VIEWS & REVIEWS OPEN ACCESS

The 2013 clinical course descriptors for multiple sclerosis

A clarification

Fred D. Lublin, MD, Timothy Coetzee, PhD, Jeffrey A. Cohen, MD, Ruth A. Marrie, MD, PhD, and Alan J. Thompson, MD, on behalf of the International Advisory Committee on Clinical Trials in MS

Correspondence
Dr. Lublin
fred.lublin@mssm.edu

Neurology® 2020;94:1088-1092. doi:10.1212/WNL.0000000000009636

Abstract

The clinical courses of multiple sclerosis were defined in 1996 and refined in 2013 to provide a time-based assessment of the current status of the individual. These definitions have been successfully used by clinicians, clinical trialists, and regulatory authorities. Recent regulatory decisions produced variations and discrepancies in the use of the clinical course descriptions. We provide here a clarification of the concepts underlying these descriptions and restate the principles used in their development. Importantly, we highlight the critical importance of time framing the disease course modifiers activity and progression and clarify the difference between the terms worsening and progressing.

Introduction

In 1996, the International Advisory Committee on Clinical Trials in MS (a body currently sponsored by the European Committee for Treatment and Research in MS and the US National Multiple Sclerosis Society) published an article defining the clinical course of multiple sclerosis (MS).[1] These definitions were subsequently updated in 2013.[2] The purpose of these consensus descriptions was to standardize the terminology used to characterize the different clinical courses of MS and (in the 2013 revision) add descriptors for the current state of the patient.

Accurate, standardized clinical course descriptors are important for several reasons. First, they facilitate communication between clinicians and persons with MS. Second, they are necessary to support studies describing the natural history of MS and facilitate accurate identification of prognostic indicators by clinical course. Third, they reduce heterogeneity in the populations recruited for clinical trials and assist in the application of trial results to appropriate patient populations in clinical practice.

The current classifications of MS have been generally accepted by clinicians, researchers, sponsors, and regulators. However, recent approvals for several disease-modifying therapies, including ocrelizumab, siponimod, and cladribine, introduced variations and some discrepancies in the use of the clinical course descriptors in the associated regulatory communications.[3–8] Variation in the application of the clinical course descriptors has the potential to create some confusion in clinical practice, the conduct of future clinical trials, and decisions by health authorities, insurers, and related entities concerning patient access

From the Department of Neurology (F.D.L.), Corinne Goldsmith Dickinson Center for Multiple Sclerosis, Icahn School of Medicine at Mount Sinai, New York, NY; National Multiple Sclerosis Society (T.C.), New York, NY; Department of Neurology (J.A.C.), Mellen Center for Multiple Sclerosis Treatment and Research, Neurological Institute, Cleveland Clinic, OH; Departments of Internal Medicine (Neurology) and Community Health Sciences (R.A.M.), Rady Faculty of Health Sciences, Max Rady College of Medicine, University of Manitoba, Winnipeg, Canada; and Faculty of Brain Sciences (A.J.T.), University College, London, United Kingdom.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

International Advisory Committee on Clinical Trials in MS coinvestigators are listed in the appendix 2 at the end of the article.

The Article Processing Charge was funded by the National Multiple Sclerosis Society and the European Committee for Treatment and Research in Multiple Sclerosis.

Glossary

MS = multiple sclerosis; **PPMS** = primary progressive multiple sclerosis; **SPMS** = secondary progressive multiple sclerosis.

to approved treatments. This situation has prompted the committee to clarify the concepts underlying these descriptions and to restate the principles used in their development.

