The challenge of progressive MS therapy

Alan J Thompson FMedSci, FRCP, FRCPI

Dean, Faculty of Brain Sciences, University College London

Garfield Weston Professor of Clinical Neurology and Neurorehabilitation

UCL Institute of Neurology

Queen Square

London WC1N 3BG

Phone number 020 3018 7916

alan.thompson@ucl.ac.uk

Key words: progressive MS; multiple sclerosis; therapies

Conflicts of Interest and Source of Funding

Alan Thompson has received honoraria/support for travel for consultancy from Eisai, Biogen (Optum Insight), and Excemed. He received support for travel from the International Progressive MS Alliance, as chair of their Scientific Steering Committee and the National MS Society (USA) as member of their Research Programs Advisory Committee. He receives an honorarium from SAGE Publishers as Editor-in-Chief of Multiple Sclerosis Journal.

No source of funding supported the writing of this review.

The challenge of progressive MS therapy

Abstract

Purpose of review

Understanding the mechanisms underlying progression in multiple sclerosis (MS) and identifying appropriate therapeutic targets is a key challenge facing the MS community. This challenge has been championed internationally by organisations such as the Progressive MS Alliance, which has raised the profile of progressive MS and identified the key obstacles to treatment. This review will outline the considerable progress against these challenges.

Recent findings

New insights into mechanisms underlying progression have opened up potential therapeutic opportunities. This has been complemented by ongoing validation of clinical and imaging outcomes for Phase II trials of progression, coupled with the development of innovative trial designs. The field has been greatly encouraged by recent positive Phase III trials in both primary and secondary progressive multiple sclerosis, albeit with modest benefit. Early trials of neuroprotection and repair have provided important new data with which to drive the field. Improving symptom management and advancing rehabilitation approaches, critical for this patient population which, taken together with identifying and managing co-morbidities and risk factors, has an appreciable impact on health-related quality of life.

Summary

Raising the profile of progressive MS has resulted in the first effective treatments with the promise of more to come.

Introduction

The challenge of finding treatments for and improving the management of progressive multiple sclerosis subsumes a number of fundamental issues, outlined in a publication from the International Progressive Multiple Sclerosis Alliance (PMSA)[1]. They include (i) understanding the mechanisms underlying progression and identifying potential targets (ii) appropriate trial design and outcome measures (iii) improving symptomatic treatment and rehabilitation.

The recent exploration of the MS phenotype and, in particular, comparison of the two progressive forms of MS has been helpful in that it acknowledges the consensus that while there are some differences between those that are progressive from onset (primary progressive) and those that develop progression after a period of relapses and remissions (secondary progressive); these differences are relative rather than absolute. This is not to dismiss the primary progressive phenotype which is considered by many to be the ideal model with which to study progression. An interesting paper by Kantarci and colleagues[2] - followed a cohort of 453 subjects with so-called radiologically-isolated syndromes (RIS), studied in 22 clinical sites. During a 15-year follow-up, 128 patients evolved to symptomatic MS and 15 of those developed PPMS with a median time to conversion of 3.5 years, demonstrating that subjects with RIS evolve to PPMS in the same frequency as would be expected in general MS populations. The strongest predictors of evolution of PPMS included male gender, more advanced age, and the initial presence of asymptomatic spinal cord lesions. This frequency is however challenged by a recent Scandinavian study

which suggests that the incidence of PPMS is reducing, falling from 19.2% to 2.2% over 30 years, a finding which needs verification in other populations[3]. The clinical definition of secondary progressive has also been quite challenging as it is invariably done retrospectively and tends to be further delayed because of impact on therapeutic options. The MSBase cohort study group worked through a bewildering number of options before reaching a definition which included the absence of a relapse, confirmed at three months, a score on the Expanded Disability Scale greater or equal to 4 and a pyramidal score greater or equal to 2[4].

