Utility of the Canadian Treatment Optimization Recommendations (TOR) in MS Care

François Grand’Maison, Virender Bhan, Mark S. Freedman, Mary L. Myles, David G. Patry, Daniel H. Selchen, Patrick Moriarty, Anthony L. Traboulsee

ABSTRACT: Objectives: Criteria for Treatment Optimization Recommendations (TOR) for patients with multiple sclerosis (MS) identify suboptimal response to disease-modifying treatment (DMT). The Canadian TOR (CanTOR) were used to indicate recommendations for treatment switches or treatment maintenance based on relapse, disease progression and magnetic resonance imaging (MRI) criteria in patients. We assessed concordance between the TOR and clinicians’ decisions regarding treatment response and identified prevalence of patients with MS receiving DMT meeting medium/high levels of concern according to TOR. Methods: Prospective baseline and end-of-study assessments of patients with relapsing–remitting MS (RRMS) or clinically isolated syndrome were conducted in this open-label, 12-month, Phase IV, observational Canadian study. Results: Data were reported for 184 patients (female 72%, mean age 39 years) of which 96% had RRMS. The TOR criteria identified 19 (10.3%) patients with suboptimal response to treatment. Twelve patients had ≥1 high level of concern. Two patients had ≥2 medium levels of concern. Concordance between TOR and clinician decision in maintaining treatment was 95.3%. Where treatment change was recommended by the TOR, concordance was 29.4%. Clinicians identified the TOR as the principal reason for changing treatment in 50.0% of cases where the TOR identified suboptimal response. The TOR were considered useful by 70.6% of clinicians when treatment optimization was recommended and by 55.3% when maintaining treatment was recommended. Conclusions: The TOR criteria can identify suboptimal response in this patient cohort. Concordance between TOR and clinician decision was high when maintaining treatment was recommended. Usefulness of the TOR was most apparent when treatment optimization was recommended.
ensure that patients receive the appropriate treatment, standardized criteria to determine whether treatment response is suboptimal in the patient is required.

Based on a previous model representing an important first step in the development of defining optimal and suboptimal responses to DMTs, the Canadian Multiple Sclerosis Working Group proposed practice guidelines, the Treatment Optimization Recommendations (TOR) (summarized in Table 1) to enable clinicians to assess the status of patients with relapsing–remitting MS (RRMS) receiving DMTs, define suboptimal treatment responses, and on these bases determine when treatment optimization by modification or a switch in treatment should be considered.

The Canadian TOR (CanTOR) utilize relapse, disease progression and magnetic resonance imaging (MRI) criteria to define a threshold for considering suboptimal treatment response in a patient. The CanTOR categorize – by level of concern (high, medium or low) – any changes in relapse and disease progression. Any changes in MRI findings can be classified as medium or low concern only (as the CanTOR stipulate that no single MRI change would be considered an indication in itself to alter treatment).

A change in treatment should be considered when all three outcomes are classified as ‘low’, any two are classified as ‘medium’ or if relapse or disease progression is classified as ‘high’ concern.

Several studies have evaluated the applicability and utility of the CanTOR in clinical practice. Freedman et al retrospectively applied a modified CanTOR from Year 1 of the four-year Phase III, multicentre, randomized, double-blind, placebo-controlled (two years) followed by randomized, double-blind, active treatment at two doses (two years) PRISMS (Prevention of Relapses and Disability by Interferon beta-1a [IFN β-1a] Subcutaneously in Multiple Sclerosis) study evaluating data for 362 patients who received IFN β-1a treatment. Overall, 39% of patients receiving treatment showed either a medium or high level of concern after one year of treatment, 89% of whom went on to develop further disease breakthrough over Years 2-4. Among the 61% of patients having no or low levels of concern after one year of treatment, 67% experienced further disease breakthrough. Although this is a substantial proportion of patients, suggesting that these patients were not accurately classified, the rate was still significantly lower than that observed in the medium- or high-concern group. These findings suggest

