

Progressive MS Trials: Lessons Learned

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ABSTRACT

Up to very recently, no treatments had proved effective in progressive multiple sclerosis (MS). In 2016, four drugs, two tested in phase 3 and two in phase 2 trials, showed a beneficial effect in primary or secondary progressive MS. Although this could indicate a turning point in progressive MS treatment, most of these successes have been modest and mainly restricted to patients with active inflammation, in the context of trials with powerful anti-inflammatory agents. In April 2017, an International Panel of experts in MS met to discuss the reasons behind the recent successes and past failures in progressive MS trials. This paper summarises these reasons, particularly focusing on the main lessons learned for the design of future trials. First, drugs' mechanism of action should tackle the specific pathogenic mechanisms that characterise progressive MS. Secondly, trial populations where new drugs are to be tested should be carefully chosen, possibly including younger patients with shorter disease durations, which have greater chances of showing active deterioration during the trial, therefore increasing the power to detect treatment effects. Thirdly, outcome measures used in future phase 2 and phase 3 trials should be highly sensitive and be accompanied by smart trial designs.

INTRODUCTION

Up to very recently, no treatments had proved effective in progressive MS (PMS). In 2016, though, four drugs, two tested in phase 3 trials^{1, 2} and two in phase 2 trials^{3, 4} showed a beneficial effect in PPMS or SPMS. This change in direction has prompted the revision of the reasons underlying recent chain of successes and past failures.

In this paper, we aim to focus on those reasons behind past failures and recent successes. First, we will focus on the drugs tested in past PMS trials, most of them not specifically designed to tackle the pathogenic mechanisms that characterise the PMS phenotype. Second, we will discuss the type of patient included in PMS trials, which has probably had an enormous influence over the observed results. Finally, we will mention some methodological issues of these trials, mainly related to outcome measures and trial designs, that could have played a role in past failures as well as in recent achievements.

DRUGS IN PROGRESSIVE MS TRIALS

Many of the drugs that have been tested in PMS trials were not initially designed to tackle the specific pathogenic mechanisms that characterise the PMS phenotype. Instead, they tended to be the same as those tested in RRMS trials (**Tables 1 and 2**). This could be justified by the fact that all pathological traits in MS are thought to coexist throughout the disease, as part of a continuum, being the differences between stages or phenotypes more quantitative than qualitative^{5, 6}. However, these differences, even if relatively small, may have played a part in the negative results found so far in PMS trials. In addition, the rationale for some of the phase 3 trials carried out in PMS was provided by the results of phase 2 studies performed in RRMS⁷⁻⁹ (not in PMS) or by the post-hoc subgroup analyses of PMS trials which had

overall had negative results¹⁰⁻¹². Therefore, the non-optimal choice of the drug might have been aggravated by the performance of large phase 3 trials without a previous phase 2 trial in progressive MS with the same drug, which could have helped to save time and economic resources.

However, not all drugs tested in PMS have failed to show a beneficial effect in delaying disability progression. In 1998, the European Study Group on interferon beta (IFN)-1b in SPMS published the results of the first phase 3 trial in SPMS⁹ (i.e. the EUSPMS trial), and these were positive for the primary endpoint (**Table 1**). Additionally, mitoxantrone, a powerful anti-inflammatory treatment, also showed a beneficial effect in a phase 3 trial with SPMS patients, published in 2002¹³. Unfortunately, though, despite these initially promising results, the use of IFN β or mitoxantrone in PMS has been progressively reduced in the clinic, for different reasons. With regard to IFN β , the initial positive results could not be confirmed by the rest of the phase 3 trials also carried out with IFN β in SPMS¹⁴⁻¹⁶ or PPMS^{17, 18}. This was attributed to EUSPMS trial population being younger and with higher inflammatory activity, i.e. more similar to the RRMS phenotype, than other trial populations¹⁹. This implied a loss of confidence in the use of IFN β for SPMS, for which it had been approved in some countries, especially in those patients without any clear evidence of acute macroscopic inflammation, visible with T2-weighted MRI sequences. In relation to mitoxantrone, it is its poor safety profile²⁰ that has limited its use, which is nowadays almost anecdotal in western countries.

