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EDITORIAL

# Multiple Sclerosis: Unprecedented Progress But Significant Challenges Ahead

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One of the most challenging aspects of our role as guest editors for this special issue of *Neurotherapeutics* was deciding on the topics for review. Progress in the field of multiple sclerosis (MS) research has been substantial over the last several years. Whereas it may once have been possible to cover the entire field of MS in a single issue, that is certainly not the case today. Thus, rather than trying to be comprehensive, we selected topics that we felt would be the most high impact for our readers, allowing them to treat, educate, and advise patients with MS through the varied and complicated circumstances that they often present in the clinic. Additionally, despite much progress, several significant challenges in MS management remain, which we have attempted to highlight.

The issue focuses on 4 main themes. First, several disease modifying therapies (DMTs) with complex safety profiles recently received regulatory approval, and we felt it important to cover these agents. Second, despite the rapid proliferation of DMTs over the last 10 years, situations sometimes arise in which no available treatment option is sufficiently potent for a patient. Further, unmet needs with respect to remyelination and neuroprotection, especially in progressive MS, are quite urgent. Thus, we wanted to acquaint our readers with the current pipeline of treatments and procedures that will hopefully be routinely available for patients with MS in the near future. Third, MS clinical trials are a constantly evolving subject, especially with respect to outcomes, which prompted us to review some of the newest concepts in clinical trial design. Finally, with so many DMTs available, the decision of which to use and when requires greater sophistication than ever before. Not only is the choice a delicate balance of safety, efficacy, and cost, but there are also special populations to consider, such as pregnant women and children. Therefore, we conclude with a series of articles addressing important treatment considerations.

With respect to currently available therapies, ocrelizumab has generated significant excitement not only due to its potent efficacy in relapsing–remitting MS, but also as the first agent to receive approval for the treatment of primary progressive MS. Gelfand et al. [1] provide a comprehensive review of B-cell biology and its relationship to MS, as well as covering ocrelizumab, rituximab, and ofatumumab. Daclizumab is a recently approved agent that requires intensive safety monitoring, especially with respect to hepatotoxicity and cutaneous events. Baldassari and Rose [2] provide a thoughtful analysis of its place in the DMT landscape. Finally, Chaudhry et al. [3] review fingolimod and present a bridge into the pipeline section with a discussion of second-generation sphingosine-1-phosphate receptor modulators with greater receptor subtype specificity.

Pipeline treatments include cladribine, which was rejected by the Food and Drug Administration and the European Medicines Agency several years ago but recently received approval from the European Medicines Agency. Gavin Giovannoni [4] contributes a review of this medication, which will soon be joining the MS therapeutic landscape in Europe. There has been significant enthusiasm around immunoablation followed by autologous hematopoetic stem cell transplantation, a treatment with

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impressive efficacy but with serious safety concerns. Atkins and Freedman [5] answer 5 important questions about the procedure. Bove and Green [6] conclude this section with a review of remyelinating pharmacotherapies, which could perhaps be considered the holy grail of MS therapeutics at this time.

As we move forward in the development of new therapeutics, our discussion shifts to challenges for future trials. One roadblock in the development of neuroprotective and restorative agents is the lack of an adequate clinical biomarker. Mahajan and Ontaneda [7] provide an overview of current advanced magnetic resonance imaging techniques which have the potential to address this need, while Sormani and Pardini [8] focus on how magnetic resonance imaging, positron emission tomography, optical coherence tomography, and visual evoked potentials can be incorporated into phase II trials assessing repair. There is increased recognition of the importance of understanding how patients are affected by their disease, and Nowinski et al. [9] provide a useful analysis on the evolution of patient-reported outcomes with particular attention paid to the importance of measuring patient-reported outcomes in MS clinical research. Lastly, there are patients and patient organizations that have come together to take a more active role in directing MS research, but this has many potential ethical conflicts. Amezcua and Nelson [10] provide a thoughtful review on the ethical issues surrounding patient-funded research from the clinician–scientist point of view, and provide recommendations on how to maintain scientific integrity while addressing unmet funding needs in MS research.

The last collection of articles cover various topics facing clinicians who care for MS patients. First, Smith et al. [11] cover treatments to achieve target goals (no evidence of disease activity) with medications in current use and discuss potential future additions to the no evidence of disease activity target to better achieve reduction of long-term disability. The discussion of improving treatment targets often leads to questions of when to use highly efficacious treatments in MS, so we must also be cognizant of the serious safety issues associated with some of our therapies. Williamson and Berger [12] take on the task of updating us on progressive multifocal leukoencephalopathy as a consequence of MS therapies and potential progressive multifocal leukoencephalopathy treatment approaches. We then transition to the care of special populations. Voskuhl and Momtazee [13] provide a thorough review on the effects of pregnancy on MS and recent trials, and additionally provide a comprehensive guide to MS care during pregnancy and breastfeeding. McGinley and Rossman [14] offer a detailed discussion on pediatric MS and present a potential high efficacy treatment algorithm as a future direction to be studied in the pediatric population. Next, Moss et al. [15] remind us that caring for the MS population also includes attending to their comorbidities and wellness, and offer useful recommendations for lifestyle modifications. Finally, Hartung [16] does a commendable job in describing the complex issues behind the pricing of MS therapies, particularly in the USA, the difficulties in determining the economic value of MS therapies, and covers potential solutions on this important topic.

