Therapeutics Initiative

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THE UNIVERSITY OF BRITISH COLUMBIA

MS Therapeutic Review

July 2020

Relative efficacy of drugs for relapsing remitting multiple sclerosis

EXECUTIVE SUMMARY

Drug Assessment Working Group

Therapeutics Initiative

University of British Columbia

Abbreviations/ Glossary

AE	adverse event
BC	British Columbia
CI	confidence interval
DMT	disease modifying therapy – this commonly used term is avoided in this document because it contains an embedded knowledge claim
EDSS	Expanded Disability Status Scale
FDA	United States Federal Food and Drug Agency
INF	interferon
MS	multiple sclerosis
NMA	network meta-analyses
MRI	magnetic resonance imaging
PSD	Pharmaceutical Services Division
PML	progressive multifocal leukoencephalopathy
PICOS	population, intervention, comparator, outcome, study design
RCT	randomised controlled trial
RR	risk ratio
RRMS	relapsing remitting multiple sclerosis
SAE	serious adverse event

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Executive Summary

The Pharmaceutical Services Division (PSD) of the British Columbia Ministry of Health requested a systematic review comparing drugs funded in British Columbia to treat relapsing remitting multiple sclerosis (RRMS). Eleven drugs were included: older injectable drugs (3 beta interferons plus glatiramer acetate), oral drugs (fingolimod, teriflunomide, dimethyl fumarate) and newer biologic MS drugs provided intravenously (rituximab, alemtuzumab, natalizumab, ocrelizumab).

PSD has funded the older injectable drugs (interferons and glatiramer) as first-line therapy for RRMS for almost 20 years. This policy is consistent with policy in other jurisdictions based on evidence reviews (1-3). In Canada, a 2013 CADTH report to assess the comparative clinical and cost effectiveness of drug therapies for the treatment of RRMS recommended glatiramer acetate or interferon beta 1b to provinces as the initial pharmacotherapies of choice for patients with RRMS (4). If patients failed to respond or had contraindications to one of these drugs then the other one should be tried. If patients failed to respond or had contraindications to both these drugs then subsequent pharmacotherapies should be selected….(4)

The current PSD issue is whether they should fund newer drugs instead of interferons and glatiramer as first-line therapy.

Methods: Two literature searches were conducted in March 2020 to identify: 1) research syntheses published during the last 5 years and 2) comparative trials published in the last 2 years (after the search cut-off dates for published research syntheses). Selection criteria were:

- **P**opulation: Adults with relapsing remitting multiple sclerosis.
- **I**ntervention: One of the 11 MS drugs of interest.
- **C**omparator: Another MS drug.
- **O**utcomes: TI hierarchy of outcomes – all-cause mortality, serious adverse events, quality of life, disability progression, freedom from relapse, relapse rates confirmed over 24 months or longer, duration and severity of relapse, time to relapse, discontinuation rates, and specific adverse events.

Research syntheses: Twenty-eight research syntheses were identified. Of these, 8 were systematic reviews with meta-analyses (5 Cochrane and 3 non-Cochrane), 11 were network meta-analyses which combine placebo and drug comparative trials (1 Cochrane and 10 non-Cochrane) and 9 were systematic reviews without meta-analyses (9 non-Cochrane).

The Cochrane reviews were useful in identifying head-to-head trials, providing a critique of the evidence and implications for clinical practice and policy:

Zhang 2017 (5) – Alemtuzumab versus interferon beta 1a

Riera 2016 (6) – Alemtuzumab versus active comparator

La Mantia 2016a (7) – Fingolimod versus active comparator

La Mantia 2016b (8) – Interferon beta versus glatiramer acetate

He 2016 (9) – Teriflunomide versus active comparator

Tramacere 2015 (10) – NMA, multiple MS drugs

Xu 2015 (11) – Dimethyl fumarate versus active comparator

A recent network meta-analysis by Li 2019 compared the efficacy of MS drugs for RRMS (12).

Active Comparator summary

Twenty-seven unique randomized controlled trials (RCTs) were identified yielding 35 comparisons of one MS drug to another MS drug of interest in adult patients with RRMS. Out of the 55 possible drug-to-drug combinations of 11 different drugs, because of redundancy, there were only 12 different drug-to-drug comparisons.

- Interferon (INF) beta 1a (Rebif) was the comparator in **18** of the 27 comparative trials identified:
  - vs. alemtuzumab (3 trials; 1755 patients; 2 to 3 years)
  - vs. natalizumab (1 trial terminated)
  - vs. ocrelizumab (2 trials; 1656 patients; 96 weeks)
  - vs. teriflunomide (1 trial; 324 patients; 64 weeks)
  - vs. fingolimod as one of injectable drug choices (4 trials; 2278 patients; 24 to 76 weeks)
  - vs. INF beta 1a (Avonex) (4 trials; 876 patients; 1 to 2 years)
  - vs. glatiramer acetate (3 trials; 1453 patients; 2 to 3 years)
- Glatiramer acetate, was the comparator in **14** trials:
  - vs. natalizumab (1 trial terminated)
  - vs. fingolimod as one option among various injectable MS drugs (5 trials; 3342; 6 to 12 months).
  - vs. dimethyl fumarate (1 trial; 709 patients; 2 years)
  - vs. INF beta 1b (Betaseron) (2 trials; 2345 patients; 1 to 2 years)
  - vs. INF beta 1a (Avonex) (2 trials; 604 patients; 2 to 3 years)
  - vs. INF beta 1a (Rebif) (3 trials; 897 patients; 96 to 108 weeks)
- Interferons and glatiramer acetate were compared to one another in **12** trials (multiple treatment arms):
  - INF beta 1b (Betaseron) vs. INF beta 1a (Avonex) (3 trials; 371 patients; 1-2 years)
  - INF beta 1b (Betaseron) vs. INF beta 1a (Rebif) (4 trials; 609 patients; 12 weeks-2 years)
  - INF beta 1a (Avonex) vs. INF beta 1a (Rebif) (4 trials; 876 patients; 48 weeks to 2 years)
  - Glatiramer acetate (Copaxone) vs. INF beta 1b (Betaseron) (2 trials; 2295 patients; 1-2 years with some follow-up to 3.5 years)

- Glatiramer acetate (Copaxone) vs. INF beta 1a (Avonex) (2 trials; 604 patients; 36 months to 2 years)
- Glatiramer acetate (Copaxone) vs. INF beta 1a (Rebif) (3 trials; 897 patients; 2 years)

Of relevance to BC MS drug policy, it is important to note that:

- No RCTs compare oral MS drugs to one another.
- No RCTs compare newer biologic MS drug to one-another.
- No RCTs compare an oral MS drug to a newer biologic drug.