In 2014, the scenario of treatments for MS started to change when the results of the phase 2 MS-STAT trial, which evaluated the efficacy of high doses of simvastatin versus placebo in SPMS, were published⁴. Simvastatin showed an ability to reduce the rate of brain volume loss, the primary outcome, and to delay the

progression of disability^{4, 21}. Remarkably, unlike the IFN β and the mitoxantrone trials, the choice of the drug in the MS-STAT trial was based on a careful evaluation of its possible neuroprotective effects²².

In 2016, the results of the phase 3 ORATORIO trial were published¹, meaning the major breakthrough in PMS treatment. The ORATORIO trial showed a clear superiority of ocrelizumab, an anti-CD20 monoclonal antibody, as compared to placebo, in delaying the accrual of disability in patients with PPMS. Remarkably, it was the first time that a drug showed efficacy in PPMS¹. In this case, although no evidence from any phase 2 trials of ocrelizumab in PMS was available before the start of the trial, several studies had already shown a potential role of CD20 B-cells in the pathogenesis of progressive MS²³⁻²⁵. B-cells accumulate in the subarachnoid space of patients with PMS, in the so-called meningeal follicles²³⁻²⁵, and this constituted the main rationale for the ORATORIO trial. Additionally, a post-hoc subgroup analysis of the OLYMPUS trial (published in 2009) had shown some beneficial effect of rituximab, another anti-CD20 monoclonal antibody similar to ocrelizumab, in younger PPMS patients with inflammatory activity²⁶. So, although the OLYMPUS trial had been deemed overall negative, the results of this subgroup analysis also contributed to the rationale for the use of ocrelizumab in the ORATORIO trial.

The biotin trial for PMS, also published in 2016, showed as well significant results in the primary endpoint³. As happened in the ORATORIO trial, the rationale for the use of biotin was not its efficacy in RRMS, but its unique mechanism of action: biotin activates carboxylases which enhance either the synthesis of fatty acids, therefore supporting myelin repair, or the energy production in neurons, therefore protecting against hypoxia-driven axonal degeneration²⁷.

Finally, the phase 3 EXPAND trial of siponimod in SPMS, presented at ECTRIMS 2016, has also shown a beneficial effect versus placebo², contributing to the list of recent trials successful in PMS. Here, although the drug had proved effective in a phase 2 RRMS trial (BOLD study) and had a clear anti-inflammatory effect²⁸, it also seemed to have neuroprotective effects within the CNS after crossing the blood-brain barrier²⁹. This latter characteristic constituted the main rationale for its use in SPMS⁴.

Thus, it seems that with all these recent successes, a new era of PMS trials might have started. However, a few considerations need to be made. First, unfortunately, a careful selection of the drug has not always meant obtaining significant results. A clear example is the phase 3 INFORMS trial with fingolimod, a drug with a similar profile to that of siponimod, which failed to show efficacy in PPMS⁸. Second, since most of the successful drugs in PMS also had a clear direct anti-inflammatory effect, it could be argued that this was in fact the main responsible for their success, rather than their neuroprotective effect. In fact, even in those trials with positive results, the benefits have been modest and have been predominantly restricted to patients with active inflammation, indicating that effective therapies positively impacting the pathophysiology of later stages of progressive MS are still elusive. Therefore, more research into the pathogenic mechanisms of PMS and the mechanisms of action of the potential drugs for PMS is still needed.

TRIAL POPULATIONS

The choice of the trial population is crucial to be able to capture treatment effects, should they exist. There are at least two potential causes of an eventual unfortunate choice of trial population: first, the lack of an appropriate definition of progressive

MS; second, the ignoring of patients' disease severity when defining the inclusion criteria.

In relation to the definition problem, in 1996, Lublin and Reingold published the first definitions of MS phenotypes³⁰. These could be homogeneously used across the scientific community and meant a significant improvement in trial design³⁰. However, the lack of precision of the definitions of SPMS and PPMS, which could not easily incorporate the presence of clinical or MRI activity, prompted the publication of the new definitions of the progressive forms of MS, in 2014⁶. These allowed us to use MS disease modifiers to specify whether the patient had clinical/MRI inflammatory activity or active progression, on top of the diagnosis of SPMS or PPMS, which could be very useful for future trial selection.

