although there is great interest in applying imaging modalities such as neuromelanin or free water MRI as a structural measure of progression particularly in early PD.[6]

Both papers therefore have immediate potential implications for future trial designs in this population suffering with ongoing or imminent neurodegeneration. Sample sizes required are feasible and can galvanise investigators into exploring the impact of a large number of candidate interventions. Of course, there are also other means of manipulating sample size calculations such as increasing the duration of follow up. However, in the prodromal cohort, while increasing the duration of follow up from 1 to 2 years had quite a major impact on sample size required, increasing the duration from 2 to 3 years had only a marginal additional benefit.

A problem that still needs to be better addressed is how to disentangle those patients with prodromal alpha synucleinopathy who eventually progress to a diagnosis of MSA. Although a small subgroup, these individuals clearly have a different pathology from PD/DLB (Glial cytoplasmic inclusions, rather than Lewy bodies) as well as a different rate of disease progression. Examining the precise kinetics of the alpha synuclein seed amplification assay should allow MSA at risk individuals to be distinguished for analysis or recruitment into separate clinical trials[7]. Additionally the routine application of additional wet biomarkers such as seed amplification assays for different tau isoforms[8] to further define the pathophysiological process(es) underway among at risk cohorts, in combination with structural neuroimaging, is an intuitive next step.

In addition to these approaches, it is vital to consider in trial design other aspects of disease heterogeneity and how this might relate to the intervention planned, e.g., tailoring a LRRK2 inhibitor to LRRK2 mutation carriers irrespective of phenotype[9], as well as planning methods to confirm that an intervention has in fact engaged with the proposed target. Of course, we also need to consider whether surrogate outcomes strongly predict meaningful clinical benefit as perceived by people with these diseases. Finally, the approach of testing one agent at a time is extremely inefficient. In this regard, the development of platform trials capable of assessing multiple agents simultaneously could vastly improve efficiency and accelerate the identification of useful disease modifying agents[10].

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