Multiple sclerosis phenotypes

Since 2013, the phenotypes that have been used to characterize MS are clinically isolated syndrome (monophasic clinical episode typical of CNS demyelination in a patient not known to have MS), relapsing-remitting MS, primary progressive MS (PPMS), and secondary progressive MS (SPMS), and they are referenced in the recently published MS diagnostic criteria.[9] The modifiers describing the current disease state are (1) assessments of activity—evidenced either by clinical relapses or imaging (gadolinium-enhancing lesions or new or unequivocally enlarging T2 lesions)—and (2) an assessment of progression—clinical evidence of disability worsening, independent of relapses, over a given period of time in patients who are in a progressive phase of the disease (i.e., PPMS or SPMS).[2]

A critical aspect of the 2013 addition of modifiers for activity and progression was that these terms must be framed in time.[2] Although a specific time frame was not initially specified, we recommended and reaffirm that at a minimum, disease activity and progression should be evaluated annually. When used in this manner, the modifiers represent a current assessment of the disease and can enable monitoring of changes over time.

As stated in the committee's previous articles, these recommended characterizations were based on the clinician's determination of the patient's clinical course.[1,2] Although these characterizations are informed by our understanding of the pathobiology underlying the clinical courses, this pathobiology is incompletely understood. There is a common view that the underlying pathology of MS involves both inflammation and neurodegeneration. However, the relationship between the clinical evolution of the disease and these mechanisms is complex and requires further characterization. Although MRI remains an incomplete indicator of disease course, it has increasing utility as a measure of activity, as discussed below.

Challenges

The phenotype characterizations are widely used, but we have observed increasing inconsistency in how they are applied, particularly by regulatory authorities. Specific areas of concern include the use of the terms activity, progression, and worsening.

Regulators in Europe and the United States have used different definitions of activity in recent marketing authorizations for ocrelizumab, siponimod, and cladribine. Whereas European regulators have defined activity as evidenced by relapses or imaging features of inflammatory activity, US regulators limited the definition of activity to clinical relapses; MRI criteria for activity were not mentioned. These definitions are further complicated by the absence of a time frame in the product labels, which have included the terms active SPMS or SPMS with active disease in the United States and Europe.[5–7] Without a time frame, these terms have little meaning, as all patients with SPMS (which by definition follows a relapsing-remitting phase) experienced active disease at some point. Inclusion of a time frame is critical for effective clinical decision making. A better approach would have been for the US labels for siponimod and cladribine (and the subsequent labeling updates of other approved DMTs) to have used the full definition of activity (i.e., either clinical or MRI activity) and include a specified time period for designating activity in those who are considered active SPMS, as discussed above. This more specific characterization would be understandable based on the concepts we had proposed and could be applied readily by clinicians, health systems, and related entities. The divergence between European and US regulators in use of the clinical course descriptors is problematic as it introduces potential confusion for drug developers, researchers publishing results, clinicians, and persons with MS.[8] Although a broader labeled indication may provide prescribers greater latitude in determining the indications for an agent, there is a risk that in the absence of a standardized definition, payors, health authorities, and related bodies might use this as an opportunity to restrict access to a needed medication.

For purposes of clarity, we recommend that the more general term worsening be used to describe any increase in impairment/disability irrespective of whether it has resulted from residual deficits following a relapse or increasing disability during the progressive phase of the illness. We recommend reserving the term progressing or disease progression to describe those in a progressive phase of MS (PPMS or SPMS) who are accruing disability, independent of any relapse activity.

Conclusion

In summary, the committee urges clinicians, investigators, and regulators to consistently and fully use the 2013 phenotype

Table Definitions and time frames referenced in this article

Term	Definition	Recommended time frame for evaluation
Active disease	Clinical: relapses, acute or subacute episodes of new or increasing neurologic dysfunction, followed by full or partial recovery, in the absence of fever or infection	Annually (but can be another time frame, as long as it is specified)
	and/or	
	Imaging: gadolinium-enhancing lesions or new or unequivocally enlarging T2 lesions	Annually (but can be another time frame, as long as it is specified)
Progressing disease or disease progression	Accrual of disability, independent of any relapse activity, during the progressive phase of MS (PPMS or SPMS)	Annually by clinical assessment (but can be another time frame, as long as it is specified)
Worsening disease	Any increase in impairment/disability irrespective of whether it has resulted from residual deficits following a relapse or (increasing) progressive disability during the progressive phase of the illness	Not required

Abbreviations: PPMS = primary progressive multiple sclerosis; SPMS = secondary progressive multiple sclerosis.

characterizations by (1) using the full definition of activity, that is, the occurrence of a relapse or new activity on an MRI scan (a gadolinium-enhancing lesion or a new/unequivocally enlarging T2 lesion)[2]; (2) framing activity and progression in time; and (3) using the terms worsening and progressing or disease progression more precisely when describing MS course. The recommended terms and relevant time frames are defined in the table.