The problem related to ignoring patients' severity in the inclusion criteria has started to be tackled more recently. A trial population with slower disease progression than that considered when estimating the required sample size may not be powered to detect differences between groups, should they exist. For instance, when in 2007 the phase 3 PROMISE trial was published³¹, one of the reasons attributed to its negative results was the low progression rate in the placebo arm, which was not predicted when designing the trial. A strategy used to avoid unexpected low rates of progression of disability has been the inclusion of patients with greater chances of having an active disease over the course of the trial. This was the strategy of the ORATORIO trial¹. In this study, one of the inclusion criteria was to have a relatively short disease duration, especially if the patient was not too disabled. This ensured that only patients with steeper accrual of disability were included. However, high progression rates have also been seen in negative studies, such as the INFORMS trial, where the proportion of patients with progression in the

placebo arm was 70%⁸. This suggests that other factors apart from the presence of high progression rates may have also been involved in the success of the ORATORIO trial. In fact, in the ORATORIO trial, an additional inclusion criteria was that patients had to be 55 years old or younger, whereas previous studies had allowed the inclusion of patients with ages up to 65³¹. So, this younger trial population ensured the participation of patients with greater inflammatory activity¹, more likely to respond to anti-inflammatory treatment regimes. Of note, although the ORATORIO trial did not show any statistical differences between subgroups defined by inflammatory activity, this was attributed to the lack of power¹. Thus, it may be possible that the success in the ORATORIO trial was more strongly related to the presence of a population with a more inflammatory phenotype¹, possibly as a consequence of choosing younger participants, than to the presence of high progression rates, although both may have contributed.

In general, these trials where the study populations are carefully selected to increase their power are considered 'enriched' trials. Importantly, despite the advantages of enriched trials, they may also entail some drawbacks, such as questioning the generalisability of the results to all PMS patients, with and without the trial population features. An alternative to enriched trials may be the performance of subgroup analyses within the trial population to assess whether the efficacy of a drug is similar in different subpopulations. Subgroup analyses are generally performed if previously defined in the trial protocol. In that case, the trial is usually adequately powered for that. Nevertheless, if there is a scientific rationale, it is not inappropriate to conduct a subgroup analysis that was not previously defined in the trial protocol. Thus, it may be reasonable to approach these post-hoc analyses as exploratory and recognise their limited power.

OUTCOME MEASURES AND TRIAL DESIGNS

Phase 3 trials in PMS have clinical measures as primary endpoints. Among these, the EDSS-related measures are the most widely used (see **Tables 1** and **2**). However, the EDSS has limitations³²⁻³⁴, which may well have been responsible for the lack of significant results in PMS trials.

Over the years, phase 3 trials in progressive MS have tried different strategies to overcome the limitations of the EDSS. One of these was to substitute the EDSS by another clinical score with a greater sensitivity to clinical progression, such as the Multiple Sclerosis Functional Composite (MSFC) score³³, which reflects better than the EDSS the upper limb and cognitive functions. For instance, the IMPACT study, which in 2002 showed a beneficial effect of IFN β -1a in SPMS when compared to placebo, had used the changes in MSFC scores during the trial as primary endpoint. Another strategy to overcome the limitations of the EDSS has consisted of using composite outcomes of clinical progression instead of a single score. For example the MIMS (mitoxantrone, SPMS)¹³, the CUPID (dronabinol, SPMS)³⁵, the ASCEND (natalizumab, SPMS)³⁶ and the INFORMS (fingolimod, PPMS)⁸ trials used composite measures of clinical progression, always involving the EDSS. Nevertheless, despite the use of composite primary endpoints, only the MIMS study¹³ of all these was significant. Also following this strategy, in the ORATORIO study, the composite NEP (no evidence of progression) was used as an exploratory secondary endpoint¹, emulating the commonly used NECA (no evidence of clinical activity) and NEDA (no evidence of disease activity) for RRMS trials³⁷⁻⁴⁰. In the