Table 1: Treatment Optimization Recommendations criteria for determining level of concern for patients with changes in relapse, disease progression and MRI outcomes (adapted with permission from Freedman et al. Can J Neurol Sci 2004;31(2):157–68)

<table>
<thead>
<tr>
<th>Relapse</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
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<tbody>
<tr>
<td>Rate</td>
<td>Moderate reduction versus BL (76–&lt;100%)</td>
<td>Must reduction versus BL (35–75%)</td>
<td>Minimal reduction versus BL (0–35%)</td>
</tr>
<tr>
<td>Severity</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>Steroids required</td>
<td>No</td>
<td>Yes</td>
<td>Yes/hospitalization</td>
</tr>
<tr>
<td>Effect on ADL</td>
<td>Minimal</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>Functional domain affected</td>
<td>1</td>
<td>&gt;1</td>
<td>&gt;1</td>
</tr>
<tr>
<td>Motor/cerebellar involvement</td>
<td>None or mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>Recovery</td>
<td>Prompt</td>
<td>Incomplete at 3 months</td>
<td>Incomplete at 6 months</td>
</tr>
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<table>
<thead>
<tr>
<th>Disease progression</th>
<th></th>
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<tbody>
<tr>
<td>EDSS score ≤3.5</td>
<td>&lt;2 points</td>
<td>2 points confirmed at 6 months</td>
<td>&gt;2 points confirmed at 6 months 2 points confirmed at 12 months</td>
</tr>
<tr>
<td>EDSS score 4–5</td>
<td>&lt;1 point</td>
<td>1 point confirmed at 6 months</td>
<td>&gt;1 point confirmed at 6 months 1 point confirmed at 12 months</td>
</tr>
<tr>
<td>EDSS score ≥5.5</td>
<td>0.5 point confirmed at 6 months</td>
<td>&gt;0.5 point confirmed at 6 months</td>
<td></td>
</tr>
<tr>
<td>Clinically documented progression</td>
<td>No motor</td>
<td>Some motor/cerebellar or cognitive involvement; Multiple domains affected</td>
<td>Pronounced motor/cerebellar or cognitive involvement; Multiple domains affected</td>
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<table>
<thead>
<tr>
<th>MRI†</th>
<th></th>
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<tbody>
<tr>
<td>Categories</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New Gd-enhancing lesions</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>New T2 lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enlarging T2 (burden of disease)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New T1-hypointense lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enlarging T1-hypointense lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrophy</td>
<td>Any new lesion</td>
<td>Increase in ≥2 categories</td>
<td></td>
</tr>
</tbody>
</table>

Note: Reference time frame ≥2 years prior to treatment initiation. Ideally, prospective and objective relapse data should be obtained during the reference period. *Suggests treatment is no better than placebo; †Routine follow-up MRI is not recommended in established MS; MRI must have been performed according to a standardized protocol; treatment modification should not be considered based on MRI outcomes alone; ADL, activities of daily living; BL, baseline; EDSS, Expanded Disability Status Scale; Gd, gadolinium; MRI, magnetic resonance imaging; MS, Multiple Sclerosis; >, more than; ≥, more than or equal to; <, less than.
that the CanTOR may be important for forming a comprehensive approach to early treatment optimization with DMTs.11

Ruiz-Pena et al12 retrospectively applied the CanTOR to a Spanish cohort of 55 patients treated with intramuscular IFN β-1a between 1998 and 2004, 22 (40%) of whom met the criteria for considering a change in treatment. The annualized relapse rate (ARR) at Year 5 was significantly higher in patients who met the ‘change treatment’ criteria than in those who did not (0.7 and 0.07, respectively; P < 0.001). Similar results were found for disease progression, demonstrating the utility of the CanTOR as an accurate predictor of disease activity (relapses) and disability progression.

