Optimising MRI in Multiple Sclerosis Drug Development

Multiple Sclerosis (MS) is a devastating disease affecting approximately one million people worldwide and is the most frequent cause of disability in young adults, after car accidents. MS predominantly affects the white matter of the central nervous system. The key feature is autoimmune neuroinflammation leading to demyelination and neurodegeneration. MS exhibits an unpredictable and variable clinical course, making treatment challenging. The classical description of three dissimilar clinical courses of MS suggest three diverse forms: relapsing-remitting (RR) which is the most common course; secondary progressive (SP); and primary progressive (PP) MS. Regardless of phenotype, pharmacotherapy of MS is directed at relapse management, symptomatic treatment of specific symptoms, and disease-modifying therapy (DMT). MRI has several important roles in MS research. It is becoming an invaluable tool in early diagnosis of RRMS; it is the gold standard in the detection of anti-inflammatory effects of new chemical entities (NCE) in early clinical development, and t also serves as a surrogate measure in the assessment of axonal degeneration and remyelinisation. This review will summarize important design issues in proof of concept studies of RRMS with an emphasis on optimizing neuroimaging outcome measures designed to help speed clinical development of novel drugs and biologics.

The development of new products in MS face many inherent challenges including but not limited to: a) intra and inter- individual variability of disease biology; b) availability of partially effective licensed therapies which render long term placebo controlled clinical studies ethically questionable; c) lack of DMT naive subjects, particularly in North America and Western Europe, which increases the possibility of recruiting non-responders or subjects in more advanced stage of disease; d) difficulties in ensuring blinding of clinical assessments; e) increasing sample size requirements to detect progressively smaller therapeutic effects; f) insufficient trial duration to assess chronic effect; and g) and relatively high cost of drug development. When designing POC studies in MS it is best not to attempt to address too many questions but to focus on the most salient issues dealing with proof of principle/target engagement of the proposed agent and dosing information. Safety monitoring is always a primary consideration that should not only take into account adverse events stemming from the experimental agent but also whether the agent might have a negative effect on disease course. This can be monitored by assessing changes in relapse rate, level of disability (a more difficult outcome to monitor in phase II trials) or an increase in MRI activity.

