Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

CADTH Therapeutic Review

October 2013
Volume 1, Issue 2C

Recommendations for Drug Therapies for Relapsing-Remitting Multiple Sclerosis

Supporting Informed Decisions

TABLE OF CONTENTS

ABBREVIATIONS

CADTH	Canadian Agency for Drugs and Technologies in Health
CDEC	Canadian Drug Expert Committee
EDSS	Expanded Disability Scale Score
ICUR	incremental cost-utility ratio
MRI	magnetic resonance imaging
MS	multiple sclerosis
NMA	network meta-analysis
PML	progressive multifocal leukoencephalopathy
QALY	quality-adjusted life-year
RCT	randomized controlled trial
RRMS	relapsing-remitting multiple sclerosis

BACKGROUND

Multiple sclerosis (MS) is a chronic inflammatory disorder of the central nervous system (CNS) that is approximately three times more common in women than in men.[1,2] Canada has the fifth highest worldwide prevalence, at 240 per 100,000 persons.[3]

MS is classified into four subtypes; approximately 85% to 90% of persons with MS have the relapsing-remitting type of MS (RRMS).[4] In RRMS, the frequency of relapse is highly variable but tends to be more frequent in the first few years of disease onset.[4] The therapeutic aims of MS drugs are to lower the frequency of relapses, decrease the lasting effects of relapses, prevent or decrease disability that is the result of disease progression, and promote tissue repair.[5,6]

In Canada, the earliest available disease-modifying treatments for MS include interferons (interferon beta-1a and interferon beta-1b) and glatiramer acetate, injectable agents that were approved by Health Canada in the 1990s. Natalizumab, administered via intravenous infusion, was approved by Health Canada in 2006 for the treatment of RRMS; however, there are safety concerns regarding natalizumab because of its association with progressive multifocal leukoencephalopathy (PML), a rare demyelinating neurological disorder caused by the reactivation of the John Cunningham (JC) virus.[7,8] More recently, fingolimod, the first oral agent for the treatment of RRMS, was approved by Health Canada in 2011. Patient-group input, solicited for the Canadian Agency for Drugs and Technologies in Health (CADTH) Therapeutic Review, suggests persons living with MS prefer oral agents over injectable agents. However, the price of fingolimod is considerably higher than that of either the interferons or glatiramer acetate, and fingolimod has not been considered cost-effective in all patients studied.[9] In addition, Health Canada monographs for both natalizumab and fingolimod indicate that these agents are generally recommended for patients with inadequate response or intolerance to other therapies for MS.

Dimethyl fumarate, a new oral agent, was approved by Health Canada for the treatment of RRMS during the undertaking of this CADTH Therapeutic Review in 2013. In addition, a number of new disease-modifying therapies (both oral and injectable) for the treatment of MS are in development. These include alemtuzumab (injectable) and teriflunomide (oral), which are expected to enter the Canadian market soon.

The effectiveness and safety of available MS treatments, relative to one another, is not well-established. The emergence of novel oral and injectable agents necessitates consideration of their place in therapy, including the potential for combination therapy. Thus, the comparative clinical and cost-effectiveness of currently available and emerging disease-modifying agents for RRMS, both alone and in combination, need to be determined.

Evidence-informed recommendations were developed by the Canadian Drug Expert Committee (CDEC) to address the following policy questions:

1. For patients with RRMS, what are the preferred initial pharmacological treatment strategies?
2. For patients with RRMS, what are the pharmacological strategies for patients not adequately controlled on initial pharmacotherapy?
3. Should combination strategies be considered for treatment of patients with RRMS? If so, what are the appropriate treatment options?

At the time of this report, alemtuzumab and teriflunomide were not approved by Health Canada for the treatment of RRMS. Therefore, while the science reports included alemtuzumab and teriflunomide in addition to interferon beta-1a, interferon beta-1b, glatiramer acetate, natalizumab, fingolimod, and dimethyl fumarate, the recommendations presented in this report apply at present only to the aforementioned treatments that are approved for RRMS in Canada.