Summary of Findings of Comparative RCTs:

Note: The main report provides an overview of the clinical trial findings by outcome hierarchy.

Newer Biologics: Regulatory approval for the newer biologic drugs was based on comparisons with older injectable beta interferon products.

Alemtuzumab was approved in 2014 based on 3 RCTs versus INF beta 1a (Rebif)): MMS223 2008 (NCT00050778), CARE MS I/ (Cohen 2012) (13) and CARE MS II (Coles 2012). (13) These 3 RCTs were included in two Cochrane reviews as well as the Cochrane NMA (14-16). (See **Cochrane analyses of comparative RCTs** section below.)

Ocrelizumab was approved in 2017 based on 2 RCTs versus INF beta 1a (Rebif) (17). A Cochrane review protocol was published in January 2019 but has not yet been completed. The following is our summary of the findings: Two studies (OPERA I and OPERA II) included 1656 participants with active RRMS (pre-study relapse frequency ranging from 1.31 to 1.34) and a disability score of 2.5 using the Expanded Disability Status Scale (EDSS). RRMS was diagnosed using McDonald 2010 criteria. Baseline characteristics of participants - mean age (37 years); age range (18 to 55 years); Caucasians (90 %); females (65%); mean disease duration ranged from 3.8 to 4.2 years.

No difference in mortality or total serious adverse events (SAEs). However serious infection was significantly lower in the ocrelizumab group risk ratio (RR) 0.46 (95% confidence interval (CI) 0.23 to 0.93); P = 0.03. QoL scores were reported but the minimal clinically important difference in SF-36 score was not demonstrated. Relapse rates [RR 0.54 (95% CI, 0.44 to 0.66) as well as confirmed disability progression at 24 weeks [RR 0.66 (95% CI 0.48 to 0.90); P = 0.010)] were lower in ocrelizumab group. However, the FDA noted that the disease progression observed in the OPERA-I and OPERA-II trials was typically reversible and not reflective of permanent disability progression. A greater proportion of ocrelizumab-treated patients achieved no evidence of disease activity outcome at week 96 compared to interferon beta 1a RR 1.84 (95% CI 1.54 to 2.20) p < 0.00001. Total withdrawals [RR 0.60 (95% CI 0.48 to 0.75); P < 0.00001] as well as withdrawals due to AE [RR 0.57 (95% CI 0.37 to 0.89); P = 0.01] were significantly lower in the ocrelizumab group. A significant increase in specific adverse effects such as infusion-related reactions was observed in the ocrelizumab group compared to interferon beta 1a [RR 3.55 (95% CI 2.82 to 4.46); P < 0.00001].

No cases of progressive multifocal leukoencephalopathy (PML) have been reported in patients who have been treated with ocrelizumab; however, the Canadian product monograph for ocrelizumab contains a warning about this potential risk. The product monograph recommends that patients be monitored for early signs and symptoms of PML, noting these can appear similar to an MS relapse (e.g., worsening of neurological signs or symptoms). Several other MS drug therapies approved for use in Canada include warnings regarding the risk of PML, including natalizumab and alemtuzumab, which have black box warnings, and dimethyl fumarate and fingolimod, which have non–black box warnings. The clinical expert consulted by CADTH noted that patients treated with ocrelizumab are not likely to receive the specialized monitoring for PML that is provided to patients being treated with natalizumab. Across these two 96-week trials, four neoplasms (in 0.5% of patients) occurred in the ocrelizumab group (two cases of invasive ductal breast carcinoma, one case of renal-cell carcinoma, and one case of malignant melanoma), and two occurred (in 0.2%) in the interferon beta-1a group (one case of mantle-cell lymphoma and one case of squamous-cell carcinoma in the chest).

Natalizumab was approved in November 2004, then withdrawn from the market in February 2005 and ongoing trials were terminated due to the emergence of PML during routine use. Patient lobbying resulted in it returning to use in 2006 under a special prescribing program in the USA and with extra warnings and precautions.

Natalizumab does not have data from comparative RCTs. The unpublished SURPASS study compared natalizumab to INF beta 1a (Rebif) and glatiramer acetate (NCT01058005). This trial was stopped for slow enrollment. A second RCT comparing natalizumab to fingolimod was terminated for “business reasons” (NCT02342704).

Rituximab was licensed in 1997 for autoimmune disease indications including rheumatoid arthritis and some cancers. It is not approved by Health Canada or other regulators for RRMS. It is listed as a first-line drug for BC special authorization coverage for RRMS for intravenous use. It is the only monoclonal antibody therapy for RRMS listed for first-line use in BC. The harm profile of ritixumab is better understood than other new biologics due to its longer and broader clinical use.

No RCT was identified that compares rituximab with any other active comparator treatments available for adult patients with RRMS.

Oral drugs: Eight comparator RCTs of **fingolimod** were identified including 2 terminated unpublished trials (**NCT02342704** compared to natalizumab; **NCT01633112** compared to glatiramer acetate) that provide some unreliable data on adverse events. The other six RCTs compared fingolimod to various older injectable MS drugs.

In an RCT that compared fingolimod to INF beta 1a (Avonex) over a 1-year period, an excess of deaths was found in the 1.25 mg daily fingolimod dosage group. All 4 deaths were in the 1.25 mg group with 2 during the trial (1 simplex encephalitis, 1 varicella zoster infection) and 2 in the year after the trial ended (metastatic breast cancer, 1 pneumonia following neurological deterioration). This led to the 1.25 mg

daily dosage being discontinued (Cohen 2011) (18). An open label study (1053 patients) provided some data on adverse events and quality of life outcomes over 18 months (Calkwood 2014) (19).

Comi 2017 investigated cognitive outcomes of fingolmod vs INF beta 1b (20) in 157 participants with both groups showing improvements at 18 months. Cree 2018 reported on patient retention on treatment in 875 participants at 48 weeks (21). Three 6-month RCTs in the EPOC series reported patient outcomes on switching to fingolimod in 3 distinct geographical areas (North America, Italy, Russia).

