EDITORIAL

Navigating the TOR of Multiple Sclerosis

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In this issue of CJNS, the Canadian Multiple Sclerosis Working Group (CMSWG) unveil a contemporary edition of Treatment Optimization Recommendations (TOR).[1] Similar to a geographical tor or summit, the TOR are a culmination or peak of current knowledge in multiple sclerosis (MS). This collaborative effort is a guide written by expert clinicians based on available evidence rather than formal clinical practice guidelines. The intent of the TOR is to help neurologists navigate treatment decisions in a shared decision-making process with individuals with MS.

Since the original CMSWG recommendations in 2004, the objective has been to develop practical recommendations to empower neurologists to assess response to disease-modifying therapy (DMT) and make an informed decision regarding change in treatment to optimize outcome.[2] The original recommendations were based on a model assessing response to DMT in three domains: relapses, progression, and magnetic resonance imaging (MRI) outcomes.[3] This clinically practical model was developed to apply to the first agents (interferon-β and glatiramer acetate) shown to change the natural history of relapsing MS.[2] Over the next decade, there was a rapid expansion in DMT options for relapsing MS. In response, the revised CMSWG recommendations in 2013 introduced the concept of evaluating treatment response to inform switching DMT to a lateral treatment versus escalation treatment.[4]

The current CMSWG recommendations provide guidance in the increasingly complex landscape of MS treatment.[1] As DMT options increase for relapsing MS, it is clear that key points include (1) recommending treatment initiation soon after diagnosis, (2) performing risk stratification to inform initial DMT selection, and (3) re-evaluating at regular intervals to enable escalation of therapy for suboptimal treatment response. There is increasing evidence that early initiation of therapy results in improved long-term outcome.[5] Striving to initiate DMT early in the disease course is facilitated by the updated McDonald criteria which enable earlier MS diagnosis.[6] While some individuals have risk factors favoring a high-efficacy therapy as initial DMT, the most common treatment course remains initiation of a platform therapy with an escalation approach for suboptimal response. High-efficacy therapies (alemtuzumab, cladribine, fingolimod, natalizumab, and ocrelizumab) have greater efficacy but a more substantial side effect profile than platform therapies (dimethyl fumarate, glatiramer acetate, interferon-β, and teriflunomide). It is worth noting that there is mounting evidence that starting a high-efficacy therapy as initial DMT is associated with improved long-term outcome.[7,8] At this point, the optimal approach (initial high-efficacy therapy versus escalation therapy) for the majority of individuals with relapsing MS remains an unresolved debate.[9] If an escalation approach is adopted, then it is important to adjust treatment for suboptimal response and not fall into therapeutic inertia.[10]

An exciting new addition to the current CMSWG recommendations is the introduction of DMT for progressive forms of MS. Ocrelizumab has demonstrated a benefit in disability progression for primary progressive MS among individuals aged 18–55 years with ~25% having gadolinium-enhancing lesions at baseline.[11] Siponimod has demonstrated a benefit in disability progression for secondary progressive MS among individuals aged 18–60 years with active inflammatory disease.[12] Given that the mechanism of these medications is believed to be immunomodulatory, it is likely that these medications will be most beneficial early in progressive MS while there is active inflammatory disease.

Although the current CMSWG recommendations provide advice on when to consider switching therapy based on major/minor criteria for evaluating relapses and MRI activity, the optimal goal for MS disease activity remains unclear. No evidence of disease activity (NEDA) is most commonly defined as absence of relapses, progression measured by Expanded Disability Status Scale (EDSS), and new/enlarging MRI lesions.[13] Although NEDA is difficult to achieve, it remains inadequate in communicating the manifestations and pathophysiology of MS. Additional considerations include cognition, brain/spinal cord atrophy, and biomarkers. While cognition should be evaluated with a tool such as the Symbol Digit Modalities Test, there is insufficient evidence that changing DMT will improve cognitive decline and switching DMT for this indication should be avoided. Brain and spinal cord atrophy are emerging indicators of disease severity but it is premature to recommend use in routine clinical practice given lack of standardization in image acquisition and interpretation. Biomarkers, particularly neurofilament light chain, are an emerging measure of disease activity but it is premature to recommend biomarker testing to guide clinical practice. Despite NEDA being inadequate to express the breadth of MS, it is uncertain whether NEDA versus minimal evidence of disease activity result in different long-term outcome.[14]