The evidence for developing recommendations was derived from the following reports:

- Canadian Agency for Drugs and Technologies in Health. CADTH therapeutic review. Comparative clinical and cost-effectiveness of drug therapies for relapsing-remitting multiple sclerosis [Internet]. Ottawa: The Agency; 2013 Oct. (CADTH Therapeutic Review vol.1, no. 2b). [cited 2013 Oct 31]. Available from: http://www.cadth.ca/en/products/therapeutic-reviews/relapsing-remit-multiple-sclerosis/reports
- Patient Group Input to CADTH submitted by the Multiple Sclerosis Society of Canada. [cited: 2013 Oct 31]. Available from: http://www.cadth.ca/media/pdf/TR0004_PatientInputSubmission_e.pdf

The Committee considered the evidence and its limitations primarily from a population-based perspective. The anticipated absolute benefits, harms, and cost-effectiveness of the therapies compared with each other, along with patient group input, were considered to be fundamental in the development of system-level recommendations. The Committee also recognized that recommendations for treatment optimization related to the use of disease-modifying treatments have been developed by the Canadian Multiple Sclerosis Working Group and are based on clinical judgment and consideration of individual patient characteristics.[10]

SUMMARY OF RECOMMENDATIONS

1. The Canadian Drug Expert Committee (CDEC) recommends glatiramer acetate or interferon beta-1b as the initial pharmacotherapies of choice for patients with RRMS.

2. CDEC recommends that patients with RRMS who have failed to respond to, or have contraindications to, glatiramer acetate as the initial treatment be treated with interferon beta-1b. Similarly, CDEC recommends that patients with RRMS who have failed to respond to, or have contraindications to, interferon-beta-1b as the initial treatment be treated with glatiramer acetate.

3. CDEC recommends that subsequent pharmacotherapies for patients with RRMS who have failed to respond to, or have contraindications to, glatiramer acetate and interferon beta-1b be selected from dimethyl fumarate, fingolimod, and natalizumab. The selection should be based on cost and individual safety concerns.

4. CDEC recommends that combination therapy for treatment of RRMS not be used.

CDEC Values and Preferences

CDEC sought to balance patient perspectives with clinical and economic evidence. The Committee identified the values of efficacy, safety, cost-effectiveness and patient preference as particularly important in making these recommendations. In considering patient perspectives, the Committee noted patients' preference for access to a wide variety of treatments for RRMS and for oral treatments specifically. Considering all perspectives, CDEC identified two treatment options for initial therapy, based on a systematic review of clinical trials and a cost-effectiveness analysis. For patients who fail to respond to, or have contraindications to, these treatments, the Committee recommends access to other less cost-effective treatments, including oral therapies.

At the time of this report, alemtuzumab and teriflunomide were not approved by Health Canada for the treatment of RRMS. Therefore, the aforementioned recommendations should be restricted at present to treatments approved for RRMS in Canada, including interferon beta-1a, interferon beta-1b, glatiramer acetate, natalizumab, fingolimod, and dimethyl fumarate.

RECOMMENDATIONS

Recommendation 1:

CDEC recommends glatiramer acetate or interferon beta-1b as the initial pharmacotherapies of choice for patients with RRMS.

Of Note:

1. The cost-effectiveness results are unfavourable for all available pharmacotherapies included in the pharmacoeconomic model except interferon beta-1b and glatiramer acetate.
2. Subcutaneous interferon beta-1b is available as more than one brand name product. CDEC noted that the choice of interferon beta-1b product funded by drug plans should be based on price.
3. Compared with placebo, subcutaneous interferons beta-1a 44 mcg and beta-1b 250 mcg produced similar reductions in the annualized relapse rate, based on both direct and indirect evidence; however, interferon beta-1a 44 mcg was more costly.
4. Intramuscular interferon beta-1a 30 mcg was considered to be less efficacious, as assessed by the annualized relapse rate, compared with subcutaneous interferons beta-1b 250 mcg and beta-1a 44 mcg, based on both direct and indirect evidence. The cost of interferon beta-1a 30 mcg is more than interferon beta-1b 250 mcg, but less than the cost of interferon beta-1a 44 mcg.
5. At the manufacturer-provided price for the Therapeutic Review, dimethyl fumarate is not a cost-effective option for initial treatment of RRMS.