A 2016 Cochrane review of fingolimod comprehensively reviewed the published head-to-head RCT as well as pivotal placebo-controlled RCT data available through 2015 (22).

Dimethyl fumarate was compared to glatiramer acetate over 2 years (Fox 2012) (23). This trial was comprehensively reviewed in a 2012 Cochrane review (24).

Teriflunomide was compared to INF beta 1a (Rebif) by Vermersch 2014 (25). This study was reviewed in a 2016 Cochrane review (26).

Older Injectable MS drugs: Older injectable drugs were the most common comparator in the 27 RCTs included in this review. In addition, the older drugs were also compared with each other. However, given that these drugs are already positioned as first-line drugs in BC, the evidence on differences between them was not considered relevant to to the current drug funding policy issues. The comparative trials of the older injectable drugs and the Cochrane reviews of them are presented in the main report for completeness.

Cochrane analyses of comparative RCTs: The conclusions of the Cochrane reviews of individual oral drugs (fingolimod, dimethyl fumarate and teriflunomide) as well as alemtuzumab are provided below. These reviews included the comparator RCTs of relevance here as well as placebo-controlled studies:

> **Fingolimod**: “The evidence on the risk/benefit profile of fingolimod compared with intramuscular interferon beta-1a was uncertain, based on a low number of head-to-head RCTs with short follow-up duration” (22, 27).
>
> **Dimethyl fumarate**: Compared to glatiramer acetate “there was a significant difference in reducing the number of patients with relapse for high dosage [240 mg 3 times daily] of dimethyl fumarate (RR = 0.75, 95% CI 0.59 to 0.96, P = 0.02); but no difference for low dosage [240 mg daily] (RR = 0.91, 95% CI 0.72 to 1.13, P = 0.38…there was no significant difference in reducing the number of patients with disability worsening for both dosages of dimethyl fumarate (high dosage: RR = 0.82, 95% CI 0.57 to 1.17, P = 0.27; low dosage: RR = 0.82, 95% CI 0.57 to 1.17, P = 0.27)… Quality of evidence for relapse outcome was moderate, but for disability worsening was low.” (24) (p 16, 17).
>
> **Teriflunomide**: “The quality of available data was too low to evaluate the benefit of teriflunomide as monotherapy versus INF-beta 1a” (26).

Alemtuzumab: Two Cochrane systematic reviews evaluated the same 3 RCTs against INF beta 1a (Rebif or Avonex). One protocol was designed to include all types of MS but only found trials of RRMS and the other was exclusive to RRMS. Zhang 2017 found that: "Compared with interferon beta 1a, alemtuzumab given at a dose of 12 mg per day probably reduces the risk of relapse RR 0.60, 95% CI 0.52 to 0.70, moderate quality evidence), may reduce the risk of worsening disability (RR 0.60, 95% CI 0.45 to 0.79, low quality evidence)… Mean EDSS scores may be similar between the treatment regimens (mean difference (MD) -0.35, 95% CI -0.73 to 0.03, low quality evidence)… The risk of experiencing an adverse event in either alemtuzumab 12 mg or interferon groups may be similar (RR 1.03, 95% CI 0.98 to 1.08, low quality evidence). The risk of serious adverse events is probably similar between treatments (RR 1.03, 95% CI 0.82 to 1.29, moderate quality evidence). The risk of any adverse event may be similar between alemtuzumab 24 mg and interferon (RR 1.02, 95% CI 0.96 to 1.08, low quality evidence). The risk of serious adverse events is probably similar between treatments (RR 0.95, 95% CI 0.70 to 1.31, moderate quality evidence)" (15).

Riera 2016 found: "At 24 months, alemtuzumab 12 mg was associated with: (a) higher relapse-free survival (hazard ratio (HR) 0.50, 95% CI 0.41 to 0.60; 1248 participants, two studies, moderate quality evidence); (b) higher sustained disease progression-free survival (HR 0.62, 95% CI 0.44 to 0.87; 1191 participants; two studies; moderate quality evidence); (c) a slightly higher number of participants with at least one adverse event (RR 1.04, 95% CI 1.01 to 1.06; 1248 participants; two studies; moderate quality evidence)… At 36 months, alemtuzumab 24 mg was associated with: (a) higher relapse-free survival (45 versus 17; HR 0.21, 95% CI 0.11 to 0.40; one study; 221 participants); (b) a higher sustained disease progression-free survival (HR 0.33, 95% CI 0.16 to 0.69; one study; 221 participants); and (c) no statistical difference in the rate of participants with at least one adverse event. We did not find any study that reported any of the following outcomes: rate of participants free of clinical disease activity, quality of life, fatigue or change in the numbers of [magnetic resonance imaging] (MRI) T2- and T1-weighted lesions after treatment" (14).

INF beta 1a or 1b vs glatiramer acetate: La Mantia 2016 concluded that the effects of INF beta and GA in adult patients with RRMS on reduction in relapse rate or disability progression were "similar or showed small differences". For clinical endpoints the quality of evidence was judged as moderate, for safety outcomes the quality of evidence was judged as low (28).

Note: The detailed findings of the available head-to-head RCTs of MS drugs by outcome hierarchy (all-cause mortality, non-fatal SAE and specific adverse event data) in the main report. It is beyond the scope of this report however to comprehensively review what is known about the harm profile of each individual MS drug of interest.

General issues with RCTs in RRMS

1. RCTs comparing drugs to treat adults with RRMS versus either placebo or to an active comparator drug are of short duration (1 to 3 years) given the natural history of RRMS of up to 3

to 4 decades. Also, rare infrequent SAEs are difficult to identify over the shorter RCT time frame.