Mechanisms underpinning progression

The fundamental issue in identifying treatments for progressive MS is a better understanding of the pathological mechanisms underlying progression, without which targets which are critical to that process cannot be identified with certainty[5]. This was the focus of a workshop which combined basic neuroscientists and clinicians which emphasised the urgent need to identify new therapeutic targets[6]. While the role of some players such as microglia, mitochondria and the innate immune system has been emphasised recently, the precise part they play is yet to be confirmed. A recent review explored potential mechanisms leading to secondary progression discussing a range of mechanisms, including aging, cumulative inflammatory injury exhausting resources and distinct intrinsic mechanisms[7]. An intriguing study utilising induced pluripotent stem (iPS) cells, has suggested a defect in myelin injury response in PPMs, which could help explain the nature of progression[8]. While, more recently, an interesting study has highlighted the potential role of the kynurenine pathway in the development of progression, possibly through interaction with quinolinic acid produced by activated microglia and implicated in excitotoxic neurodegeneration[9]

In addition, several papers have attempted to clarify the pathological processes underpinning MS which have direct implications for progression. The first describes a simplified classification of lesions[10] and the second provides a description of the topography of demyelination and neurodegeneration in MS and outlines two different patterns of neurodegeneration relating to oxidative injury and retrograde neurodegeneration[11].

Mechanisms underlying progression can also be studied utilising magnetic resonance imaging (MRI). A recent study paper has explored the temporal relationship between white and grey matter damage in early PPMS by applying both conventional and magnetization transfer imaging to specific cortical areas and their connected tracts[12]. Results suggested that in the main, cortical damage is a sequelae of normal-appearing white matter pathology which in turn is determined by abnormalities within white matter lesions.

Trial design and outcomes

Moving from mechanisms, the next major challenge is around the practicalities of clinical trials and particularly the optimal trial design to evaluate an effect on progression and the ideal outcome measure to incorporate into such a trial, both at Phase II and Phase III level. Outcomes should include a clinical measure and a biomarker reflecting the underlying pathology and both pose challenges in progressive MS. Clinical evaluation continues to depend on the less than satisfactory Expanded Disability Status Scale. Biomarkers fall heavily towards MRI though work continues on CSF markers, notably neurofilaments and a recent paper has suggested that they may have a predictive role in the development of atrophy in progressive MS[13]. Atrophy is the favoured imaging measure and has been used in a

number of recent studies including the Phase II trial of simvastatin in progressive MS[14]. Efforts are tending to focus on regional atrophy, particularly deep grey matter and also on the spinal cord which may be particularly sensitive in trials of PPMS. Finally biomarkers reflecting abnormalities of the visual pathway are becoming more prominent, most notably optical coherence tomography, a non-invasive technique which provides high resolution quantification of the retinal nerve fibre layer, and directly reflects axonal integrity of the optic nerves and correlates with clinical disability[15].

Clinical trials in progressive MS

The last year has seen the publication of a number of clinical trials in progressive MS and while some have been disappointingly negative, most recently we have seen a positive trial in PPMS. The trial of fingolimod, an oral sphingosine 1-phosphate modulator receptor, which it was thought might have neuroprotective effects, was carried out in primary progressive MS, following the successful trial in the relapsing remitting cohort[16]. A three year study of 970 patients utilising a novel primary outcome which was a composite of the EDSS, 25 foot timed-walk test and the nine-hole peg test. The trial showed no difference between the treatment and placebo arms on any of the outcomes measured. An innovative trial of the co-factor Biotin involving 154 patients with secondary progressive MS was also published[17]. The proposed modes of action include supporting myelin repair and protecting against hypoxia-driven axonal degeneration (by enhancing energy production). The primary end point was unusual – the proportion of patients with disability reversal at month 9 confirmed at month 12. The study was positive and Phase III trials are planned. A Phase III trial of simvastatin in secondary progressive MS will commence later in 2017 – following on from the positive Phase II study[12]. Finally, and most

encouragingly, a Phase III trial of Ocrelizumab, a humanised monoclonal antibody, related to rituximab, that selectively depletes CD-20 expressing B cells, was successful in primary progressive MS[18]. The trial included 732 patients and showed a 24% effect on the primary outcome - 12 week confirmed disability progression. Although relatively modest, this effect is a milestone in the therapeutics of progressive MS, reminiscent of the first positive trials of beta interferon in relapsing/remitting MS.

Perhaps as encouraging, is the focus on neuroprotection for progressive MS. A study by Raftopolous et al[19] has demonstrated that neuroprotection may be an important way forward. The study was carried out in an acute model - optic neuritis, applying phenytoin and demonstrated a positive effect. Currently there are two neuroprotective studies under way, both of which have been fully recruited. The first, SPRINT-MS, a trial of the neuroprotective agent ibudilast involves 155 patients with progressive MS[20]. The primary end point is change in whole brain atrophy as measured by parenchymal brain fraction over 96 weeks. There is also a range of advanced imaging measures. The second study, MS-SMART, has utilised an adaptive trial design to evaluate three neuroprotective agents – amiloride, riluzole and fluoxetine in secondary progressive MS[21].