Reasons for Recommendation 1

- The clinical evidence suggests that glatiramer acetate and interferon beta-1b have statistically significant and clinically meaningful effects on the annualized relapse rate relative to placebo (relative rates of 0.67), and are the most cost-effective initial pharmacotherapies for treatment of RRMS.
- Results of the probabilistic sensitivity analysis indicate that there is considerable uncertainty regarding whether glatiramer acetate is the most cost-effective treatment; interferon beta-1b may also be the most cost-effective treatment.

Recommendation 2:

CDEC recommends that patients with RRMS who have failed to respond to, or have contraindications to, glatiramer acetate as the initial treatment be treated with interferon beta-1b. Similarly, CDEC recommends that patients with RRMS who have failed to respond to, or have contraindications to, interferon-beta-1b as the initial treatment be treated with glatiramer acetate.

Recommendation 3:

CDEC recommends that subsequent pharmacotherapies for patients with RRMS who have failed to respond to, or have contraindications to, glatiramer acetate and interferon beta-1b be selected from dimethyl fumarate, fingolimod, and natalizumab. The selection should be based on cost and individual safety concerns.

Of Note:

1. Most of the included trials did not distinguish between initial therapy and subsequent therapy and enrolled both treatment-experienced and treatment-naïve patients. Therefore, these recommendations are premised on the assumption that the relative efficacy will not change by the sequence in therapy.
2. With regard to the aforementioned recommendations, patients with RRMS previously or currently treated with interferon beta-1a who fail to respond do not require a trial of interferon beta-1b to be eligible for treatment with one of dimethyl fumarate, fingolimod, or natalizumab.
3. Evolving safety considerations may influence the choice of subsequent pharmacotherapies in patients with RRMS who have failed to respond to, or have contraindications to, both glatiramer acetate and interferon beta-1b.
4. CDEC considered the importance of having a wide selection of effective treatments available to patients and practitioners. The recommendations strike a balance between providing choice of both initial and subsequent treatments, while considering the relative cost-effectiveness of treatments.

Reason for Recommendation 2

Interferon beta-1b and glatiramer acetate had similar efficacy, as assessed by the annualized relapse rate, based on both direct and indirect evidence, but belong to different therapeutic classes.

Reason for Recommendation 3

Dimethyl fumarate, fingolimod, and natalizumab were not cost-effective as initial treatment, and there were insufficient data to determine their relative efficacy and cost-effectiveness as sequential treatments.

Recommendation 4:
CDEC recommends that combination therapy for treatment of RRMS not be used.

Of Note:

While combination therapies resulted in some radiological improvements, the clinical significance of these improvements is uncertain.

Reason for Recommendation 4

The systematic review demonstrated no clinical advantage of combination therapy over monotherapy for RRMS.

PATIENT-GROUP INPUT

Committee discussions were informed by a submission to CADTH by the Multiple Sclerosis Society of Canada. The following points summarize the concerns of patients and caregivers, as documented in the patient-group submission:

- The vast majority of people living with MS report that the disease has had a negative impact on almost all aspects of their lives. MS affects not only the person with the disease but also his or her family members. Partners and parents often become caregivers.
- People living with MS most frequently stated that progression of disability and frequency of relapse were the most important symptoms to control. However, patients living with MS also noted that a number of symptoms common to MS had major impacts on their lives: fatigue, difficulty walking, memory or attention problems, bladder problems, numbness or tingling, and pain.
- Side effects from current treatments — including injection-site reactions, fatigue, sore muscles and joints, headache, loss of fatty tissue at injection sites, thyroid problems, liver toxicity, poor sleep, nausea, low white blood cell count, and skin bruising — were frequent complaints. Among patients who altered their therapy because of side effects, the most frequently cited reasons were fatigue and injection-site reactions.
- Patients and caregivers noted that the cost of treatments for RRMS represent a considerable financial burden.
- People living with MS firmly believe that an oral disease-modifying therapy will significantly improve their quality of life, as it will eliminate the need for frequent injections. In particular, people living with MS noted that disease-related coordination problems and the loss of fatty tissue at injection sites led to difficulties in self-administering injections. For people living with MS, oral therapies represent the potential to be more independent and to gain control of their treatment regimen.
- Maintaining quality of life is a significant concern for people living with MS. The availability of drug and drug-delivery options that fit an individual's disease and life situation would allow patients to choose their best options to conserve and sustain their quality of life.

SUMMARY OF THE EVIDENCE

Clinical Evidence

The Committee considered the results of a systematic review of randomized controlled trials (RCTs) conducted to assess the comparative clinical efficacy and safety of drug therapies for RRMS.[11] The review included 30 unique trials, of which 27[12-38] provided comparisons of monotherapies (sole comparator was placebo in 14 trials) and four[38-41] compared monotherapies with combination therapy. Trials were selected for inclusion in the systematic review and subsequent analyses if they were active- or placebo-controlled trials, published in English, involved patients with RRMS, had treatment arms consisting of currently available or emerging disease-modifying agents expected to shortly enter the Canadian market, and reported any of the protocol-specified outcomes related to clinical efficacy and safety. Trials that included mixed populations of MS patients were also included if the proportion of RRMS patients was more than 50% of the total population. For interventions currently approved by Health Canada for treatment of RRMS, only approved formulations and doses were included in the systematic review. Emerging agents not yet approved by Health Canada were not restricted to specific doses or formulations. Included interventions were interferon beta-1a subcutaneous (22 mcg and 44 mcg), interferon beta-1a intramuscular (30 mcg and 60 mcg), interferon beta-1b subcutaneous (250 mcg), glatiramer acetate, natalizumab, fingolimod, and dimethyl fumarate. In addition, two emerging agents were included: alemtuzumab (12 mg and 24 mg), and teriflunomide (7 mg and 14 mg).

Of the included RCTs, 11 were rater-blind,[13-18,21,23,24,33,37] three were open label,[28,33,37] and the remainder were double-blind. Of the 24 trials that specified a primary end point, 13 had a primary end point of relapse,[14,21,22,24-26,28,29,32,33,35,36,38] two had disability as a primary end point,[19,30] five had an magnetic resonance imaging (MRI) outcome as a primary end point,[20,27,31,34,37] and four had co-primary end points of relapse and disability.[12,16-18] The most common duration of follow-up was two years. The shortest follow-up was 16 weeks, and the longest duration of follow-up was up to 3.5 years.

All trials of monotherapy included patients with RRMS; however, four trials also included small proportions of patients with other MS classifications.[13,19,31,35] The range of mean Kurtzke Expanded Disability Status Scale (EDSS) scores at baseline was 2.0 to 2.9 in 24 trials,[12-18,20-26,28-36,38] and 3.3 and 3.6 in two trials.[19,37] One trial did not report baseline EDSS.[27] The majority of patients were female (64% to 84%), were Caucasian (78% to 98%), and had a mean age range from 29 to 41 years. The mean number of relapses in the year before the study ranged from 1.0 to 1.8. The mean number of years since symptom onset varied widely between 1.1 years and 9.2 years. Twelve trials involved treatment-naïve patients,[13,14,16,17,26,28-33,38] six had mixed populations,[21,22,25,35-37] one had a treatment-experienced population,[18] and eight had an unclear treatment history.[12,15,19,20,23,24,27,34]