ORATORIO study, significant treatment effects were not only seen in the primary endpoint, but also in the NEP endpoint: the proportion of patients without progression in the EDSS, NHPT and TWT (all three) was higher among those receiving ocrelizumab than in the placebo arm¹. A final strategy has resided in changing completely the focus of the outcome measure from clinical progression to clinical improvement. Although 'percentage of patients with clinical improvement' had been already used as secondary endpoint in a few RRMS trials such as the phase 3 Copolymer-1⁴¹ and CARE-MS II³⁹, it was used as primary endpoint for the first time in the biotin trial for progressive MS³ (**Table 1**). Of note, although the use of improvement of disability (instead of delayed progression) as trial primary endpoint is still debatable, it is possible that it reflects a genuine aspect of some drugs for progressive MS. This would be especially true for drugs with a neuroprotective or restorative mechanism of action, as was the case for biotin^{3, 27, 42}.

Phase 2 trial endpoints mainly consist of non-clinical outcome measures. In progressive MS, the most widely used is the brain atrophy rate, which in the MS-STAT trial was the responsible for the differences between treatment groups in favour of simvastatin²¹. On the other hand, its responsiveness is still limited and great efforts are being made to develop new phase 2 outcome measures able to detect treatment effects in 6-12 months, instead of the conventional 24 months (**Tables 1 and 2**)^{43, 44}. Along these lines, the recently completed SPRINT-MS trial, apart from aiming at the comparison of ibudilast versus placebo to delay the disability accumulation in SPMS and PPMS, aimed at head-to-head comparisons of several imaging measures in terms of their ability to reflect treatment effects⁴⁵.

Regarding the trial design, the vast majority of the PMS trials –and of the MS trials in general– so far have used the classic 1:1 scheme, where one active arm is

compared to one placebo arm. And in those few trials with two active arms compared to one placebo arm^{13, 16, 17, 46}, the two active arms tested two doses of the same drug, rather than two active components (**Tables 1 and 2**). Recent evidence from Oncology trials suggests that this trial design could be improved by comparing several active drugs to the placebo arm⁴⁷. Following this innovative multi-arm trial suggestion, the phase 2 MS-SMART study was born. It aimed to compare three active drugs, fluoxetine, amiloride and riluzole, to placebo, in a proof-of-concept drug-repurposing four-arm placebo-controlled trial, which finished the recruitment in June 2016 and is currently ongoing⁴⁸.

CONCLUSIONS

The recent chain of successes in SPMS and PPMS trials has brought some light to the bleak prospect we used to have in relation to treatment options for PMS. So far, one of these newly tested drugs, the ocrelizumab, has already been approved for patients with PPMS⁴⁹ and it is likely that more drugs are approved in the near future. Thus, this set of fortunate concatenated events might be meaning a turning point in the history of trials for PMS, enabling us to assess the reasons behind past failures and latest achievements. On the other hand, most of these successes have been modest, mainly restricted to patients with active inflammation and in the context of trials with powerful anti-inflammatory agents. Thus, although inflammation in progressive MS exists and the presence of meningeal follicles is a well-known pathogenic mechanism, there are other processes beyond inflammation that have not been successfully addressed by many of the drugs recently tested. Therefore, it is not surprising that a number of significant failures have also occurred over the previous years, despite a careful choice of the tested drug.

In sum, it has become clearer that drugs' mechanism of action must tackle the specific pathogenic mechanisms that characterise progressive MS in order to increase the chances of success. Also, the trial populations where new drugs are to be tested should be carefully chosen. Younger populations with shorter disease durations and more rapid progression rates have greater chances of showing active deterioration during the years of the trial, therefore increasing the power to detect treatment effects, should these exist. Finally, outcome measures in both phase 2 and phase 3 trials should be as sensitive as possible to detect treatment effects within a short time frame, and be accompanied by a smart trial design able to maximise the potential of the trial to find effective drugs in a quick and efficient manner.