Risk factors, symptomatic management, rehabilitation and co-morbidities

Finally, optimum management of progressive MS includes a range of approaches, beyond potential pharmacological interventions to modify disease course, including (i) the identification of risk factors which worsen disability, (ii) symptomatic management and rehabilitation and (iii) the management of co-morbidities. Identifying and (iv) quantifying the role of risk factors with potential to modify the

evolution of the progressive phase. This latter point is of paramount importance for patients and clinicians and while many factors are frequently cited as having an impact on disease course, surprisingly few have the necessary evidence-base to support this contention. A recent systematic review focused on fourteen risk factors and found that there was sufficient evidence to make definitive statements about only three of them; Lower Vitamin D levels were associated with higher EDSS scores and cigarette smokers had an increased risk of progression while there was no evidence of an association between disease progression and the use of epidural analgesics during childbirth[22]. For the other eleven risk factors, which included diet, alcohol, exercise and trauma there was insufficient evidence to determine a compelling relationship with progression. In their companion paper, 37 trials of the effect of modifiable risk factor interventions on progression were reviewed and no clear beneficial effect from any risk factor was identified[23]. The evidence base for rehabilitation and symptomatic management in progressive MS is also quite limited[24]. However a recent systematic review of physiotherapy in this population suggested some efficacy though there was a major concern around methodology[25].

A recently acknowledged area which has a major impact on MS and perhaps particularly on the progressive MS population, is the issue of co-morbidities[26]. Two recent papers which emanated from an international workshop clarify the prevalence of key co-morbidities in MS[27] and, importantly, determine how they should be incorporated into clinical trials both in terms of safety and efficacy of the intervention under study[28].

Conclusion

Activity within the progressive space has increased dramatically and the profile of progressive MS has risen substantially. The blocks to treatment are being actively addressed and we have the first effective agent in primary progressive MS. These advances give cause for optimism but shouldn't be allowed to slow the momentum towards more effective treatments which strike at the very heart of the mechanisms underpinning progression.

Bullet points

- Developing effective treatments for Progressive MS is one of the key challenges for the MS community
- Understanding the mechanisms underpinning progression is fundamental to the identification of drugable targets
- Progress is being made in the development of appropriate trial design and outcome measure releavent to progression
- We now have the first effective treatment for primary progressive MS
- Increased focus on modifiable risk factors, symptom management, rehabilitation and co-morbidies will improve health-related quality of life for people with progressive MS

References

1. Fox R, Thompson A, Baker D, *et al.* Setting a research agenda for Progressive Multiple Sclerosis. The International Collaborative on Progressive MS. Mult Scler 2012; 18:1534-1540.

2. Kantarci OH, Lebrun C, Siva A, *et al.* Primary progressive multiple sclerosis evolving from radiologically isolated syndrome. Ann Neurol 2016; 79: 288-294.

** Carefully executed study of radiologically isolated syndromes which provides sound evidence for the frequency of primary progressive MS.

3. Westerlind H, Stawiarz L, Fink K, *et al.* A significant decrease in diagnosis of primary progressive multiple sclerosis: A cohort study. Mult Scler 2016; 22:1071-1079.

4. Lorscheider J, Buzzard K, Jokubaitis V, *et al.* Defining secondary progressive multiple sclerosis. Brain 2016; 139; 2395 – 2405.

**Comprehensive and exhaustive assessment of a wide range of potential components of a valid and reliable definition of secondary progressive MS

5. Correale J, Gaitán MI, Ysrraelit MC, *et al.* Progressive multiple sclerosis: from pathogenic mechanisms to treatment. Brain 2016 [Epub ahead of print]

6. Salvetti M, Landsman D, Schwarz-Lam P, *et al.* Progressive MS – from pathophysiology to drug discovery. A meeting review. Mult Scler 2015; 21:1376-1384.

7. Larochelle C, Uphaus T, Prat A, Zipp F. Secondary progression in multiple sclerosis: Neuronal exhaustion or distinct pathology Trends in Neuroscience 2016; 39 : 325 – 339.

8. Nicaise AM, Banda E, Guzzo RM, *et al*. iPS-derived neural progenitor cells from PPMS patients reveal defect in myelin injury response. Exp Neurol 2017; 288:114 - 121.