The fast pace of growth in the MS therapeutics field makes it challenging to stay abreast of all the developments. We therefore thank Dr. Maral Mouradian, Editor-in-Chief of *Neurotherapeutics*, for providing us with the opportunity to compile this special issue on MS. We are very grateful to our contributors and pleased to be able to recruit so many distinguished individuals to share their insights on these important themes. We are also grateful to the reviewers who provided their expertise and invaluable guidance. Of course, this issue would not have been possible without the editorial assistance of Linda Powell, who was instrumental with her gentle reminders and technical assistance to keep us on target. We hope the readers of *Neurotherapeutics* find that this issue provides useful updates on the status of MS therapeutics and the key challenges to be addressed in the upcoming years.

**Required Author Forms** Disclosure forms provided by the authors are available with the online version of this article.

## References


1. Gelfand JM, Cree BAC, Hauser SL. Ocrelizumab and other CD20$^+$ B-cell-depleting therapies in multiple sclerosis. Neurotherapeutics 2017; 14:4. https://doi.org/10.1007/s13311-017-0557-4
2. Baldassari LE, Rose JW. Daclizumab: development, clinical trials, and practical aspects of use in multiple sclerosis. Neurotherapeutics 2017; 14:4. https://doi.org/10.1007/s13311-017-0553-8
3. Chaudhry BZ, Cohen JA, Conway DS. Sphingosine 1-phosphate receptor modulators for the treatment of multiple sclerosis. Neurotherapeutics 2017; 14:4. https://doi.org/10.1007/s13311-017-0565-4
4. Giovannoni G. Cladribine to treat relapsing forms of multiple sclerosis. Neurotherapeutics 2017; 14:4. https://doi.org/10.1007/s13311-017-0573-4
5. Atkins HL, Freedman MS. Five questions answered: a review of autologous hematopoietic stem cell transplantation for the treatment of multiple sclerosis. Neurotherapeutics 2017; 14:4. https://doi.org/10.1007/s13311-017-0564-5
6. Bove RM, Green AJ. Remyelinating pharmacotherapies in multiple sclerosis. Neurotherapeutics 2017; 14:4. https://doi.org/10.1007/s13311-017-0577-0
7. Mahajan KR, Ontaneda D. The role of advanced magnetic resonance imaging techniques in multiple sclerosis clinical trials. Neurotherapeutics 2017; 14:4. https://doi.org/10.1007/s13311-017-0561-8
8. Sormani MP, Pardini M. Assessing repair in multiple sclerosis: outcomes for phase II clinical trials. Neurotherapeutics 2017; 14:4. https://doi.org/10.1007/s13311-017-0558-3
9. Nowinski CM, Miller DM, Cella D. Evolution of patient-reported outcomes and their role in multiple sclerosis clinical trials. Neurotherapeutics 2017; 14:4. https://doi.org/10.1007/s13311-017-0571-6
10. Amezcua L, Nelson F. Ethical considerations of patient-funded research for multiple sclerosis therapeutics. Neurotherapeutics 2017; 14:4. https://doi.org/10.1007/s13311-017-0560-9

11. Smith AL, Cohen JA, Hua LH. Therapeutic targets for multiple sclerosis: current treatment goals and future directions. Neurotherapeutics 2017; 14:4. https://doi.org/10.1007/s13311-017-0548-5
12. Williamson EML, Berger JR. Diagnosis and treatment of progressive multifocal leukoencephalopathy associated with multiple sclerosis therapies. Neurotherapeutics 2017; 14:4. https://doi.org/10.1007/s13311-017-0570-7
13. Voskuhl R, Momtazee C. Pregnancy: effect on multiple sclerosis, treatment considerations, and breastfeeding. Neurotherapeutics 2017; 14:4. https://doi.org/10.1007/s13311-017-0562-7
14. McGinley MP, Rossman IT. Bringing the HEET: the argument for high-efficacy early treatment for pediatric-onset multiple sclerosis. Neurotherapeutics 2017; 14:4. https://doi.org/10.1007/s13311-017-0568-1
15. Moss BP, Rensel MR, Hersh CM. Wellness and the role of comorbidities in multiple sclerosis. Neurotherapeutics 2017; 14:4. https://doi.org/10.1007/s13311-017-0563-6
16. Hartung DM. Economics and cost-effectiveness of multiple sclerosis therapies in the USA. Neurotherapeutics 2017; 14:4. https://doi.org/10.1007/s13311-017-0566-3