EDITORIAL

Evolving trial design in secondary progressive multiple sclerosis

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Multiple sclerosis (MS) is a progressive, disabling disorder of the brain and spinal cord that affects approximately 100,000 people in the UK and 2.5 million worldwide [101]. Most patients with MS experience two phases of the disease: early, relapsing–remitting MS (RRMS), due to episodes of generally reversible inflammation-mediated nerve damage (relapses) and late, secondary progressive MS (SPMS), which affects 60% of patients. This occurs after 10–15 years and causes accumulating and irreversible disability due to nerve degeneration. The destruction of the CNS results in progressive difficulties with walking, balance, vision, urinary control and cognition. Total societal costs are high, estimated to be up to GB£30,000/patient/year [1–3].

Over the last 20 years, a variety of increasingly powerful drugs have been tested and demonstrated to reduce relapse rate in RRMS by up to 70% [4]. Although rare but serious side effects have emerged, these compounds are now in clinical use. The use of MRI was important in their development and is discussed below.

However, unlike RRMS, there is no proven treatment for SPMS to slow, stop or even reverse its progression. Unsurprisingly, a number of drugs used in RRMS have been trialed in SPMS, but without success, presumably because of changing biology. Using the classical parallel arm control/active trial design, it can take >10 years from a Phase I trial inception to Phase III trial finish [5]. Over the last two decades, more than 4500 SPMS patients have completed major Phase III trials, with trial durations of 2–3 years. The overwhelming conclusion is that all these have been negative, with the few positive signals actually observed being due to coenrollment of a more transitional RRMS/SPMS population or a subscore of the primary outcome being positive. The current consensus therefore, is that SPMS is most likely to respond to a neuroprotective strategy, and indeed there are a number of promising candidate drugs to test. The clear challenge therefore is to test multiple drugs simultaneously, in a timely and efficient manner, whilst preserving trial integrity. This article will discuss pathology, outcome measurement, alternative trial design approaches to the problem and end with a worked example.

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Pathology

Central to MS is the repeated attack on the myelin (demyelination), a fatty sheath produced by the oligodendrocyte that surrounds the axon (the electrical cable). It is the damage to the axons (and neurons) that is generally felt to be the pathological correlate of progressive disability: early events that lead to later disability. Extrapolating this means that a successful neuroprotective approach in SPMS could potentially be useful in RRMS and *vice versa*. Animal models of MS suggest a variety of candidate pathways: sodium and calcium channel blockade

(e.g., phenytoin and amiloride), glutamate antagonists (e.g., riluzole), HMG-CoA reductase inhibitors (e.g., simvastatin) and cannabinoids [6].

Outcomes

Measuring a chronic disease such as SPMS is difficult: it is not fatal, so mortality cannot be used; it comes on 10–20 years after the onset of MS and then slowly progresses over the next two to three decades; by definition it affects numerous parts of the nervous system, at different times, differentially from person to person. The classical measurement tool is the extended disability status scale (EDSS) [7], introduced over 50 years ago, based largely on neurological examination (with some history) and scoring seven major domains. The scoring is complex, although as disease severity increases it is largely ambulatory. SPMS trials generally have entry criteria of 4.0–6.5, that is, walking >500 m to using bilateral assistance (e.g., a frame) to walk. EDSS has poor precision, fails to capture cognition well and is a nonlinear ordinal scale. Nonetheless, it is widely used and supported by the US FDA and other regulatory authorities. SPMS trials often use time to confirmed (3 or 6 months) EDSS progression as the primary outcome, rather than differences in mean change in EDSS. A variety of attempts have been made to replace it with alternative scoring methods such as The Multiple Sclerosis Functional Composite (MSFC) score, which comprises quantitative tests of walking, arm function and a simple cognitive task, with each component converted to a Z-score; or even one of the components of the MSFC, the timed 25-foot walk. Patient-reported outcomes, such as the MS Impact Scale-29 (MSIS29), which measures physical and psychological wellbeing over the previous 2 weeks, are sometimes used and can form part of iterative algorithms (item response theory). Yet, currently, the dominant final clinical outcome for SPMS remains the EDSS.

MRI was vital in the development of novel drugs in RRMS and potentially will have a similar pivotal role in SPMS trial design. In Phase II trials in RRMS, reduction in inflammatory activity, proxied by gadolinium-enhancing lesions or newly appearing T2-weighted lesions, has come to be a mandatory step in demonstrating potential efficacy before proceeding to the primary Phase III outcome, reduction in relapse rate. In SPMS, whilst there may be some effect on T2-lesion burden, the main MRI area of interest seems likely to be brain volume. There is an accelerated reduction in brain volume over time in SPMS, termed atrophy rate, which can be quantified by MRI. However, this is an evolving science, with fewer longitudinal data available to correlate change in SPMS brain volume with change in EDSS [8].

Trial design

As mentioned above, traditional parallel group 'fixed sample size' approaches to Phase III clinical trial design in MS can mean long study durations involving the participation of many hundreds, if not thousands, of patients. In recent years, this issue has also been faced in other therapeutic areas and in pharmaceuticals development in general, and there has been a drive to shorten the time to market of new therapies, saving both time and costs. From a trial design perspective, recently developed methodology for 'adaptive trial design' provides one way in which the above goal might be met. In the setting of a comparative evaluation of alternative treatment regimes, such designs allow treatment or dose selection amongst several competing experimental treatments at an interim analysis, together with formal evaluation of efficacy of selected experimental treatments with a control treatment in the same study. Effectively, this combines Phases II and III of the traditional drug-development process.

The setting of SPMS provides a number of challenges for the implementation of adaptive designs. In particular, much of the statistical methodology initially developed for this type of 'combined phases' design focused on settings where the treatment selection at the interim analysis is based on the final outcome. In the case of MS, the final outcome is clearly one based upon the EDSS, which will not change in the early/interim stage of a trial. MRI, however, has the capacity to show disease change earlier in the trial. Methodology has now been developed for this case, making adaptive designs potentially attractive [9–11]. When deciding on the choice of both the short-term (interim) and the long-term (final) outcomes for use in such an adaptive design, it is crucial that these end points must be sensitive to treatment changes. We have described how to approach the question of end point choice in an article published in 2011 [12].

Many of the other challenges associated with implementing an adaptive design arise precisely because of the flexibility of the methodology and are related to factors including: optimal recruitment rate, anticipated treatment effects, the number of available experimental treatments to be tested and the split of resources between the selection and confirmatory part of the trial [12]. In addition, the feasibility of using an adaptive design in SPMS has been demonstrated through consideration of a specific trial design, the outline of which is given in the worked example below. In simulations, sample size savings of up to 40% compared with traditional designs were found

to be possible.

Worked example

In order to design an adaptive clinical trial we must start by specifying certain characteristics of the proposed trial. Suppose five arms are to be included, initially with 70 patients/arm (four experimental treatments and a placebo group), with brain volume data measured at baseline and 18 months. Simulations were conducted to determine the sample size to give 90% power to detect a reduction in the proportion of EDSS progression at 3 years from 40 to 28% (based on the placebo arms of the North American and European studies of IFN-β-1b [13,14]), if this was accompanied by a 30% change relative to placebo on the 18-month MRI. The total trial cohort required would be approximately 1850, allowing for dropouts. This would effectively enable four Phase II trials to occur simultaneously and after adaptation, move seamlessly into Phase III with a final clinical end point.

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■ Website

101 Multiple Sclerosis International Federation. Atlas of Multiple Sclerosis database. www.atlasofms.org