Here, we report the findings from the open-label, 12-month, observational CanTOR study of 191 patients with RRMS or clinically isolated syndrome (CIS) (note that not all DMTs are indicated for the treatment of CIS and not all provinces cover CIS or have the same guidelines for coverage in relapsing MS) to identify candidates for treatment optimization or maintenance of current treatment at baseline (BL) and end of study (EOS).

METHODS

Study design

The CanTOR study was a 12-month, open-label, observational, multicentre, Phase IV study of Canadian patients with RRMS or CIS, conducted under Institutional Review Board approval (ClinicalTrials.gov identifier: NCT01142583).

Objectives

The primary objectives were to assess whether the application of the CanTOR influenced clinicians’ decisions regarding DMTs in the Canadian clinic setting, and to evaluate the perceived utility of the TOR in the DMT decision-making process. The secondary objective was to determine the proportion of patients meeting a medium or high level of concern according to the TOR in this setting.

Patients

Patients were recruited from community and academic clinics in Canada. The main eligibility criteria were: aged 18-55 years with a diagnosis of CIS or RRMS, onset of symptoms ≤10 years prior to recruitment; Expanded Disability Status Scale (EDSS) score 0-4; consistent, single DMT (IFN β-1a, IFN β-1b, or glatiramer acetate [GA]) for ≥12 months; and relapse and EDSS data over the previous 12 months. Patients were excluded if it was expected that they could not be followed reliably over the course of the study, were participating in any other study involving investigational or marketed products, had previously responded poorly or switched DMTs to minimize situations in which a treatment switch was not possible because of a lack of treatment options.

At each study site, consecutive patients were screened until ten eligible patients were enrolled. All patients provided written informed consent, with the understanding that the patient could withdraw consent at any time without prejudice to future medical care.

Data collection and analysis

Patients were assessed using the CanTOR criteria (Table 1 and described previously)5 at BL and EOS, over a prospective 12-month period (Supplementary Figure). The EOS visits were at 12 months after the BL visit, or earlier if treatment modification was considered due to clinical reasons other than intolerance.

Assessments included disease history, current EDSS score, relapse status and, if available, MRI findings. Levels of concern (low, medium or high) for any changes in relapse rate, disease progression (progression of EDSS score) and MRI outcomes were determined based on TOR criteria. A collective level of concern was recorded based on these categories. Treatment decisions after each TOR assessment at the BL and EOS visits were recorded. The decision to continue or change treatment was at the discretion of the usual practice for individual clinicians. Clinicians’ perceptions on the utility of the TOR in their decision-making process (not useful, somewhat useful and very useful) were captured.

Additional feedback on the TOR was collected from clinicians at EOS through a separate evaluation questionnaire and descriptive statistics were generated. Clinicians answered (yes/no) whether they: (1) found the TOR helpful in assessing DMT response; (2) found the TOR easy to use; and (3) would use the TOR on a regular basis.

RESULTS

Patients

Between June 2006 and February 2009, a total of 192 patients were enrolled from 21 sites: 80 patients from 16 community clinics and 112 patients from five academic clinics. Patient disposition is shown in Figure 1. Data for both BL and EOS visits were available for 184 patients, and BL-only data for seven patients; these data collectively represent a total of 375 treatment decisions. One patient withdrew consent before collection of BL data.

Most patients (95.3%) were Caucasian and 71.7% were women. Mean (standard deviation) age at BL was 39 (8.4) years. The majority of patients (n=183, 95.8%) had RRMS while the remainder had CIS; 124 patients (67.4%) were receiving IFN β (any dose) and 60 patients (32.6%) were receiving GA (Table 2).

Of the 184 patients with BL and EOS data, 31 (16.8%) experienced ≥1 relapse during the study. The median (range) number of relapses was 1 (range 1-3). In total, there were 38 relapses over 180 patient-years of follow-up, yielding an ARR of 0.21. Disease progression (as defined by progression of EDSS score) occurred in 36/184 (19.6%) of patients during the study.