2. The included RCTs were conducted over a span of 2 decades and included patients diagnosed as RRMS using different diagnostic criteria (Poser criteria or several revisions of the McDonald criteria 2001, 2005, 2010 criteria).
    - The diagnostic criteria for MS have evolved over time leading to an expansion in the number of patients being diagnosed at earlier stages in the course of disease. This leads to significant heterogeneity in the RCT study populations.
    - Early diagnostic criteria for MS were based primarily on clinical evidence. Subsequent criteria incorporated imaging, other para clinical markers in response to technological advances (brain and spinal cord MRI) and laboratory tests (cerebrospinal fluid (CSF) examination - oligoclonal bands and immunoglobulin (IgG) index).
        - The Poser criteria established the framework for diagnosing MS in 1983 (definite or probable or laboratory supported). It disregarded subclinical disease activity and required at least 2 clinical events to diagnose MS.
        - Since the introduction of McDonald 2001 criteria “asymptomatic attack”, defined as new lesion formation but no new symptoms, also qualifies as a precursor to diagnose MS. MRI has become a powerful tool to bridge the gap between clinical symptoms and silent demyelinating lesions, and has been used for the diagnosis of multiple sclerosis since 2001. Sets of diagnostic criteria that establish dissemination in space as well as in time by MRI are included in the McDonald criteria 2001, which was revised in 2005, 2010 and 2017. Therefore, the new diagnostic criteria have enabled diagnosis of MS earlier and in more patients compared to earlier criteria.
        - The original McDonald 2001 criteria led to a 2-fold to 4-fold increase in diagnosis of definite MS in the first 12 months. The 2001 and 2005 criteria required 2 MRI time points to meet dissemination in time criteria. However, since 2010 modification of the criteria a single MRI may be sufficient to meet both DIT and DIS criteria.
        - The 2017 McDonald criteria identified a significant number of patients with clinically isolated syndrome with MRI evidence of dissemination of time and space in the absence of further clinical events, and the numbers have increased as the criteria have been revised. The incorporation of CSF specific oligoclonal bands can be used as a substitute for dissemination in time in 2017 criteria. Retrospective analysis of diagnosing MS using McDonald 2017 vs 2010 criteria showed a 31% increase in diagnosis of MS based on 6 cohort studies (29).

None of the 27 included comparative RCTs used the recently revised McDonald 2017 criteria. The median time to diagnosis of MS is reduced from 7.4 months using McDonald 2010 criteria to 2.3 months using McDonald 2017 criteria (30). The newer 2017 criteria are identifying a milder form of MS than in the past when the diagnosis was based on clinical course alone. Therefore,

characteristics of patient populations included in RRMS trials may potentially change with evolving diagnostic measures.

The primary outcome measures measured in most of the 27 included studies were relapse rates and/or sustained progression of disability at 12 or 24 weeks. Most of the included RCTs did not report time to relapse or severity of relapse. RCTs used different definitions of confirmed progression of disability based on the EDSS scale which is an ordinal scale with several limitations. Most of the comparative RCTs did not report on quality of life measures including fatigue or impairment of cognition. Research using British Columbia MS registry data found that, compared to untreated natural and contemporary cohorts, the cohort using beta interferons was not associated with disability reduction following 3 to 7 years of treatment (31). A US prospective cohort study found that long-term worsening is largely independent of relapse activity (32). The uncertain connection between relapse prevention and long-term disability progression undermines the assumption that the findings of regulatory trials are valid over longer treatment periods.

3. MS drugs target different parts of the immune system. Therefore, there are major differences between the MS drug classes and specific drugs in terms of harm. Cochrane has published a protocol but not completed a review focused on comparing the AE profile of the available MS drugs (33).

4. Serious adverse events have been reported outside of the RCTs used for drug licensing. Both daclizumab and alemtuzumab were licensed based on 2-year RCTs. However, fatal and non-fatal serious adverse events were identified that were not revealed in these RCTs. Subsequently daclizumab was withdrawn in 2018 after increased cases of fulminant hepatopathy and encephalitis became evident (34). Alemtuzumab had an excess of fatal SAE from previously unrecognized harms including in the first month of treatment (35). This led the European Medicines Agency to suspended new starts in April of 2019 pending further investigation (36). New starts were permitted again with additional precautionary measures (37); however, it was noted that even under conditions of supervision and resuscitation, not all fatal SAEs were preventable.

5. The patient population included in the 27 comparative RCTs were of European descent (74 to 94%); females (65 to 95%); relatively young [age ranging from 32 to 37 years for biologics; 35 to 46 years for oral drugs and 36 to 46 years for injectable drugs]; age range for inclusion in RCTs was 18 to 65 years; mean relapse rate [ranging from 1.2 to 1.8 for newer biologics and oral drugs; and from 1.2 to 2.6 for older injectable drugs]; with minimal disability at baseline [mean EDSS score ranging from 2.0 to 2.7; and EDSS range for inclusion from 0 to 6.0]. Evidence is only relevant to the clinical populations represented in these studies.

6. The comparative RCTs do not provide an estimate of relative effects based on prior treatment history. That is, in the majority of RCTs, either the patient's prior treatment history is unclear or the RCTs included an unspecified and unstratified mixture of treatment naïve and treatment experienced patients.

7. The majority of comparative RCTs did not explicitly include patients with inadequate response or showing intolerance to prior treatment with MS drugs so it is uncertain to what extent these results are applicable to these patient populations.

Specific limitations of existing head-to-head RCTs for policy making

The set of 27 head-to-head RCTs of MS drugs has a number of serious limitations that decrease the value for determining relative effectiveness among the 11 MS drugs of interest.

Comparison limited to older injectable MS drugs: The lack of head-to-head comparisons among the 7 MS drugs in the oral (3 drugs - dimethyl fumarate, terifluniomide and fingolimod) and new biologic categories (4 drugs - alemtuzumab, ocrelizumab, natalizumab and rituximab) is the greatest limitation of this set of 27 studies. Table 1 shows that the comparative evidence is exclusively with or among the older injectable MS drugs.

Absent are direct head-to-head trials between each of fingolimod, alemtuzumab, natalizumab and ocrelizumab. It would require 6 direct comparative trials to determine relative effectiveness of these 4 biologics.

The majority of direct head-to-head RCTs (12 of 27) are between the older injectable drugs -- the 3 beta interferon products and glatiramer acetate with some of these trials comparing more than one of the injectables. These MS drugs including the head-to-head trials have been extensively reviewed by Cochrane, CADTH and other review groups.