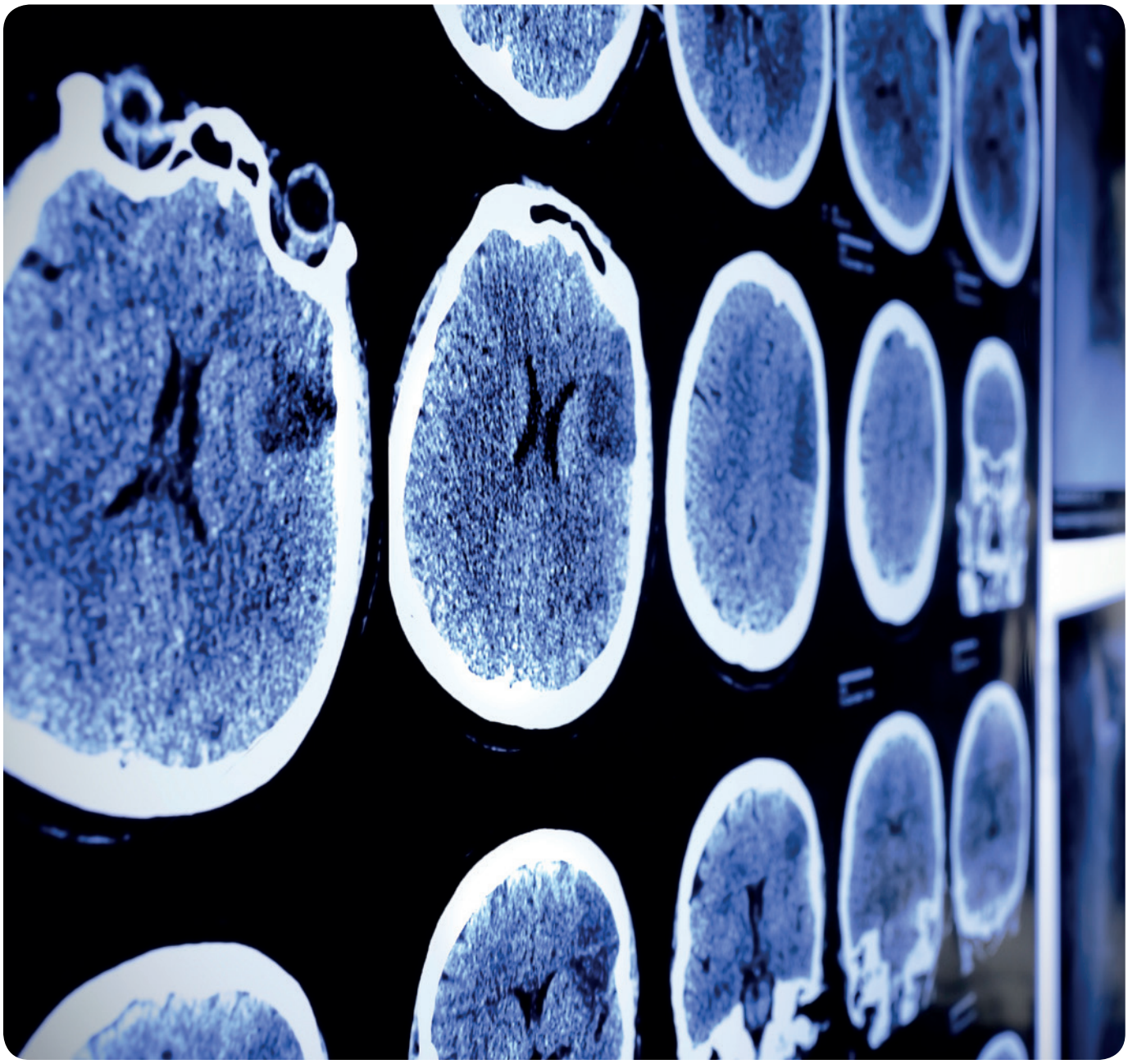
For RRMS studies these phase II trials are typically double blind placebo controlled, parallel designs involving multiple clinical sites. The primary efficacy endpoint is almost universally a relative reduction in brain MRI gadolinium enhancing T1 (Gd-T1) lesions in comparison with placebo. This is the optimal anti-inflammatory marker of NCE, and it serves as a proof-of concept for the forthcoming phase III where theprimary endpoint is always clinical. Gd-T1 lesions occur six to ten times as frequently as relapses and therefore provide greater power for detecting differences over shorter periods of time. Of note, POC trials in MS can be completed in relatively short time periods of approximately six months. The number of Combined Unique Active Lesions (CUALs), defined as new gadolinium-enhancing T1-weighted lesions and new/enlarging T2-weighted lesions without double counting has been shown to be one of the most sensitive MRI outcome measures, and even when not used as a primary efficacy variable this outcome should always be determined. As repeated (monthly) MRI scans should be performed during these trials, all possible actions should be taken to ensure high quality MRI data and maximum reliability of measurements. Updated recommendations on appropriate technical facilities and standardized procedures and training should be surveyed rigorously and reading of the images should be conducted centrally in a blinded manner.

Enrichment of the study population by enrolling only MRI active patients enhances the power of these POC studies and reduces the number of patients required. A relatively short screening phase (up to two weeks) in subjects with active RRMS (where active is defined as at least one clinical relapse within one year, or presence of at least one Gd-T1 lesion within six months) is also useful in selecting appropriate subjects as these subjects usually have two to three Gd-T1 positive lesions on average, although some may be Gd-T1 lesion free at baseline.

For most novel drugs patients should have MRIs conducted on a monthly basis following baseline, but when the full effect of the drug is delayed, patients can be evaluated from the third month onward. In all cases the primary endpoint is typically the cumulative total number of enhancing lesions on all post Gd-T1 weighted MRI images from monthly scans performed from months three to endpoint (month six). Other endpoints related to MRI disease activity can be selected as primary or secondary endpoints include but are not limited to: a) number of newly enhancing lesions; b) the total volume of enhancing lesions; c) the number of new T2 weighted lesions; d) the number of T2 weighted lesions; e) the total volume of T2 weighted lesions f) the number and volume of T1 weighted hypointense lesions; and g) measures of brain atrophy such as the thalamic atrophy or an increase in lateral ventricle volume. Of note, the use of CUAL or Gd-T1 lesions outcome measures appear to be best suited to drugs that have anti-inflammatory properties. In this

case, 60 patients per group would be sufficient over six months to detect a 50 % difference with 90 % power and a type one error =0.05 based on the assumption of 2.8 ± 3.7 new Gd enhancing T1 weighted lesions1.