Very few patients switched treatment between BL and EOS visits. Of the 124 patients receiving IFN β at BL, 2.4% switched to a different IFN, 2.4% switched to GA and 1.6% switched to treatments other than IFN or GA. No patients switched to mitoxantrone. Of the 60 patients receiving GA at BL, 1.7% switched to an IFN β (Table 2).

Clinicians

All 35 participating clinicians were neurologists and 26 of these enrolled at least one patient; 19 of these clinicians were
based at community centres and seven clinicians were based at academic centres. The participating clinicians were not necessarily the treating providers responsible for DMT prescription for the patients at study entry, nor did patients necessarily have a single care provider during the study.

**Utility of the TOR**

Over the course of the study (combined data for BL and EOS), the TOR recommended treatment optimization at 34 of 375 patient visits (9.1%) and maintaining treatment at 341 of 375 visits (90.9%).

Among the 34 visits when the TOR recommended a change in treatment, the clinician decided to change DMT in ten cases (29.4% concordance). Among the 341 visits where the TOR recommended maintaining treatment, the clinicians’ decision was also to maintain treatment in 324 cases (95.3% concordance). Concordance ranged from 80.0% for patients with two low levels of concern to 100% for patients with one low level of concern (Table 3). The overall concordance rate between the TOR and the clinicians’ decision to maintain or change treatment was 89.1% (334 of 375 patient visits).

**Usefulness of the TOR**

Clinicians considered the TOR ‘useful’ or ‘very useful’ in 24 of 34 cases (70.6%) when treatment optimization was recommended and in 188 of 340 cases (55.3%) when maintaining treatment was recommended. Overall, the model was considered useful or very useful in 56.7% of cases (212/374; Table 3).

Clinicians cited the TOR as their principal reason for changing treatment in 50.0% (5/10) of cases where change of treatment was recommended by the TOR and between 34.9% and 50.0% of cases (depending on the level of concern) when maintaining treatment was recommended.

**Clinicians’ feedback on TOR at EOS**

An EOS questionnaire to gain additional feedback on the CanTOR was completed by 17/35 clinicians. Overall, 88.2% (15/17) found the TOR helpful in assessing patients’ responses to DMT; 82.4% (14/17) found the TOR model easy to use and 64.7% (11/17) reported that they would use the TOR on a regular basis.

**Level of concern according to relapse, disease progression and MRI findings**

**Relapse**

At least one level of concern for relapse outcomes (i.e. ≥1 rating of low, medium or high level of concern) was recorded for 56/190 (29.5%) patients at BL and 31/184 (16.8%) patients at EOS. The proportion of patients at each level of concern for relapse rate, severity and recovery is shown in Figure 2. Most relapses at BL were classified as low concern. The severity of the relapse and recovery progress was also of mostly low concern. The levels of concern at EOS were similar.

**Disease progression**

At least one level of concern for disease progression was recorded for 34/190 (17.9%) patients at BL and 36/184 (19.6%)
Table 3: Concordance of the Treatment Optimization Recommendations (TOR), clinicians’ treatment decisions (n=375) and clinician-rated usefulness of the TOR