We recognize that terminology and classification of the MS disease course are dynamic and will require redefining and clarifications as new data and measurement approaches become available, with the goal of developing more biologically based disease course characterizations that provide clarity and avoid unintended consequences. To this end, the committee is planning for their next review of this topic for 2020 to revisit the clinical courses with a particular focus on progression and the contributors to progression.

Study funding

This work and the International Advisory Committee on Clinical Trials in MS are funded by the European Committee for Treatment and Research in Multiple Sclerosis and the National Multiple Sclerosis Society.

Disclosure

F.D. Lublin discloses consulting arrangements with Biogen, EMD Serono, Novartis, Teva, Actelion, Sanofi/Genzyme, Acorda, Roche/Genentech, MedImmune/Viela Bio, Receptos/Celgene, TG Therapeutics, MedDay, Atara Biotherapeutics, Polpharma, Mapi Pharma, Innate Immunotherapeutics, Apitope, Orion Biotechnology, Brainstorm Cell Therapeutics, Jazz Pharmaceuticals, GW Pharma, Mylan, Immunic, and Population Council. T. Coetzee has nothing to disclose. J.A. Cohen reports personal compensation for consulting for Convelo, Mylan, and Population Council and serving as an Editor of *Multiple Sclerosis Journal*. R A. Marrie receives funding from the Canadian Institutes of Health Research, Research Manitoba, Multiple Sclerosis Society of Canada, Multiple Sclerosis Scientific Foundation, Crohn's and Colitis Canada, National Multiple Sclerosis Society, and the Consortium of Multiple Sclerosis Centers. She is supported by the Waugh Family Chair in Multiple Sclerosis. A.J. Thompson reports personal fees paid to his institution and other from Eisai Ltd and Hoffmann-La Roche; is an editorial board member for *The Lancet Neurology* receiving a free subscription; is Editor-in-Chief for *Multiple Sclerosis Journal* receiving an honorarium from SAGE Publications; receives support for travel as Chair, Scientific Advisory Committee, International Progressive MS Alliance, and from the National MS Society (USA) as member, NMSS Research Programs Advisory Committee; and received honoraria and support for travel for lecturing from EXCEMED and Almirall. Support is acknowledged from the UCL/UCLH NIHR Biomedical Research Centre. Go to Neurology.org/N for full disclosures.

Publication history

Received by *Neurology* January 22, 2020. Accepted in final form April 1, 2020.

Appendix 1 Authors

Name	Location	Contribution
Fred D. Lublin, MD	Icahn School of Medicine at Mount Sinai, NY, United States	Drafting of the manuscript, revision of the manuscript, and approval of the final version for publication

Appendix 1 *(continued)*

Name	Location	Contribution
Timothy Coetzee, PhD	National MS Society, New York, United States	Drafting of the manuscript, revision of the manuscript, and approval of the final version for publication
Jeffrey A. Cohen, MD	Cleveland Clinic, Cleveland, United States	Revision of the manuscript and approval of the final version for publication
Ruth A. Marrie, MD, PhD	University of Manitoba, Winnipeg, Canada	Revision of the manuscript and approval of the final version for publication
Alan J. Thompson, MD	University College London, London, United Kingdom	Drafting of the manuscript, revision of the manuscript, and approval of the final version for publication