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Table 1. Main trials in SPMS

Drug tested (vs. placebo)	Trial	Condition (no. of patients randomised)	Duration	Primary endpoint(s)	Results on the primary endpoint	Reference
IFN beta-1b SC 8 million IU eod	Phase 3 (EUSPMS study) ¹	SPMS (n=718)	Early termination due to obvious superiority of IFN (initially planned: 39 months)	Time to 3-month CDP on the EDSS ²	Positive	European Study Group on IFN beta-1b in SPMS, Lancet 1998, phase 3
IFN beta-1a SC 22µg or 44µg thrice weekly	Phase 3 (SPECTRIMS study) ¹	SPMS (n=618)	36 months	Time to 3-month CDP on the EDSS ²	Negative	Li et al. (SPECTRIMS Study Group), Neurology 2001
IFNβ-1b SC 250µg or 160µg/m ² of body surface area eod	Phase 3 (NASPMS study) ¹	SPMS (n=939)	Early termination for futility (initially planned: 36 months)	Time to 6-month CDP on the EDSS ²	Negative	Panitch et al. (North American Study Group on IFN beta-1b in SPMS), Neurology 2004
IFN beta-1a IM 60mcg/week	Phase 3 (IMPACT study) ¹	SPMS (n=436)	24 months	Change in the MSFC from baseline to 24 months	Positive	Cohen et al., Neurology 2002
IFN beta-1a SC 22mcg/week	Phase 3 (The Nordic SPMS study) ¹	SPMS (n=371)	36 months	Time to 6-month CDP on the EDSS ²	Negative	Andersen et al., JNNP 2004
Mitoxantrone IV 12 mg/m ² or 5 mg/m ² of body surface area/3 months	Phase 3 (MIMS study)	SPMS or PRMS course (n=188)	24 months	Multivariate analysis of five clinical measures: -EDSS changes (baseline-final); -AI changes (baseline-final); -No. of treated relapses; -Time to first treated relapse; -Change in standardised neurological status;	Positive	Hartung et al., Lancet 2002

IVIG 1g/Kg/month	Phase 3 (ESIMS study) ³	SPMS (n=318)	24 months	Time to 3- month CDP on the EDSS ²	Negative	Hommes et al., Lancet 2004
MBP8298 IV 500mg/6 months	Phase 2	SPMS (n=32)	24 months	Change in the EDSS from baseline to 24 months	Negative ⁴	Warren et al., Eur J Neurol 2006
MBP8298 IV 500mg/6 months	Phase 3 (MAESTRO study) ⁵	SPMS (n=612)	24 months	Time to 6- month CDP on the EDSS ²	Negative	Freedman et al., Neurology 2011
Lamotrigine PO 400mg/day	Phase 2	SPMS (n=120)	24 months	Rate of change of partial (central) cerebral volume over 24 months	Negative	Kapoor et al., Lancet Neurol 2010
Dronabinol PO (max. dose: 28mg/day, titrated against bodyweight	Phase unspecified (CUPID study)	SPMS (n=302), PPMS (n=191)	36 months	-Time to 6- month CDP on the EDSS ² -Change in the MSIS-29- PHYS from baseline to 36 months	Negative	Zajicek et al., Lancet Neurol 2013
Simvastatin PO 80mg/day	Phase 2	SPMS (n=140)	24 months	Annualised rate of whole-brain atrophy	Positive	Chataway et al., Lancet 2014
Natalizumab IV 300mg/4 weeks	Phase 3 (ASCEND study)	SPMS (n=887)	24 months	Composite outcome: 6- month CDP on EDSS ² , or TWT (≥20%), or NHPT (≥20%)	Negative	Steiner et al., AAN 2016
Biotin PO 100mg/8h	Phase 2	Progressive MS: SPMS (n=99) or PPMS (n=55)	12 months	Proportion of patients with improvement of MS- related disability ⁶ at month 9, confirmed at month 12	Positive	Tourbah et al., MSJ 2016
Siponimod PO 2mg/day	Phase 3 (EXPAND study)	SPMS (n=1105)	37 months	Time to 3- month CDP on the EDSS ²	Positive	Kappos L et al. ECTRIMS 2016

Table 1 (footnote).

1: The rationale for the phase 3 trials with IFN β in SPMS was provided by the results of trials carried out in RRMS; **2:** The definition of EDSS progression depends on the baseline EDSS score; **3:** The rationale for the ESIMS trial was provided by the results of uncontrolled studies and placebo-controlled trials in RRMS; **4:** Although the results for the main analysis were negative, in the subgroup of 20 patients with HLA haplotypes DR2 and/or DR4, MBP8298 treatment had a significant effect on the primary endpoint; **5:** The rationale for the MAESTRO study was provided by the results of the subgroup analysis with HLA haplotypes DR2 and/or DR4; **6:** Improvement was defined as: decrease of ≥ 0.5 point or ≥ 1 point in EDSS (if baseline score was 6–7 or 4.5–5.5, respectively) or a $\geq 20\%$ decrease in timed walk test (TWT) time, compared with the best EDSS or TWT value recorded at either the screening or the randomisation visit.