This version of the CMSWG recommendations considers treatment throughout the life cycle including pediatric-onset MS, family planning considerations, and among older adults with MS. All of these topics are emerging areas with sparse high-quality evidence for the basis of treatment decisions. As more individuals with MS are treated with high-efficacy therapy, the issue of immunosenescence is of increasing importance. The current recommendations suggest that consideration may be given to

discontinuation of DMT among individuals aged >60 years with a period of clinical stability. Among a group of patients aged >60 years who discontinued DMT, ~90% remained off therapy although it is important to note that 80% were receiving a form of platform therapy (66% injectable, 14% oral) at the time of DMT discontinuation.[15]

Recently, the American Academy of Neurology (AAN) released practice guidelines concerning DMT for adults with MS.[16] These evidence-based recommendations on starting, switching, and stopping DMT are based on the results of a systematic review, and all recommendations are assigned a quality of evidence rating. The AAN practice guidelines are a useful compliment to the CMSWG TOR. The purpose of the TOR is not to duplicate these practice guidelines but provide a framework to guide clinical decision-making based on informed expert advice.

Personally, I find the CMSWG TOR a very practical tool in reflecting on my own practice and one that will be of use in navigating future treatment discussions with patients in the MS clinic. I believe that other clinicians who treat individuals with MS will be of a similar opinion. The TOR are a pinnacle of teamwork with current evidence and expert opinion culminating in a resource for other clinicians both nationally and internationally. In the evolving landscape of MS therapy, I foresee that as this edition of TOR is released that the next TOR is on the horizon.

Disclosures

Natalie E. Parks has provided consulting services to Biogen, EMD Serono, Roche, and Sanofi Genzyme. She has accepted funds from Biogen and Roche for travel to a scientific conference. She has acted as site sub-investigator for clinical trials for Biogen, MedDay, Sanofi Genzyme, and Roche. She is the recipient of a Killam Predoctoral Scholarship, Nova Scotia Graduate Scholarship, and Dalhousie Medical Research Foundation Multiple Sclerosis Graduate Studentship.

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References

1. Freedman MS, Devonshire V, Duquette P, et al. Treatment optimization in multiple sclerosis: Canadian MS Working Group recommendations. Can J Neurol Sci. 2020. doi: 10.1017/cjn.2020.66.
2. Freedman MS, Patry DG, Grand'Maison F, Myles ML, Paty DW, Selchen DH. Treatment optimization in multiple sclerosis. Can J Neurol Sci. 2004;31:157–68.
3. Bashir K, Buchwald L, Coyle PK, et al. MS patient management: optimizing the benefit of immunomodulatory therapy. Int J MS Care. 2002;(Suppl):1–7.
4. Freedman MS, Selchen D, Arnold DL, et al. Treatment optimization in MS: Canadian MS Working Group updated recommendations. Can J Neurol Sci. 2013;40:307–23.
5. Chalmer TA, Baggesen LM, Norgaard M, Koch-Henriksen N, Magyari M, Sorensen PS. Early versus later treatment in multiple sclerosis: a register-based cohort study. Eur J Neurol. 2018;25:1262–70.
6. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17:162–73.
7. Harding K, Williams O, Willis M, et al. Clinical outcomes of escalation vs early intensive disease-modifying therapy in patients with multiple sclerosis. JAMA Neurol. 2019;76:536–41.
8. Brown JW, Coles A, Horakova D, et al. Association of initial disease-modifying therapy with later conversion to secondary progressive multiple sclerosis. JAMA. 2019;321:175–87.
9. Burton JM, Traboulsee A. Nothing ventured, nothing gained? Navigating disease-modifying treatment in multiple sclerosis. Can J Neurol Sci. 2018;45:487–88.
10. Saposnik G, Montalban X, Selchen D, et al. Therapeutic inertia in multiple sclerosis care: a study of Canadian neurologists. Front Neurol. 2018;9:781.
11. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. N Engl J Med. 2017;376:209–20.
12. Kappos L, Bar-Or A, Cree BA, et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. Lancet. 2018;391:1263–73.
13. Parks NE, Flanagan EP, Lucchinetti CF, Wingerchuk DM. NEDA treatment target? No evident disease activity as an actionable outcome in practice. J Neurol Sci. 2017;383:31–34.
14. Prosperini L, Mancinelli C, Haggiag S, et al. Minimal evidence of disease activity (MEDA) in relapsing-remitting multiple sclerosis. J Neurol Neurosurg Psychiatry. 2020;91:271–77.
15. Hua LH, Fan TH, Conway D, Thompson N, Kinzy TG. Discontinuation of disease-modifying therapy in patients with multiple sclerosis over age 60. Mult Scler. 2019;25:699–708.
16. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis. Neurology. 2018;90:777–88.

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