This set of 12 head-to-head RCTs which focuses small differences between these injectable products is not useful for determining whether older injectable drugs should be stopped. Drug discontinuation / stopping trials comparing MS drugs would be more useful for this purpose. With a longstanding first-line designation and over 20 years of cumulative use in BC, replacement by other drugs (obsolescence) and divestment could be the next step in the life cycle of these drugs

The rigor of research is highly variable across the existing comparative trials. The RCTs of two newer biologics are well designed and powered whereas a set of head-to-head trials between fingolimod and various older injectables are not. The comparative trial evidence represented by the existing 27 head-to-head studies therefore is not useful for determining the relative effectiveness among the 11 MS drugs of interest.

Table 1 also shows that the new biologics have not been compared to other oral MS drugs or each other. Although the head-to-head RCTs found a more favorable benefit to harm profile for the new biologics alemtuzumab and ocrelizumab versus INF 1a (Rebif), the comparisons of greater relevance are to the other biologics and oral drugs which are the current 2nd line treatment options in BC. The head-to-

head trials of newer biologics using a beta interferon as the active comparator reported a reduced relapse rate and disease progression with no difference in short term adverse events. However, the 2-year RCTs used for regulatory drug approval provide very limited knowledge on the highly variable disease and long-term course of MS.

Finally, Table 1 shows that comparisons between older injectable drugs and the oral drug fingolimod and newer biologic natalizumab (a single trial that was terminated with no useful clinical data) are inadequate for evaluating the efficacy of each drug as monotherapy. Being of shorter duration these head-to-head trials are less valuable than the placebo-controlled RCTs central to regulatory approval. For these reasons, the set of head-to-head trials between the injectables and fingolimod/natalizumab are far less informative than head-to-head trials of alemtuzumab/ocrelizumab and older injectable MS drugs.

Indirect comparisons between oral and newer biologic drugs:

Indirect comparisons do not have the protection against bias found in well conducted comparative RCTs. The concentration of RCTs with direct comparisons to older injectable drugs leaves most drug-to-drug comparisons of interest to this review without direct comparative data.

Given the lack of direct evidence to compare the 11 MS drug available, numerous reviewers have turned to a network meta-analysis (NMA) modeling approach that is based on indirect comparisons. For example, to compare oral drugs and the newer biologic drugs to each other, this approach uses the findings of placebo and active comparisons using injectable MS drugs to estimate relative differences indirectly. NMA, like all modelling exercises, can be useful and provide insights. However, it depends heavily on assumptions, primarily on the assumption that the available trials are sufficiently similar, so the resulting meta-analysis can be considered valid. If assumptions are not met these analyses may provide results that are invalid and misleading.

By necessity, a mix of studies with placebo-controlled and active comparators have been used in the NMA of MS drugs for RRMS. For example, of the drugs compared by Li 2019, only 7 of the 12 MS drugs had head-to-head RCTs (12)

Table 1. Gaps in direct head-to-head RCTS between 11 MS drugs

	Ocreliz	Alemtu	Nataliz	Ritux	Fingolim	Dimethyl	Terifl	Avonex	Rebif	Betaseron	Glatir
Ocreliz									Hauser, 2017 NCT01412333		
Alemtu									NCT00050778 NCT00530348 Coles, 2012		
Nataliz					NCT02342704 Terminated				NCT01058005 Terminated		NCT01058005 Terminated
Ritux											
Fingolim			NCT02342704 Terminated					Cree BAC 2018 NCT01317004 NCT01534182 NCT01216072 Cohen, 2010	Cree BAC 2018 NCT01317004 NCT01534182 NCT01216072	Cree BAC 2018 NCT01317004 NCT01534182 NCT01216072 NCT01333501	Cree BAC 2018 NCT01633112 NCT01317004 NCT01534182 NCT01216072
Dimethyl											Fox, 2012
Terifl									Vermersch 2014		
Avonex					Cree BAC 2018 NCT01317004 NCT01534182 NCT01216072 Cohen, 2010				Calabrese 2012 Etemadifar 2006 Panitch, 2002 Mokhber 2012	Etemadifar 2006 Mokhber 2012 Durelli 2002	Calabrese 2012 Lublin 2013
Rebif	Hauser, 2017 NCT01412333	NCT00050778 NCT00530348 Coles, 2012	NCT01058005 Terminated		Cree BAC 2018 NCT01317004 NCT01534182 NCT01216072		Vermersch 2014	Calabrese 2012 Etemadifar 2006 Panitch, 2002 Mokhber 2012		Etemadifar 2006 Koch-Henriksen 2006 Mokhber 2012 Singer et al 2012	Calabrese 2012 Mikol, 2008
Betaseron					Cree BAC 2018 NCT01317004 NCT01534182 NCT01216072 NCT01333501			Etemadifar 2006 Mokhber 2012 Durelli 2002	Etemadifar 2006 Koch-Henriksen 2006 Mokhber 2012 Singer et al 2012		Cavadid 2009 O'Connor 2009
Glatir			NCT01058005 Terminated		Cree BAC 2018 NCT01317004 NCT01534182 NCT01216072	Fox, 2012		Calabrese 2012 Lublin 2013	Mikol, 2008	Cavadid 2009 O'Connor 2009	

Ocreliz: ocrelizumab; Alemtuz: alemtuzumab; Nataliz: natalizumab; Ritux: rituximab; Fingolim: fingolimod; Dimethyl: dimethyl fumarate; Terifl: Teriflunomide; Avonex: interferon beta-1a (Avonex); Rebif: interferon beta-1a (Rebif); Betaseron: interferon beta-1b (Betaseron); Glatir: glatiramer Acetate.

The following substantive limitations of a recent NMA of MS drugs for RRMS were reported by Li 2019 (12) have reported regarding their analysis:

> First, according to the GRADE framework, the quality of some comparisons was assessed as low or very low, which largely restricts the interpretation of these results.
>
> Second, network meta-analysis requires reasonably homogeneous trials. Most related trials were 2 years in length, and the review was restricted to trials with a 2-year follow-up. We excluded trials with other follow-up periods to reduce heterogeneity and inconsistency among trials in the network meta-analysis. It should also be noted that RRMS is a chronic disease lasting 30–40 years. The results of our review are limited to the first 2 years of follow-up. The efficacy and acceptability of DMTs beyond 2 years are uncertain. However, only a few studies accessed the medium and long-term efficacy of DMTs.
>
> Third, there exist heterogeneities in the participants of the network meta-analyses. We included studies between 1987 and 2018, the time span is too long. The diagnostic criteria for MS have been updated several times. And there were differences between the participants (more active disease due to lack of alternative DMTs available and newer populations with lack of disease activity or disease breakthrough while using other DMTs). The heterogeneities above produced certain influence on the results.

