Disease modifying therapy should be stopped in secondary progressive MS

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Disease modifying therapies (DMT) are not effective in non-relapsing secondary progressive multiple sclerosis (SPMS). Despite the recent progress in the treatment of relapsing remitting multiple sclerosis during the past two decades which has seen the introduction of several drugs, similar success has not been achieved for SPMS. This is primarily due to the intrinsic neurodegenerative process that drives the accumulation of disability in SPMS which is independent of focal inflammatory changes where DMT seem more effective. The underlying pathology in the progressive formof the disease is not unitary and neurodegeneration in SPMS is considered to be multi-factorial, diffuse and significantly influenced by metabolic neuroaxonal changes.

One of the characteristic features of SPMS is the involvement of normal-appearing cerebral white and grey matter which worsens in severity with disease progression over time. Current selection of DMT does not influence the wider pathology in SPMS, which is attested by the failure of treatment benefit in several completed randomised controlled clinical trials. These trials have involved over 6000 patients since 1988 and included immunosuppressive agents (Azathioprine, Ciclosporin, Cyclophosphamide, Sulfasalazine, Linomide, Mitoxantrone and Cladribine), first line DMT (Interferon beta 1-a, 1-b, and Glatiramer Acetate), human IVIg, anti-CD20 monoclonal antibody (Rituximab), Myelin Basic Protein and Cannabinoid (Dronabinol). The European and North American placebo-controlled study of interferon beta-1b in SPMS showed divergent results in the primary outcome measure (sustained EDSS progression), while treatment effects were similar on relapse and MRI-related endpoints, confirming the dissociation between disease progression, relapse and MRI markers of inflammation (Enhancing and T2 lesions). There was no clinical benefit of Alemtuzumab in a small trial of SPMS and despite a reduction in inflammatory activity,with no benefit in terms of EDSS progression or rate of brain atrophy in MRI.

Fingolimod, an oral DMT approved in relapsing remitting MS (RRMS) for patients failing first line DMT, was not shown to be effective in a large trial of patients with primary progressive multiple sclerosis (PPMS) which shares the disease pathology of SPMS. The clinical trial of Siponimod, an oral S1P superagonist similar to Fingolimod, in SPMS patients is expected to be completed in 2016, and the trial of Rituximab in SPMS will finish in 2017. An interim result of Ocrelizumab, a humanised anti-CD20 monoclonal antibody, found treatment benefit in younger (<55 years) ambulatory PPMS patients with MRI evidence of disease activity (enhancing brain lesions). Several other clinical trials in SPMS are currently ongoing, but very few of these trials are testing currently approved DMT with the exception of Natalizumab (ASCEND trial, estimated completion date in 2017).

There is clearly an unmet need of effective treatment in SPMS. This is largely due to the incompleteness in our understanding of the progressive disease pathology in MS. By the exacting standards of "no evidence of disease activity (NEDA), the goal is achieved at best in about 45% of RRMS patients in the clinical trials of DMT and in 15% of placebo-treated patients; the relative size of the difference (30%) is small compared to the size of relative risk reduction of relapse with DMT. This implies that despite the huge success of current DMT with containment of MS relapse, a larger proportion of disease pathology still remains untouched and contributes to the disability progression and transition to SPMS. There is thin evidence, little therapeutic benefit and no cost-effectiveness to support the continuation of existing DMT in patients with established SPMS. A small subgroup of patients with so called progressive-relapsing phenotype with MRI evidence of enhancing or new lesions may in theory continue to experience some benefit from current DMT but this number is small and

the presumed treatment benefit in this subgroup should not be extrapolated to all SPMS patients.

The recommended stopping criteria for disease modifying therapy (DMT) in patients currently receiving treatment for relapsing remitting disease are:

- Development of inability to walk, persistent for more than 6 months, unless unable to walk for reasons other than MS; which would imply an EDSS score >6.5, and
- Confirmed secondary progressive disease with an observable increase in disability (sustained disease progression) over a 6-12 month period. The disability progression is reflected in MRI as progressive loss of brain volume and cervical spinal cord atrophy without evidence of lesion enhancement.

Many patients develop psychological dependence on DMT after having taken it for many years, and feel apprehensive when advised to stop treatment. SPMS patients meeting stopping criteria should be counselled and withdrawn from treatment gradually over a period of 3-4 months to avoid the risk of “rebound” and pseudorelapses; these patients should ideally be offered the opportunity to enrol in new treatment trials of SPMS. Quite appropriately, new treatment trials in SPMS are moving away from the immune-inflammatory focus and aiming at neuroprotection, mitochondrial function, neuroaxonal metabolic reserve and ion transport function with promising early results reported in clinical trials of Simvastatin and Biotin. Such treatments are likely to be introduced early in the future, possibly in combination with DMT in RRMS, to arrest disease progression and conversion to SPMS.