Three of four combination trials were conducted in treatment-experienced patients, and each of the three trials provided evidence for a different combination versus monotherapy; natalizumab plus interferon beta-1a 30 mcg versus interferon beta-1a 30 mcg, natalizumab plus glatiramer acetate versus glatiramer acetate, and teriflunomide plus an interferon beta versus an interferon beta. One additional RCT in treatment-naïve patients compared interferon beta-1a 30 mcg plus glatiramer acetate to both agents alone. Two were phase 2 trials with treatment durations of 24 weeks,[39,40] and two were phase 3 trials with treatment durations of 2 to 3 years.[38,41] The

mean age ranged from 38 to 41 years, mean EDSS at baseline ranged from 2.0 to 2.7, and mean number of relapses in the year before the study ranged from 0.8 to 1.7.

The systematic review included five clinical outcomes (annualized relapse rate, proportion of patients relapse-free, proportion of patients with sustained disability progression, mean change in EDSS from baseline, and mean change in the MS Functional Composite from baseline), four radiological (MRI) outcomes (proportion of patients with gadolinium-enhancing lesions, mean number of gadolinium-enhancing lesions, proportion of patients with new or enlarging T2 lesions, mean number of new or enlarging T2 lesions), in addition to quality of life and safety events (death, serious adverse events, total adverse events, and discontinuation due to adverse events).

Direct pairwise analyses were conducted for all outcomes in the trials. Bayesian network meta-analyses (NMA) were conducted for the outcomes of annualized relapse rate and sustained disability progression, based on the monotherapy trials. The number of monotherapy trials included in the evidence networks for annualized relapse rate and proportion with sustained disability progression was 27 and 19 trials, including 16,998 and 15,982 patients, respectively. For sensitivity analyses, meta-regression and subgroup analyses were conducted for a number of patient characteristics (baseline EDSS score, time since symptom onset, number of relapses in previous year, prior treatment history) and trial characteristics (publication date and treatment duration). In the NMA of annualized relapse rate, alemtuzumab and natalizumab had the greatest activity, reducing the annualized relapse rate by approximately 70% compared with placebo. Fingolimod and dimethyl fumarate had similar activity to each other, reducing the annualized relapse rate by approximately 50% compared with placebo. Subcutaneous interferons, glatiramer acetate, and teriflunomide had similar activity to each other, reducing the annualized relapse rate by approximately 30% compared with placebo. Intramuscular interferon beta-1a had the lowest activity of all active agents. Results were robust in sensitivity analyses and were consistent with direct evidence, when available.

In the NMA of sustained disability progression, compared with placebo, all treatments exhibited a trend toward a reduced risk of sustained disability progression. Estimated effect sizes were greatest for alemtuzumab and natalizumab, followed by dimethyl fumarate and interferon beta-1b, and lowest for interferon beta-1a, glatiramer acetate, and teriflunomide. However, credible intervals were wide, and there was considerable overlap of credible intervals among all agents, resulting in unclear distinction between treatments.

The results of other clinical and MRI outcomes evaluated in direct pairwise meta-analyses were largely consistent with direct evidence for the annualized relapse rate and sustained disability progression. Health-related quality of life findings were reported for two treatments only, comparing interferon beta-1a 30 mcg versus placebo and natalizumab versus placebo. Interferon beta-1a 30 mcg improved physical scores, but not overall or psychosocial scores, in the Sickness Impact Profile. Natalizumab improved both physical and mental component summary scores in the Short Form-36, as well as the visual analogue scale of the subject global assessment.

In safety assessments, there were no differences in the overall incidence of adverse events that would favour any particular agents. Each agent had specific adverse events such as influenza-like symptoms and injection-site reactions for the interferons; hypersensitivity and injection-site reactions for glatiramer acetate; infusion reactions and risk of PML for natalizumab; infusion

reactions, thyroid disorders and infection for alemtuzumab; cardiovascular disorders (bradycardia, atrioventricular block) for fingolimod; hair loss for teriflunomide; and flushing for dimethyl fumarate. Liver enzyme elevation and gastrointestinal disorders occurred with many treatments but appeared to be transient. Serious adverse events and death were rare in all trials and did not differ statistically between treatments.