9. Lim CK, Bilgin A, Lovejoy DB, *et al*. Kynurenine pathway metabolomics predicts and provides mechanistic insight into multiple sclerosis progression. Scientific Reports 2017; 7:41473

10. Kuhlmann T, Ludwin S, Prat A, *et al.* An updated histological classification system for multiple sclerosis lesions. Acta Neuropathol 2017; 133:13-24.

11. Haider L, Zrzavy T, Hametner S, *et al.* The topography of demyelination and neurodegeneration in the multiple sclerosis brain. Brain 2016; 139: 807-815.

12. Bodini B, Chard D, Altmann DR, *et al.* White and grey matter damage in primary-progressive MS: the chicken or the egg? Neurology 2016; 86:170-176.

13. Petzold A, Steenwijk MD, Eikelenboom JM, *et al*. Elevated CSF neurofilament proteins predict brain atrophy: A 15-year follow-up study. Mult Scler 2016; 22:1154-1162.

14. Chataway J, Schuerer N, Alsanousi A, *et al*. Effect of high-dose simvastatin on brain atrophy and disability in secondary progressive multiple sclerosis (MS-STAT): a randomised, placebo-controlled, phase 2 trial. Lancet 2014; 383:2213-2221.

15. Martinez-Lapiscina EH, Arnow S, Wilson JA et al. Retinal thickness measured with optical coherence tomography and risk of disability worsening in multiple sclerosis: a cohort study. Lancet Neurol 2016; 15: 574-84.

**Emphasises the vlaue of this biomarker of axonal integrity of the optic nerve

16. Lublin F, Miller DH, Freedman MS, *et al*. Oral fingolimod in primary progressive multiple sclerosis (INFORMS): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet 2016; 387:1075-1084.

17. Tourbah A, Lebrun-Frenay C, Edan G, *et al*. MD1003 (high-dose biotin) for the treatment of progressive multiple sclerosis: A randomised, double-blind, placebo-controlled study. Mult Scler 2016; 22:1719-1731.

* Interesting therapeutic approach which invokes innovative mechanisms of action. Phase III trials will be of considerable interest.

18. Montalban X, Hauser SL, Kappos L, *et al*. Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis. New England J Med 2017; 376: 209-220.

** First positive Phase III trial in progressive MS

19. Raftopoulos R, Hickman SJ, Toosy A, *et al.* Phenytoin for neuroprotection in patients with acute optic neuritis: a randomised, placebo-controlled, phase 2 trial. Lancet Neurol 2016;15:259-269.
* suggests neuroprotection may have real benefit

20. Fox RJ, Coffey CS, Cudkowicz ME, *et al*. Design, rationale, and baseline characteristics of the randomized, double-blind, phase II clinical trial of ibudilast in progressive multiple sclerosis. Contemporary Clinical Trials 2016; 50: 166-177.

21. Chataway J. MS-SMART: Multiple Sclerosis-Secondary Progressive Multi-Arm Randomisation Trial - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/study/NCT01910259?term=ms-smart&rank=1 (accessed Feb 8, 2017).

22. Hempel S, Graham GD, Fu N, *et al.* A systematic review of modifiable risk factors in the progression of multiple sclerosis. Mult Scler 2017 [Epub ahead of print]

** Concerning lack of sound evidence base for the majority of modifiable risk factors

23. Hempel S, Graham GD, Fu N, *et al*. A systematic review of the effects of modifiable risk factor interventions on the progression of multiple sclerosis. Mult Scler 2017 [Epub ahead of print]

24. Campbell E, Coulter EH, Mattison PG, Miller L, McFayden A, Paul L. Physiotherapy rehabilitation for people with progressive multiple sclerosis: a systematic review. Arch Phys Med Rehab 2016; 97: 141-51.

25. Hupperts R, Lycke J, Short C et al. Prolonged-release fampridine and walking and balance in MS: a randomised controlled MOBILE trial Mult Scler 2016; 22: 212-21.

26. Marrie RA, Cohen J, Stuve O, *et al.* A systematic review of the incidence and prevalence of comorbidity in multiple sclerosis: Overview. Mult Scler 2015; 21:263-281.

27. Marrie RA, Miller A, Sormani MP, *et al*. Recommendations for observational studies of comorbidity in multiple sclerosis. Neurology 2016; 86:1446-1453.

28. Marrie RA, Miller A, Sormani MP, *et al.* The challenge of co-morbidity in clinical trials for multiple sclerosis. Neurology 2016; 86:1437-1445.
** Very helpful guidance which encourages the incorporation of co-morbidities in clinical trials of MS