Finally, heterogeneity of the definition of adverse events should be noted. We included 12 DMTs in the review. Different adverse events occur due to different mechanisms of action, which may affect the reliability of the comparison. Although no statistical heterogeneity was found, there exists clinical heterogeneity, which may impact the quality of the study (12).

Limitations of translating NMA findings to policy: Although existing NMA have compared and ranked many of the 11 MS drugs of interest, these analyses have little to contribute to the current BC policy review of MS drugs. For example, Li 2019 could only conclude:

> Alemtuzumab, ocrelizumab, natalizumab and fingolimod had a relatively higher response (relapse rate over 24 months) and lower dropout rates than did the other DMTs" (12).

The implication of this conclusion for policy review is not straight forward however. Alemtuzumab, natalizumab and fingolimod are currently covered as 2nd line treatments for RRMS in BC with ocrelizumab under consideration. Basing a decision to use this newer set of drugs as first-line drugs on the basis of currently available direct head-to-head RCT data or indirect NMA is far from evidence based.

Limitations relating to changing clinical practice strategies

Outcome measures: Slowing disability progression is a key clinical objective of MS treatment. However this has not been found to correlate will with reduced relapse rates. (31) Newer summary outcome measures have been proposed to overcome limitations evaluating MS drugs based on relapse rates. One such measure is 'no evidence of disease activity (NEDA) with three components: 'lack of clinical relapses, lack of disease progression measured by expanded disability status scale (EDSS) and absence of new

disease activity (new T2 lesions/enhancing lesion) on MRI over a period of observation (38). Each of the three components has competing definitions, and there are calls for additional components. Changing outcome definitions can lead to uncertainty in interpretation of trial results since differences over time may be due to changing outcome definitions rather than changes in response to treatment.

Changes over the last few decades in outcome measures used in research parallels changes in clinical practice. The EDSS scale is key to measures of relapse and disability progression over time. MRI has been increasingly used as part of diagnosis and measuring changes over time in clinical practice and research. In comparing research done in different eras, it can be unclear whether a change was due to a real change in the underlying condition or an artifact of changes in how outcomes were measured.

Earlier treatment strategies: A strategy of treatment earlier in the course of RRMS has been proposed over the last 10 years. This is likely drive in part by the implementation of the Macdonald diagnostic criteria in 2017. Diagnosing MS using McDonald 2017 criteria will identify a milder form of MS than in the past when the diagnosis was based on clinical course alone. The strategy for earlier treatment is closely tied to advocacy for a strategy of personalized treatment plans with more choice and research to guide sequencing over life cycle of RRMS disease (39).

Using the newer biologic drugs earlier in the course of is currently unproven. However, RCTs are underway (in recruitment phase) to evaluate treatment starting at an earlier stage in the disease. Results are not anticipated until 2023 at the earliest.

1. The TRaditional versus Early Aggressive Therapy for MS (TREAT-MS) trial is a pragmatic, randomized controlled trial that has two primary aims: 1) to evaluate, jointly and independently among patients deemed at higher risk vs. lower risk for disability accumulation, whether an "early aggressive" therapy approach, versus starting with a traditional, first-line therapy, influences the intermediate-term risk of disability, and 2) to evaluate if, among patients deemed at lower risk for disability who start on first-line MS therapies but experience breakthrough disease, those who switch to a higher-efficacy versus a new first-line therapy have different intermediate-term risk of disability. (https://clinicaltrials.gov/ct2/show/NCT03500328)

2. The Determining the Effectiveness of earLy Intensive Versus Escalation Approaches for RRMS (DELIVER-MS). This study seeks to answer the question: “Does early treatment with highly effective DMT improve the prognosis for people with MS? This is an area of significant controversy and no data currently exist to guide treatment choices for patients and clinicians. The study results will help guide overall treatment philosophy and will be applicable not only to a wide range of existing therapies but also to new therapies, meeting a significant unmet need in patient decision making and aiding the decision for medication approval by third parties. (https://clinicaltrials.gov/ct2/show/NCT03535298)

Summary of comparative evidence

A. 2-year relapse rates
   a. Epidemiological studies lasting up to 20 years show that a reduction in relapse rates over a 2-year period is not associated with less disability in subsequent years.
   b. Relapse rates over a 2-year period are the primary outcome in most of the comparative RCTs

B. Comparative harm profiles
   a. Outcome data on all-cause mortality, non-fatal serious adverse events and total adverse events from the 2-year comparative RCTs are inadequately reported to evaluate the relative harm profile among drugs licensed for RRMS.
   b. Drugs licensed for RRMS involve multiple mechanisms of action resulting in unique harm profiles.
   c. Available evidence typically provides frequency counts without reporting the seriousness of an adverse event.
   d. The pre-licensing evaluation of harm for drugs licensed for RRMS has been inadequate. New biologics have been withdrawn, and had major new SAEs lead to warnings. Health Canada issued a new warning regarding SAE with alemtuzumab in June of 2020.
   e. Ranking the MS drugs of interest on the basis of harm would be useful. However, this would require a comprehensive review of all available clinical trial and observation evidence. This was not within the scope of this TI review

C. Evidence supporting older injectable MS drugs
   a. Longitudinal comparative cohort studies of MS patients in BC lasting more that 20 years show no association between the use of the older injectable drugs and disability progression.
   b. Harm data compared to oral and new biologic drugs is limited 2 years in the RCTs.
   c. Observational data over several decades have thoroughly documented the harm associated with older injectable drugs, which may give physicians and patients confidence that these drugs are safer than alternatives.