<table>
<thead>
<tr>
<th>TOR outcome</th>
<th>Criteria for TOR level of concern, n</th>
<th>Clinician’s treatment decision, n</th>
<th>Concordance between TOR and clinician’s decision, % (n)</th>
<th>TOR as main reason for treatment decision, % (n)</th>
<th>Clinician-rated TOR as ‘useful’ or ‘very useful’, % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change treatment (n=34)</td>
<td>1 high 21</td>
<td>Change 10 Maintain 24</td>
<td>29.4 (10/34)</td>
<td>50.0 (5/10)</td>
<td>70.6 (24/34)</td>
</tr>
<tr>
<td></td>
<td>2 medium 7</td>
<td>Change 6 Maintain 39</td>
<td>86.7 (39/45)</td>
<td>41.0 (16/39)</td>
<td>88.9 (40/45)</td>
</tr>
<tr>
<td></td>
<td>3 low 6</td>
<td>Change 1 Maintain 4</td>
<td>80.0 (4/5)</td>
<td>0 (0/1)</td>
<td>60.0 (3/5)</td>
</tr>
<tr>
<td>Maintain treatment (n=341)</td>
<td>1 low 63</td>
<td>Change 0 Maintain 63</td>
<td>100 (63/63)</td>
<td>34.9 (22/63)</td>
<td>55.6 (35/63)</td>
</tr>
<tr>
<td></td>
<td>No concern 228</td>
<td>Change 9 Maintain 218*</td>
<td>96.0 (218/227)</td>
<td>34.9 (76/218)</td>
<td>48.5 (110/227)</td>
</tr>
<tr>
<td>Maintain treatment total</td>
<td>– –</td>
<td>Change 16 Maintain 324</td>
<td>95.3 (324/340)</td>
<td>–</td>
<td>55.3 (188/340)</td>
</tr>
<tr>
<td>Total ratings</td>
<td>– –</td>
<td>–</td>
<td>89.3 (334/374)</td>
<td>35.0 (131/374)</td>
<td>56.7 (212/374)</td>
</tr>
</tbody>
</table>

*One patient did not have a response for changing or maintaining therapy. Patient numbers were 191 at baseline and 184 at end of study, giving a total of 375 treatment decisions.

Figure 2: Level of concern based on relapse outcomes at (A) BL (n=190) and (B) EOS (n=184). *One evaluable patient at BL had all missing values for level of concern. BL, baseline; EOS, end of study

Figure 3: Level of concern based on EDSS disease progression outcomes at (A) BL (n=190) and at (B) EOS (n=184). BL, baseline; EDSS, Expanded Disability Status Scale; EOS, end of study
patients at EOS. The proportion of patients at each level of concern for EDSS progression is shown in Figure 3.

The levels of concern were generally low. As per the inclusion criteria, no patient had an EDSS score ≥4 at BL. By EOS, a small number of patients had progressed to EDSS scores >4, but most concern levels related to EDSS scores ≤3.5. Patients with clinically documented disease progression were a subgroup of patients with EDSS scores ≤3.5. For the few patients with EDSS scores ≥5.5, similar proportions were classified as low and high concern (1.6% and 1.1%, respectively).

MRI

During the study, 39/184 (21.2%) patients underwent a brain MRI scan. The MRI findings and levels of concern are summarized in Figure 4. Patients who were scored in two or more MRI categories were classified as a medium level of concern. Of the new/enlarging T2 lesions, new lesions were the most commonly reported finding, occurring in 41.7% of patients at BL and in 51.2% of patients at EOS. Of the new/enlarging T1 hypointense lesions, enlarging lesions were the least commonly observed event, occurring in 4.2% of patients at BL only.

At EOS, levels of concern in the MRI findings translated to 20/39 patients (51.3%) having a low level of concern (scoring in one category), and 4/39 (9.8%) patients having a medium level of concern (scoring in ≥2 categories). These proportions were similar to BL.

Collective levels of concern for all outcomes at BL and EOS are summarized in Figure 5. Overall, 12 patients had ≥1 high level of concern, two patients had ≥2 medium levels of concern and five patients had ≥3 low levels of concern. Considering any outcome at EOS, 67/184 (36.4%) patients had ≥1 level of concern and 19 (10.3%) patients had a combined level of concern that met the TOR criteria for changing treatment.

DISCUSSION

In this observational, 12-month study, the CanTOR identified levels of concern that warranted recommending a change of treatment at 9.1% of patient visits and in 10% (19/192) of patients. Where treatment maintenance was indicated, concordance between the TOR and clinicians’ recommendations was high. Concordance was not high in instances when treatment optimization was indicated by the TOR (29.4%), although in most cases (70.6%), clinicians felt that the TOR were useful for identifying these patients.