There are also many new agents in development, focused not only on neuroinflammation but also on neurodegeneration and reparation, and it is essential that clinical trial designs are tailored to the pharmacological characteristics of the drug, the purported mechanism of action and clinical expectations. For example, agents that do not have anti-inflammatory properties may be better suited to outcome measures that reflect a clinical change, such as relapse rate, or outcomes related to tissue damage (atrophy) or tissue repair or remyelination such as those provided by Magnetisation Transfer Ratio (MTR) or Diffusion Weighted Imagining (DWI). Specifically, for a treatment that hypothesizes a 50 % decrease in rate of atrophy in subjects with RRMS over the course of a six month study (assuming 80 % power, a 5 % drop out rate, and type one error = 0.05) approximately 283 patients per treatment arm are required when no enrichment selection criterion are applied, and 185 per treatment arm when patients are required if enriched on a high T2 lesion load at baseline. For a 70 % decrease in rate of atrophy, 144 patients per treatment arm are required in an unselected cohort and 94 per arm in a preselected cohort2. MTR is a sensitive imaging technique used to quantify the integrity of myelinated white matter in patients with MS. If a lesional MTR recovery post-enhancement is used as primary outcome measure, power calculations suggest that for a power of 80 %, approximately 136 patients per trial (with a mean number of 6 lesions per patient) are required to detect a 30 % increase in lesional MTR post-enhancement compared with placebo, whereas 48 subjects are required to detect a 50 % increase in lesional MTR compared with placebo3



Regardless of the imaging technique utilized and the choice of the imaging primary efficacy variable there are important secondary outcome measures related to relapse rate and disability that should always be addressed even in shorter duration POC study designs. These endpoints include: the number of relapses, relapse rate, time to first relapse, number of relapse-free patients and number of patients with a predefined interval EDSS progression (usually EDSS score ≥ 1), or some variation/ subset of items from the Multiple Sclerosis Functional Composite (MSFC) scores.

Given that physicians have successfully used DMTs for the treatment of MS over many years and that many of these agents like the interferons and glatiramer have favourable safety and efficacy profiles, these agents are have become attractive candidates for companies focused on biosimilar development. A biosimilar is a biological product that has been approved based on showing that it is highly similar to an approved (reference) biological product, and has no clinically meaningful differences in terms of safety and effectiveness from that reference product. Only minor differences in clinically inactive components are permissible in biosimilar products. Although gaining in popularity there is very little guidance on biosimilar development in MS. However, once such guidance comes from the European Medicines Agency (EMA) regarding the development of biosimilar medicinal products containing interferon beta 1b4. For demonstrating clinical similarity of a biosimilar and reference product, this guidance suggests that MRI imaging of disease lesions in RRMS (CUAL or Gd-T1) may be sufficient and acceptable primary endpoints, if backed up by relapse-related clinical outcomes. No formal equivalence testing is required for other clinical outcomes, which would be expected to show the same trend in effect as the MRI-based variables.

A typical biosimilar study design would entail a three-arm trial including a placebo arm for a short period of time (e.g. 4 months) sufficient to demonstrate superiority of both the biosimilar and reference products over placebo using an MRI endpoint. Patients in the placebo arm could be subsequently switched to the biosimilar product and the trial continued with the two active arms. An alternative design would be a three-arm trial with the reference product and two doses of the biosimilar product, for which differences in MRI and clinical outcomes are expected to be observed over 12 months. Should MRI not differentiate the two doses over time, interpretation of the results would be difficult as the assay sensitivity of the trial would be questionable4.

Guidance suggests that whatever the design, the duration of the trial should be sufficient to show comparable efficacy on MRI endpoints and provide relevant information on clinical outcomes, i.e. not less than 12 months4. The patient population sample should be a reference DMT naive, with confirmed diagnosis of relapsing-remitting MS (RRMS) and sufficient disease activity based on relapse frequency and/or MRI criteria to anticipate rapid changes in MRI. Finally, guidance suggests that the most sensitive patient population to detect differences between the biosimilar and reference products, should be selected and that this would be a homogeneous sample of patients with RRMS and sufficient disease activity based on relapse frequency and/or MRI criteria5. Specifically, male and females aged between 18-55 years, with diagnosis of RRMS based on McDonald revised criteria from 20105, with clinically or MRI active disease6, and clinical disability range within 0-5.5 expressed as EDSS (ambulant subjects) should be included. Specific exclusion criteria regarding patients who present with a progressive evolution defined as a sustained progression of disability evaluated by EDSS score in the year preceding the screening period can be beneficial as is the proscription of patients with relapse in the two months period preceding baseline. All criteria should be defined in order to anticipate rapid changes in MRI over shorter periods of time.

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