Reducing progression in progressive multiple sclerosis

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Multiple sclerosis (MS) therapeutics continues to evolve and is one of the most vibrant areas of research in the clinical neuroscience community. To the earlier relapsing ('inflammatory') stage of the disease a wide variety of agents can be applied, ranging from, injectable (beta-interferons, glatiramer acetate) to oral (teriflunamide, dimethyl fumarate, fingolimod, cladribine) to monoclonal agents (natalizumab, alemtuzumab, ocrelizumab).[1] Indeed in clinical practice, much time is devoted to sequencing the order of treatments and balancing effectiveness with possible side-effects, depending on the pattern of disease activity of the individual. Trials are now starting to consider induction versus escalation, combination versus single agent, and exit versus maintenance strategies. Yet despite these major advances, the problem of progression remains stubborn. Logically, the task is to prevent or delay progression using the approaches described above, or if established, to slow, stop or reverse it. Progression can be broadly characterised as inflammatory or non-inflammatory superimposed onto the primary progressive MS (PPMS) or secondary progressive MS (SPMS) classification.[2] The litany and possible causes of trial failure in progressive MS in previous decades has been regularly described.[3] However now set against this, published in *The Lancet* are the positive results of the EXPAND trial in SPMS, where there is a relative reduction in 3-month confirmed disability (CDP) by 21%.[4] This is part of quartet of large phase 3 trials in progressive MS over the last 2 years, with four different drugs, split evenly between PPMS and SPMS: two positive and two negative. All of these drugs would be seen as anti-inflammatory and have come from the relapsing-remitting MS (RRMS) arena, encompassing a variety of mechanisms: sphingosine 1-phosphate (S1P) receptor modulation, anti-CD20-expressing B cell and anti-integrin-α4. The table outlines some top-line features.[4-7]

At the heart of these results is the debate around inflammatory and non-inflammatory drivers of progression. The former might include T and B lymphocyte infiltration and B lymphocyte-rich lymphoid follicles; the latter might include injury by iron and reactive oxygen species, energy failure, calcium influx and enhanced susceptibility to vascular co-morbidities.[8] The external markers of active inflammation are relapse and/or new MRI lesion activity. What then, extrapolating from this contemporary dataset of over 4000 trial participants are the rules we could apply to the individual patient with progressive MS, knowing that the ratio of inflammatory/non-inflammatory activity will vary in each individual and will be dynamic over time?

One burning question is whether the successful agents will have the most traction in the earlier, perhaps more active stages of progression and the effect will wane (perhaps significantly) in the later less inflammatory stages. It has been argued in PPMS that the reason for the net positive result seen in ORATORIO (ocrelizumab) compared against the negative of INFORMS (fingolimod) was that the trial cohort of the former was a more active cohort with an inflammatory T1 Gadolinium enhancing (GdE) burden at baseline of 27% vs 13%.

Moving onto trials in SPMS then we see success for siponimod (a sister drug to fingolimod) but failure for natalizumab. What does the fine dissection of the EXPAND trial expose? The 3-month CDP was reduced from 32% to 26% across the whole trial, which had 21% GdE activity at baseline. Sub-group analyses (figures 2 and S3[4]) show trends in favour of more effect with more inflammatory activity and younger age, though the study was not powered to look for interactions.

This trial is instructive for other reasons. It confirms that the Expanded Disability Status Scale (EDSS), though, not sophisticated, does seem to good enough, and is unlikely to be replaced in phase 3 work in the near future, though there is clear promise for composite outcomes in terms of increased event rates. Biomarker utility is also underscored by this trial, with mean whole brain atrophy rates reduced significantly by siponimod. Whilst other potential modalities are being explored, optical coherence tomography, neurofilament light chains, and advanced MRI (eg, magnetisation transfer ratio, thalamic/spinal cord atrophy) are front runners, at present, whole brain volume looks now to be established as the phase 2/interim marker of choice in progressive MS.

Overall then for patients with progressive MS, what conclusions do these four trials and EXPAND in particular, say to us? Ocrelizumab and siponimod have overall trial effects of reducing the 3-month CDP by 21-24% in relative terms. Modest, but a start. They hint that more effect is seen in a more inflammatory environment. They underline the historic truth that not all RRMS drugs will work in established progressive MS, though it would be fascinating to re-run INFORMS with siponimod. For the individual patient they challenge us with two paradigms, either to use these agents across the board as the standard of care continuously and longitudinally, regardless of the clinical/MRI baseline characteristics. Or, alternatively, to try and individualise the risk-benefit ratio according to rough macro-measures such as clinical and MRI findings, which may vary over time. They warn us that non-inflammatory progression is likely to be (much) harder to make an impact on, though there is a pipeline of novel agents (for example, simvastatin,[9] ibudilast,[10] biotin[11]) showing phase 2 success and some starting the next stage of the journey.

A new dawn has broken, and those patients, investigators and sponsors taking part and leading this work should be congratulated, as a major health problem starts to be encircled by large, randomised and controlled studies.

Study name	INFORMS	ORATORIO	EXPAND	ASCEND
Drug	Fingolimod	Ocrelizumab	Siponimod	Natalizumab
Main mechanism	S1P receptor modulation	Anti-CD20-expressing B cell	S1P receptor$_{1,5}$ modulation	Anti-integrin-α4
NCT (date of online publication [reference])	NCT00731692 (01/2016[5])	NCT01194570 (12/2016[6])	NCT01665144 (03/2018[4])	NCT01416181 (03/2018[7])
PMS type	PPMS	PPMS	SPMS	SPMS
N	823	732	1651	887
Primary outcome for progression	Composite: time to 3-month CDP	EDSS: time to 3-month CDP	EDSS: time to 3-month CDP	Composite: time to 6-month CDP
Mean age (sd) (years)	49 (8.4)	45 (7.9 active;8.3 placebo)*	48 (7.8 active; 7.9 placebo)	47 (7.4 active; 7.8 placebo)
Mean duration of progression (sd) (years)	6 (2.4)	7 (4.0 active; 3.6 placebo)*	4 (3.6 active; 3.3 placebo)	5 (3.0 active; 3.7 placebo)
Patients with baseline T1 GdE lesions (absolute number)	13% (110)	27% (193)	21% (351)	24% (210)
Placebo vs active CDP	69% (338/487) vs 69% (232/336) [80% vs 77% KM estimate]	39% (96/244) vs 33% (160/487)	32% (173/545) vs 26% (288/1096)	48% (214/448) vs 44% (195/439)
Primary outcome Hazard ratio/Odds ratio (95% CI)	HR 0.95 (0.80-1.12)	HR 0.76 (0.59-0.98)	HR 0.79 (0.65-0.95)	OR 0.86 (0.66-1.13)
Primary outcome result	negative	positive	positive	negative

PMS=Progressive MS; PPMS=Primary progressive MS; SPMS=Secondary progressive MS; CDP=confirmed disability progression; EDSS=Expanded Disability Status Scale; Composite: one or more of progression in EDSS, 25 Foot Timed-Walk Test, Nine-Hole Peg Test; T1GdE=T1-Gadolinium-enhancing; KM=Kaplan-Meier;* mean total cohort sd not calculated, so both active and placebo given.

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