The influence of the TOR on clinicians’ treatment decisions varied according to the level of concern. The TOR appeared to be most useful in patients with one medium level of concern: both the concordance (86.7%) and the clinicians’ rating of the TOR (88.9%) were high in this group of patients. This result is not surprising as treatment recommendations are likely to be most helpful in situations where there is uncertainty about patient response to treatment. Recommendations for maintaining or changing treatment are likely to be less useful in cases where patients are doing either very well or very poorly on their current treatment and the course of action will be obvious. There is not yet a set formula for indicating when to alter treatment and so clinicians should continue to consider the evidence for suboptimal response on a case-by-case basis.8

Interestingly, although the decision to change treatment was only followed in 29.4% of cases where treatment optimization was recommended by the TOR, 70.6% of clinicians still rated the TOR as useful. The TOR may be useful for corroborating with the clinicians’ judgement. Investigators commented that the TOR were useful because they were reassured in their decision to switch drugs when treatment optimization was recommended, and were compelled to think through their decision to maintain treatment when a switch was recommended. However, the decision to change treatment is influenced by a number of factors, such as disagreement with the TOR and limited treatment options at the time of the study. For example, if a treatment switch or dose escalation was recommended in a
That clinicians did not necessarily follow the TOR for treatment optimization suggests a greater reliance on personal clinical experience and consideration of other factors beyond the TOR criteria, such as patient history, duration of DMT use, treatment access and reimbursement issues in different provinces and private insurance plans affecting options that may have prevented uniform application of the TOR. Furthermore, DMTs are not reimbursed by some provincial insurance plans for CIS. A study involving practicing clinicians with varying years of experience would be interesting, as this may reveal varying reliance on the TOR compared with a decision made without reference to the TOR. However, determining the clinicians’ independent treatment decision may be difficult to control for, in the presence of the TOR outcome. Further validation studies may consider matched patient groups where one group is assessed by a clinician only and the other group using the TOR only. Patient preference is also a consideration when making treatment decisions; how often clinicians’ decisions were affected by the input of their patients was not captured. In addition, patient compliance to treatment and patient global impression/symptom burden may affect patient response to DMT, yet these factors were not measured. Questions exploring compliance and patient influence should be incorporated into questionnaires in future studies. Regular clinical assessments of patients with MS are a recommendation of the Consortium of Multiple Sclerosis Centers and Rehabilitation in Multiple Sclerosis. Post-study ratings of helpfulness in assessing patient response to DMT was high (15/17), with 14/17 also indicating that the TOR model was easy to use. The proportion of the clinicians who completed the EOS questionnaire and indicated they would use the TOR on a regular basis (11/17, 64%) was lower than those of the helpfulness and ease of use ratings, suggesting that provincial amendments to the existing CanTOR criteria may increase the applicability of the tool in general practice.

The study did not analyze clinician feedback by community versus academic providers, although whether there are differences in the way the CanTOR are implemented between MS specialists and general practitioners may be of interest. Although the TOR are not currently a standardized tool used by all clinicians, the finding that TOR was the principal reason for treatment change in 50% of cases and in 35% to 50% of cases in all clinicians, the finding that TOR was the principal reason for treatment indicates that some clinicians found this approach useful in this study. The findings of this study should be considered in the context of the study limitations. The on-study ARR of 0.21 was very low, although this is consistent with the on-treatment ARR reported in recent clinical trials of IFNs and GA. The resulting number of patients recommended for treatment optimization based on relapse outcomes was relatively small and may limit the strength of the conclusions.

These results do suggest that clinicians’ experience of using the TOR was similar to that reported in previous studies, where the tool was deemed an important, non-time-consuming and easy-to-use tool to facilitate treatment optimization in clinical practice. The inclusion of MRI data in this study also addresses limitations cited by previous studies where not all of the TOR criteria for assessment of disease activity were used.

As this study was non-interventional, treatment was administered as per clinical practice of the treating clinician.