For combination therapy, teriflunomide as add-on therapy for patients previously treated with interferon betas, or natalizumab as add-on therapy for patients previously treated with glatiramer acetate, did not exhibit any statistically significant differences in relapse or disability compared with interferon beta or glatiramer acetate alone, respectively. Natalizumab as add-on to interferon beta-1a 30 mcg resulted in statistically significant differences in relapse and disability that favoured the combination over interferon beta-1a 30 mcg alone. The combination therapy of interferon beta-1a 30 mcg plus glatiramer acetate in treatment-naïve patients was not statistically different from either agent alone for most outcomes, with the exception of a lower annualized relapse rate for patients treated with the combination compared with interferon beta-1a 30 mcg alone. There were no apparent differences between combination therapy and monotherapy in safety events.

Economic Evidence

The Committee considered the results of an economic model developed to assess the comparative cost-effectiveness among individual disease-modifying agents in RRMS. The model was in the form of a cost-utility analysis, with treatments compared in terms of the incremental cost per quality-adjusted life-year (QALY) gained over a time horizon of 25 years. The target population was Canadians with RRMS, with a typical patient profile adopted from the RCTs identified in the systematic review: an average age of 36 years, gender distribution of 68% female, time since symptom onset of five years, and an initial discrete distribution of EDSS score with a mean score of 2.3. The analysis was conducted from the perspective of a provincial Ministry of Health in Canada.

The current treatments that are approved and available in Canada were included in the primary analysis: dimethyl fumarate 240 mg, fingolimod 0.5 mg, glatiramer acetate 20 mg/mL, interferon beta-1a 30 mcg, interferon beta-1a 22 mcg, interferon beta-1a 44 mcg, interferon beta-1b 250 mcg, and natalizumab 300 mg/15 mL. Emerging treatments in RRMS (alemtuzumab and teriflunomide) for which regulatory approval has not been granted were included in an exploratory analysis.

The annual costs for all treatments considered in the primary analysis are presented in Table1.

Table 1: Annual Drug Costs		
Drug	**Base Estimate ($)**	**Reference**
Dimethyl fumarate 240 mg (Tecfidera)	23,019	Manufacturer's information
Fingolimod (Gilenya)	31,170	Ontario MoH (2013)
Glatiramer acetate (Copaxone)	16,286	Ontario MoH (2013)
Interferon beta-1a 30 mcg (Avonex)	20,597	Ontario MoH (2013)
Interferon beta-1a 22 mcg (Rebif)	20,210	Ontario MoH (2013)
Interferon beta-1a 44 mcg (Rebif)	24,604	Ontario MoH (2013)
Interferon beta-1b 250 mcg (Betaseron)	20,130	Ontario MoH (2013)
Interferon beta-1b 250 mcg (Extavia)	18,183	Ontario MoH (2013)
Natalizumab (Tysabri)	40,281	Ontario MoH (2013)

A Markov cohort approach was taken for the analysis, based on a series of health states that reflect the progression of patients with RRMS. Health states were defined according to the EDSS (EDSS 0 to 2.5, 3 to 5.5, 6 to 7.5, 8 to 9.5, and 10), as well as severity of relapse (defined as mild/moderate or severe. During one cycle, patients could remain in the current health state; progress to the next, more severe state; improve to a less severe state; transition to a secondary progressive MS; withdraw from treatment; or die. Because of limited clinical evidence, sequential use of treatments was not considered; therefore, the analysis assessed the cost-effectiveness of the treatments used as initial therapy only.