Appendix 2 Coinvestigators

Name	Location	Role	Contribution
Maria Pia Amato	University of Florence Florence, Italy	Committee member	Reviewed the manuscript
Frederik Barkhof	VU University Amsterdam, Amsterdam, Netherlands	Committee member	Reviewed the manuscript
Tanuja Chitnis	Brigham and Women's Hospital, Boston	Committee member	Reviewed the manuscript
Giancarlo Comi	University Vita-Salute San Raffaele, Milan, Italy	Committee member	Reviewed the manuscript
Jorge Correale	Raúl Carrea Institute for Neurologic Research (FLENI) Buenos Aires, Argentina	Committee member	Reviewed the manuscript
Gary Cutter	University of Alabama at Birmingham, Birmingham	Committee member	Reviewed the manuscript
Tobias Derfuss	University Basel, Basel, Switzerland	Committee member	Reviewed the manuscript
Marcia Finlayson	Queens University, London, Canada	Committee member	Reviewed the manuscript
Ari Green	University of California San Francisco, San Francisco	Committee member	Reviewed the manuscript
Hans-Peter Hartung	Heinrich-Heine-University, Düsseldorf, Germany	Committee member	Reviewed the manuscript
Bernhard Hemmer	Technical University of Munich, Munich, Germany	Committee member	Reviewed the manuscript
Aaron Miller	Mount Sinai School of Medicine, New York	Committee member	Reviewed the manuscript
Xavier Montalban	University of Toronto, Toronto, Canada	Committee member	Reviewed the manuscript
Ellen Mowry	Johns Hopkins University, Baltimore	Committee member	Reviewed the manuscript
Alex Rovira Cañellas	Universitat Autònoma de Barcelona, Barcelona Spain	Committee member	Reviewed the manuscript
Amber Salter	Washington University St. Louis, St. Louis	Committee member	Reviewed the manuscript
Per Soelberg Sørensen	Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark	Committee member	Reviewed the manuscript
Maria Pia Sormani	University of Genoa, Genoa, Italy	Committee member	Reviewed the manuscript
Mar Tintore	Universitat Autònoma de Barcelona, Barcelona, Spain	Committee member	Reviewed the manuscript
Maria Trojano	University of Bari, Bari, Italy	Committee member	Reviewed the manuscript
Bernard Uitdehaag	VU University Medical Center, Amsterdam, Netherlands	Committee member	Reviewed the manuscript
Sandra Vukusic	Hôpital Neurologique Pierre Werthemier—GHE, Lyon, France	Committee member	Reviewed the manuscript
Emmanuelle Waubant	University of California San Francisco, San Francisco	Committee member	Reviewed the manuscript
Dean Wingerchuk	Mayo Clinic, Scottsdale	Committee member	Reviewed the manuscript

References

1. Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. National multiple sclerosis society (USA) advisory committee on clinical trials of new agents in multiple sclerosis. Neurology 1996; 46:907–911.
2. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology 2014;83:278–286.
3. Food and Drug Administration (USA). Ocrelizumab Summary Review; 2017. Available at: accessdata.fda.gov/drugsatfda_docs/nda/2017/761053Orig1s000-SumR.pdf. Accessed November 23, 2019.
4. European Medicines Agency. Summary of Opinion—Ocrevus; 2017. Available at: ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-ocrevus_en.pdf. Accessed September 23, 2019.
5. European Medicines Agency. Summary of Opinion—Mayzent; 2019. Available at: ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-mayzent_en.pdf. Accessed September 23, 2019.

6. Food and Drug Administration (USA). Siponimod Summary Review; 2019. Available at: accessdata.fda.gov/drugsatfda_docs/nda/2019/209884Orig1s000SumR.pdf. Accessed September 23, 2019.
7. Food and Drug Administration (USA). Cladribine Summary Review; 2019. Available at: accessdata.fda.gov/drugsatfda_docs/nda/2019/022561Orig1s000SumR.pdf. Accessed September 23, 2019.
8. Coetzee T, Thompson AJ. Unified understanding of MS course is required for drug development. Nat Rev Neurol 2018;14:191–192.
9. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 2018;17:162–173.