D. Evidence supporting newer injectable, oral and biologic drugs
   a. Comparative RCTs show the newer drugs may result in fewer MS relapses than the older injectable drugs over 2 years.
      a. The newer drugs have much shorter population exposure, therefore fatal and non-fatal SAEs may still emerge

E. Evidence to support treatment with biologics and oral drugs with early presumptive MS diagnosis
   a. There is insufficient RCT evidence for early treatment with MS drugs.
   b. RCTs are in process and will be available within 3 to 5 years

F. Clinical decision-making using MRI

   MRI is playing an increasingly central role in RRMS diagnosis and treatment (40). However, efficacy of using MRIs in diagnosing and managing patients has not been demonstrated in a clinical study. That is, trials are needed to show that a measured CNS change associated with MS drug use leads to better patient outcomes

G. Patient convenience and preferences
   a. Patient convenience and preferences are out of scope as a topic of this review but highly relevant because of the substantial burden of each drug regimen

Conclusions

- RCT evidence and synthesis based on them are of minimal usefulness for evaluating the relative efficacy of the MS drugs of interest.
- Most comparative RCTs use INFs as comparators, drugs which have not been shown in observational cohort studies in BC patients to reduce disability as compared to untreated natural and contemporary cohorts
- The variable and long natural history of MS means that even if the correct comparators were used in the RCTs, 2 to 3-years of evidence is inadequate to assess the long-term effectiveness.
- Adverse events, particularly serious AE, are poorly evaluated and vary in type and health impact by specific MS drug.
- Trials evaluating whether early treatment with biologics is beneficial are ongoing but will not be provide results before 2023.

Implications for policy development

A. 2-year relapse rates as a relative efficacy measure
    a. Relapse rates over a two-year period are a weak predictor of subsequent disability in patients with RRMS.
    b. Relapses are variously defined, have weak reliability, and are incompletely reported in RCTs.
    c. Relapse rates are only reported on a subset of randomized patients due to attrition of 30-40%.
    d. Relapse rates therefore are not considered reliable for relative efficacy assessment.

B. Comparative harm profiles
    a. Data on all-cause mortality, non-fatal serious adverse events and total adverse events are minimal from the 2-year RCTs.
    b. Harm data from 2-year RCTs has proven inadequate to establish the harm associated with MS drugs. New biologicals have been withdrawn, had major new SAEs lead to warnings and updates following licensing. This continues with a new Health Canada warning regarding SAE with alemtuzumab in June of 2020.
    c. Harm, if reported, relies on frequency counts without providing details of the seriousness of the adverse event.
    d. Ranking the MS drugs on the basis of harm was outside the scope of this review.

C. Comparing new oral and biologic drugs with older injectable drugs
    a. Observational evidence from BC and elsewhere show no impact of older injectable drug therapy (INF and glatiramer) on long-term disability.
    b. There are decades of experience with the harm associated with the older injectable drugs, which may give physicians and patients confidence that these drugs are safer than alternatives.
    c. Measuring relative efficacy of the newer drugs with these older injectable drugs does not seem justified, particularly when relapse rates are used to try to distinguish between the newer drugs.

D. Comparing new oral and biologic drugs
    a. The new biologics have not been compared to oral MS drugs (dimethyl fumarate, terifluniomide and fingolimod) or each other.
    b. There are no head-to-head RCTs between fingolimod, alemtuzumab, natalizumab or ocrelizumab.
    c. Therefore, these drugs cannot be ranked based on RCT evidence.
E. Biologic drugs for first-line therapy for early treatment
    a. No RCT evidence supports early treatment with biologic drugs.
    b. Research will be available within a 3 to 5-years.
    c. Drug funding with evidence development seems necessary with this level of uncertainty.
F. Network Meta-analysis
    a. NMA have compared and ranked many of the 11 MS drugs of interest. However, because of heterogeneity of patients and outcome measures, these analyses have little to contribute to the current BC policy review of MS drugs.
G. Cost
    a. Cost considerations are out of scope but relevant.
H. Patient convenience and preferences
    a. Patient convenience and preferences are out of scope.
    b. Preserving multiple and sufficient MS drug options is important given drug intolerances and the uncertainty about relative harms and benefits of the 11 MS drugs reviewed in this report.

References

1. Rae-Grant A, Day GS, Marrie RA, Rabinstein A, Cree BAC, Gronseth GS, et al. Comprehensive systematic review summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2018;90(17):789-800.
2. Biotti D, Ciron J. First-line therapy in relapsing remitting multiple sclerosis. Rev Neurol (Paris). 2018;174(6):419-28.
3. Montalban X, Gold R, Thompson AJ, Otero-Romero S, Amato MP, Chandraratna D, et al. ECTRIMS/EAN Guideline on the pharmacological treatment of people with multiple sclerosis. Mult Scler. 2018;24(2):96-120.
4. CADTH. CADTH Therapeutic Reviews. Recommendations for Drug Therapies for Relapsing-Remitting Multiple Sclerosis. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health Copyright (c) CADTH March 2013.; 2013.
5. Zhang J, Shi S, Zhang Y, Luo J, Xiao Y, Meng L, et al. Alemtuzumab versus interferon beta 1a for relapsing-remitting multiple sclerosis. Cochrane Database of Systematic Reviews. 2017(11).
6. Riera R, Porfírio GJM, Torloni MR. Alemtuzumab for multiple sclerosis. Cochrane Database of Systematic Reviews. 2016(4).
7. La Mantia L, Tramacere I, Firwana B, Pacchetti I, Palumbo R, Filippini G. Fingolimod for relapsing-remitting multiple sclerosis. Cochrane Database of Systematic Reviews. 2016(4).
8. La Mantia L, Di Pietrantonj C, Rovaris M, Rigon G, Frau S, Berardo F, et al. Interferons-beta versus glatiramer acetate for relapsing-remitting multiple sclerosis. Cochrane Database of Systematic Reviews. 2016(11).
9. He D, Zhang C, Zhao X, Zhang Y, Dai Q, Li Y, et al. Teriflunomide for multiple sclerosis. The Cochrane database of systematic reviews. 2016;3:Cd009882.