The progression to more severe states was based on natural history data for MS from London, Ontario, and British Columbia cohort studies.[42,43] Treatment effects were based on NMA for the outcomes of annualized relapse rate and sustained disability progression. The cost of managing RRMS and utility values for the health states were derived from published literature. A variety of deterministic and probabilistic sensitivity analyses as well as a value-of-information analysis were carried out.

In the base case, glatiramer acetate was the most cost-effective treatment, unless willingness to pay exceeds $118,242 per QALY, at which point interferon beta-1b 250 mcg was the most cost-effective treatment (Table 2). The cost-effectiveness frontier (lines connecting the treatments that are not dominated) is comprised of glatiramer acetate, interferon beta-1b 250 mcg, dimethyl fumarate, and natalizumab. The sequential incremental cost-utility ratios (ICURs) of dimethyl fumarate versus interferon beta-1b was $425,655 per QALY and natalizumab versus dimethyl fumarate was $872,972 per QALY – not considered cost-effective initial treatments. Fingolimod and interferon beta-1a 30 mcg, 22 mcg, and 44 mcg were dominated by the treatments comprising the cost-effectiveness frontier.

Table 2: Results of Base Case Deterministic Analysis				
Treatment	**Total Cost ($)**	**Total QALYs**	**ICUR versus glatiramer acetate ($)**	**Sequential ICUR ($)**
Glatiramer acetate (Copaxone)	321,589	11.272	Reference drug	Reference drug
Interferon beta-1b (Extavia)	333,923	11.376	118,242	118,242
Dimethyl fumarate (Tecfidera)	361,688	11.442	236,518	425,655
Natalizumab (Tysabri)	482,436	11.580	522,472	872,972

QALY = quality-adjusted life-year; ICUR = incremental cost-utility ratio.
Note: Other treatments were ruled out by dominance or extended dominance.

Although the results of the probabilistic sensitivity analysis were consistent with the deterministic base case results, they indicated uncertainty regarding which treatments are cost-effective depending on the willingness-to-pay threshold. When the decision-maker is willing to pay a maximum of $50,000 per QALY (λ = $50,000), glatiramer acetate was the cost-effective treatment in 70% of replications, followed by interferon beta-1b (Extavia) in 26% and beta-1b (Betaseron) in 3% of replications. When the decision-maker is willing to pay a maximum of $100,000 per QALY (λ = $100,000), glatiramer acetate was the cost-effective treatment in 42% of replications, followed by interferon beta-1b (Extavia) in 38% and beta-1b (Betaseron) in 11%.

Based on the deterministic sensitivity analyses conducted, the results were most sensitive to data inputs for treatment effects of disability progression and drug costs. Other inputs, such as RRMS-related treatment costs, the natural history of disease progression, the model time horizon, and the stopping rule were shown to impact ICURs, as well. Influence of patient baseline characteristics were also assessed in sensitivity analyses: ICURs decreased for younger patients and for patients with higher baseline EDSS score. With the exception of treatment effects of disability progression and drug costs, none of these analyses changed the conclusion from the base case scenario.

The clinical evidence was sufficient to support the inclusion of combination therapy in the economic model; therefore, the cost-effectiveness of combination therapy in RRMS remains unknown.

Limitations of the Evidence

There were a limited number of RCTs directly comparing treatments for RRMS, necessitating indirect treatment comparisons using NMA. Indirect treatment comparisons, based on the NMA of studies conducted over a 20-year time period, were complicated by the heterogeneity of study and patient characteristics; control of these characteristics was limited by the small number of studies in relation to the number of treatment strategies.

A key limitation of the review was the inability to estimate relative treatment effects based on prior treatment history, as in the majority of monotherapy trials either the patients' prior treatment history was unclear, or the trial included a mixture of treatment-naïve and treatment-experienced patients.

An additional limitation included the relatively short duration of RCTs, which does not allow for between-treatment comparisons of effects on long-term disability. In addition, there were limited quality of life data to support comparisons between treatments, including comparisons of oral and injectable therapies.