Abbreviations: AI: ambulation index; EDSS: expanded disability status scale; CDP: confirmed disability progression; IFN β -1a/1b: interferon beta 1a/1b; IV: intravenous; MSFC: multiple sclerosis functional composite; MSIS-29-PHYS: physical impact subscale of the 29-item multiple sclerosis impact scale; NHPT: nine-hole peg test; PO: per oral; PPMS: primary progressive multiple sclerosis; PRMS: progressive-relapsing MS; RRMS: relapsing-remitting MS; SC: subcutaneous; SPMS: secondary progressive MS; TWT: timed walk test;

Table 2. Main trials in PPMS

Drug tested (vs. placebo)	Trial	Condition (no. of patients randomised)	Duration	Primary endpoint	Results on the primary endpoint	Reference
GA SC 15mg/12h	Phase 2	Chronic progressive MS (n=106); out of these, 31 had PPMS (n=23) or 'transitional progressive MS' (n=8)	24 months	Time to confirmed progression on the EDSS ¹	Negative ²	Bornstein et al., Neurology 1991
GA SC 20mg/day	Phase 3 (PROMiSe study)	PPMS (n=943)	Early termination for futility (initially planned: 36 months)	Time to 3-month CDP on the EDSS ¹	Negative	Wolinsky et al., Ann Neurol 2007
IFNb-1a IM 30µg or 60µg weekly	Phase 2	PPMS (n=50)	24 months	Time to 3-month CDP on the EDSS ¹	Negative	Leary et al., Neurology 2003
IFNb-1b SC 8 MIU eod	Phase 2	PPMS and 'transitional progressive MS' (n=73)	24 months	Time to 3-month CDP on the EDSS ¹	Negative	Montalban et al., MSJ 2009
Rituximab IV 1000mg/24 weeks	Phase 2/3 (OLYMPUS study)	PPMS (n=439)	96 weeks	Time to 3-month CDP on the EDSS ¹	Negative ³	Hawker et al., Ann Neurol 2009
Fingolimod PO 0.5mg/day	Phase 3 (INFORMS study) ⁴	PPMS (n=970)	36 months	Composite endpoint: Time to 3-month CDP on either EDSS, or TWT, or NHPT	Negative	Lublin et al., Lancet 2016
Ocrelizumab IV 600mg (300mg x2) /24 weeks	Phase 3 (ORATORIO study) ⁵	PPMS (n=732)	120 weeks	Percentage of patients with 3-month CDP on the EDSS ^{1,6}	Positive	Montalban et al., N Engl J Med. 2016

Table 2 (footnote).

1: The definition of EDSS progression depends on the baseline EDSS score; **2:** In the subset of 31 patients with either PPMS or transitional progressive MS, some hint of efficacy was observed; this motivated the phase 3 trial; **3:** In the subgroup of 72 patients with age <51 years and presence of gadolinium-enhancing lesions in the MRI, rituximab significantly delayed progression of disability (vs. placebo); **4:** The rationale for the INFORMS trial was provided by in-vitro and in-vivo studies that suggested that fingolimod could inhibit neurodegeneration. No phase 2 trial was performed with fingolimod in PPMS; **5:** The rationale for the ORATORIO trial was provided by the results of the subgroup analysis of the OLYMPUS trial (in younger patients with inflammatory activity). No phase 2 trial was performed with ocrelizumab in PPMS; **6:** Although the primary endpoint was the percentage of patients with CDP, this percentage was obtained through a time-to-event analysis.

Abbreviations: EDSS: expanded disability status scale; CDP: confirmed disability progression; IFN β -1a/1b: interferon beta 1a/1b; IV: intravenous; NHPT: nine-hole peg test; PO: per oral; PPMS: primary progressive multiple sclerosis.