10. Tramacere I, Del Giovane C, Salanti G, D'Amico R, Filippini G. Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis. Cochrane Database of Systematic Reviews. 2015(9).
11. Xu Z, Zhang F, Sun F, Gu K, Dong S, He D. Dimethyl fumarate for multiple sclerosis. Cochrane Database of Systematic Reviews. 2015(4).
12. Li H, Hu F, Zhang Y, Li K. Comparative efficacy and acceptability of disease-modifying therapies in patients with relapsing-remitting multiple sclerosis: a systematic review and network meta-analysis. Journal of Neurology. 2019;25:25.
13. Cohen JA, Coles AJ, Arnold DL, Confavreux C, Fox EJ, Hartung HP, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. Lancet. 2012;380(9856):1819-28.
14. Riera R, Porfirio GJ, Torloni MR. Alemtuzumab for multiple sclerosis. Cochrane Database of Systematic Reviews. 2016;4:CD011203.
15. Zhang J, Shi S, Zhang Y, Luo J, Xiao Y, Meng L, et al. Alemtuzumab versus interferon beta 1a for relapsing-remitting multiple sclerosis. Cochrane Database of Systematic Reviews. 2017;11:CD010968.
16. Tramacere I, Del Giovane C, Salanti G, D'Amico R, Filippini G. Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis. Cochrane Database of Systematic Reviews. 2015(9):CD011381.
17. Hauser SL, Bar-Or A, Comi G, Giovannoni G, Hartung HP, Hemmer B, et al. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. N Engl J Med. 2017;376(3):221-34.
18. Cohen JA, Barkhof F, Comi G, Hartung HP, Khatri BO, Montalban X, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med. 2010;362(5):402-15.
19. Calkwood J, Cree B, Crayton H, Kantor D, Steingo B, Barbato L, et al. Impact of a switch to fingolimod versus staying on glatiramer acetate or beta interferons on patient- and physician-reported outcomes in relapsing multiple sclerosis: post hoc analyses of the EPOC trial. BMC Neurol. 2014;14:220.
20. Comi G, Patti F, Rocca MA, Mattioli FC, Amato MP, Gallo P, et al. Efficacy of fingolimod and interferon beta-1b on cognitive, MRI, and clinical outcomes in relapsing-remitting multiple sclerosis: an 18-month, open-label, rater-blinded, randomised, multicentre study (the GOLDEN study). Journal of Neurology. 2017;264(12):2436-49.
21. Cree BAC, Arnold DL, Cascione M, Fox EJ, Williams IM, Meng X, et al. Phase IV study of retention on fingolimod versus injectable multiple sclerosis therapies: a randomized clinical trial. Therapeutic Advances in Neurological Disorders. 2018;11:1756286418774338.
22. La Mantia L, Tramacere I, Firwana B, Pacchetti I, Palumbo R, Filippini G. Fingolimod for relapsing-remitting multiple sclerosis. Cochrane Database of Systematic Reviews. 2016;4:CD009371.
23. Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, Kita M, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med. 2012;367(12):1087-97.
24. Xu Z, Zhang F, Sun F, Gu K, Dong S, He D. Dimethyl fumarate for multiple sclerosis. Cochrane Database of Systematic Reviews. 2015(4):CD011076.
25. Vermersch P, Czlonkowska A, Grimaldi LM, Confavreux C, Comi G, Kappos L, et al. Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial. Mult Scler. 2014;20(6):705-16.
26. He D, Zhang C, Zhao X, Zhang Y, Dai Q, Li Y, et al. Teriflunomide for multiple sclerosis. Cochrane Database of Systematic Reviews. 2016;3:CD009882.
27. Fox E, Edwards K, Burch G, Wynn DR, LaGanke C, Crayton H, et al. Outcomes of switching directly to oral fingolimod from injectable therapies: Results of the randomized, open-label,

multicenter, Evaluate Patient OutComes (EPOC) study in relapsing multiple sclerosis. Mult Scler Relat Disord. 2014;3(5):607-19.
28. La Mantia L, Di Pietrantonj C, Rovaris M, Rigon G, Frau S, Berardo F, et al. Interferons-beta versus glatiramer acetate for relapsing-remitting multiple sclerosis. Cochrane Database of Systematic Reviews. 2016;11:CD009333.
29. Diaz J, Jover Sanchez J, Ferreiro Arguelles I, Rodriguez G. Diagnosis of multiple sclerosis: Comparison of the 2010 McDonald criteria, MAGNIMS 2016 and the new 2017 McDonald criteria [Conference Abstract] Multiple Sclerosis Journal 34th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS 2018. 2018;24(2 Supplement):332-3.
30. McNicholas N, Lockhart A, Yap SM, O'Connell K, Tubridy N, Hutchinson M, et al. New versus old: Implications of evolving diagnostic criteria for relapsing-remitting multiple sclerosis. Mult Scler. 2019;25(6):867-70.
31. Shirani A, Zhao Y, Karim ME, Evans C, Kingwell E, van der Kop ML, et al. Association between use of interferon beta and progression of disability in patients with relapsing-remitting multiple sclerosis. Jama. 2012;308(3):247-56.
32. University of California San Francisco MS Epic Team, Cree BAC, Hollenbach JA, Bove R, Kirkish G, Sacco S, et al. Silent progression in disease activity-free relapsing multiple sclerosis. Annals of neurology. 2019;85(5):653-66.
33. Tramacere I, Benedetti DM, Capobussi M, Castellini G, Citterio A, Del Giovane C, et al. Adverse effects of immunotherapies for multiple sclerosis: a network meta-analysis. Cochrane Database of Systematic Reviews. 2016(5).
34. Perez-Miralles FC. Daclizumab in multiple sclerosis. Rev Neurol. 2018;66(8):271-82.
35. Holmoy T, Fevang B, Olsen DB, Spigset O, Bo L. Adverse events with fatal outcome associated with alemtuzumab treatment in multiple sclerosis. BMC Res Notes. 2019;12(1):497.
36. Use of multiple sclerosis medicine Lemtrada restricted while EMA review is ongoing. [press release]. 12/04/2019 2019.
37. Measures to minimise risk of serious side effects of multiple sclerosis medicine Lemtrada [press release]. 15/11/2019 2019.
38. Pandit L. No Evidence of Disease Activity (NEDA) in Multiple Sclerosis - Shifting the Goal Posts. Ann Indian Acad Neurol. 2019;22(3):261-3.
39. Gehr S, Kaiser T, Kreutz R, Ludwig WD, Paul F. Suggestions for improving the design of clinical trials in multiple sclerosis-results of a systematic analysis of completed phase III trials. EPMA Journal. 2019;10(4):425-36.
40. Oh J, Ontaneda D, Azevedo C, Klawiter EC, Absinta M, Arnold DL, et al. Imaging outcome measures of neuroprotection and repair in MS: A consensus statement from NAIMS. Neurology. 2019;92(11):519-33.