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**Figure 5: Summary of level of concern for relapse, disease progression and MRI findings at (A) BL (n=190) and (B) EOS (n=184).** BL, baseline; EOS, end of study; MRI, magnetic resonance imaging

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patient who was known to have poor tolerance to IFN or GA; the options were limited to mitoxantrone. Notably, natalizumab and fingolimod were not available at the time of this study and access to these agents may be restricted in some regions owing to reimbursement issues. However, the upcoming MS therapy pipeline is innovative, and includes oral therapies, gene therapies, stem cell transplantation techniques and vaccines.

The results reported in this study could suggest that the TOR are not sufficiently conservative for current practice and recommend a change in treatment in some cases when it is not deemed necessary by the treating clinician, which may explain the discrepancies in concordance. Expanding treatment options as new agents become available may increase concordance between clinicians’ decisions and the TOR (i.e. clinicians may be more likely to recommend a change in treatment in the light of greater treatment choice), although future studies will be needed to confirm this. When new agents become available, the TOR may be considered to be too conservative and so further updating and validation of the TOR in the consideration of new therapies on an on-going basis is recommended.
Therefore, these results from the various clinical centres go some way to demonstrating that the TOR was well received in a widespread community clinical practice. As the treatment of MS becomes more complex and choices offer potentially greater efficacy, with perhaps greater toxicity, clinicians may welcome some guidance on making therapeutic decisions. The results of this study validate further the usefulness of a clinical tool like the TOR in RRMS and CIS, particularly in cases when maintaining treatment was recommended, providing welcome reassurance for clinicians.

ACKNOWLEDGEMENTS

This manuscript was supported by an educational grant from Merck Serono (an affiliate of Merck KGaA, Darmstadt, Germany). The authors thank Esther Law of Caudex Medical, Oxford, UK (supported by EMD Serono Canada) for providing editorial assistance with this manuscript, collating the comments of the authors and assembling tables and figures, and Catherine Kidd of Caudex Medical, Oxford, UK (supported by EMD Serono Canada) for assistance in editing for English, formatting the manuscript to meet journal guidelines and coordinating submission requirements.

FUNDING

This study was sponsored by Merck Serono (an affiliate of Merck KGaA, Darmstadt, Germany).

CONFLICT OF INTEREST STATEMENT

F. Grand’Maison has received research grants from Genzyme, Novartis, Biogen Idec, Teva and EMD Serono.

V. Bhan has received honoraria for presentations and travel grants to attend educational events from Bayer, Biogen Idec, Novartis, Sanofi-Aventis, Merck Serono and Teva Canada.

M.S. Freedman has received research or educational grants from Genzyme and Bayer Healthcare; honoraria or consultation fees from Bayer Healthcare, Biogen Idec, EMD Canada, Novartis, Sanofi-Aventis and Teva Canada Innovation. He is a consultant and Steering Committee member for Merck Serono, Bayer Healthcare, Biogen Idec, Sanofi-Aventis, Novartis and Celgene.

M.L. Myles has received honoraria for presentations and travel grants to attend educational events from Serono, Teva and Berlex.

D.G. Patry has served on a scientific advisory board for BioMS Medical; has received speaker honoraria from EMD Serono, Inc., Novartis, Teva Pharmaceutical Industries Ltd and Biogen Idec; and receives research support from Bristol-Myers Squibb, Sanofi-Aventis, Lundbeck Inc., Elan Corporation and the MS Society of Canada.

D.H. Selchen has received honoraria as a speaker and attended advisory boards for EMD Serono, Teva, Novartis, Biogen Idec, Bayer and Dan.

P. Moriarty is an employee of EMD Serono, Canada.

A.L. Traboulsee is a data safety monitoring board member for EMD Serono and has received lecture honoraria from EMD Serono, Bayer, Biogen Idec, and Novartis; has attended advisory boards for Roche; and received a research grant from Bayer, Biogen Idec, MS Society of Canada, Canadian Institute for Health Research and Vancouver Hospital Foundation.

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**Supplementary Figure:** Study design. BL, baseline; EOS, end of study; Rx, prescription; TOR, Treatment Optimization Recommendations; ≥, more than or equal to; ≤, less than or equal to.

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