DISCUSSION POINTS

Efficacy and Cost-Effectiveness

- The Committee considered that the reviewed trials were of insufficient duration to identify potential between-treatment differences in long-term disability. The Committee discussed that disability manifests over long periods of time in RRMS and that there were few statistical between-treatment differences for the outcome of sustained disability progression in the reviewed trials.
- The Committee noted the absence of reporting of many outcomes important to patients (including fatigue, walking ability, cognition, and quality of life) in many of the included trials.
- The Committee acknowledged that the economic analysis assessing the cost-effectiveness of treatments used as initial therapy only, because of limited clinical evidence of sequential use or switching among the treatments. Therefore, the cost-effectiveness of treatments for RRMS when used sequentially is not known.
- The Committee notes that all treatment options result in greater QALYs than no treatment, and that glatiramer acetate, interferon beta formulations, and dimethyl fumarate dominated no treatment, based on the economic analysis.
- The Committee discussed the availability of two interferon beta-1b 250 mcg formulations (Extavia and Betaseron) and the difference in price between them in some jurisdictions, which would lead to more favourable cost-effectiveness for the less expensive formulation, as a result of their equal efficacy and safety profiles.
- The Committee acknowledged that the base case scenario in the economic model included a distribution around a starting EDSS score with mean 2.3, to reflect the average patient group based on the baseline characteristics of the clinical trials included in the systematic review. To measure the impact of the starting EDSS score, this parameter was varied in the economic model. The results showed that early treatment with the more expensive treatments leads to significantly higher ICURs; however, this analysis was limited by the assumption of equal efficacy across baseline EDSS scores, as subgroup analysis by baseline EDSS score for the systematic review was not available.

Safety

- The Committee discussed that more is known regarding the safety profile of interferons and glatiramer acetate than regarding newer treatments for MS, by virtue of their longer time in clinical usage. The Committee further acknowledged that clinical trials are insufficiently powered and are too short to identify adverse events that are rare or have a long latency. CDEC discussed the association of natalizumab with PML, which has been identified post-marketing.
- The Committee noted that treatments for RRMS have varying adverse event profiles and monitoring requirements, which may be expected to influence treatment selection for an individual.
- The Committee acknowledged that the Health Canada-approved product monographs for natalizumab and fingolimod indicate that these treatments are generally recommended for patients with inadequate response or intolerance to other therapies for MS. CDEC further noted that the Health Canada-approved monograph for dimethyl fumarate does not include a similar recommendation.

Patient Considerations

- CDEC recognized that interferon beta-1a (both subcutaneous and intramuscular formulations) are commonly used pharmacotherapies in patients with RRMS and that patient preference may have been a factor in the selection of the interferon formulation.
- CDEC discussed patient-group input that revealed patients' desire for new treatments that improve everyday function, with greater convenience and affordability, as well as reduced adverse effects.
- CDEC recognized the strong stated preference of the patient group for oral therapies and the expectation that use of oral therapies will result in important improvements in quality of life. However, quality of life data that reflect patients' values for improvement in everyday function are limited in the available trials. There is also limited knowledge of the long-term side effects of current oral therapies. At current prices, the cost-effectiveness ratios are relatively unattractive for oral agents and do not support the use of these agents as initial therapy.

Other Discussion Points

- The cost-effectiveness analyses were from a Ministry of Health perspective. Analyses from a societal perspective might have yielded more favourable ratios, given the young age and the disability associated with MS.
- Agents that are currently in development for the treatment of RRMS (e.g., laquinimod, daclizumab, and ocrelizumab) but that were not included in the current Therapeutic Review may necessitate future Therapeutic Reviews of RRMS treatments.
- CDEC noted that clinical experts indicated that combination therapies are rarely used in Canada.

RESEARCH GAPS

The Committee proposed that the following issues be addressed through research as a high priority in future to facilitate comparisons of treatments for RRMS:

Safety

- Identification of long-term harms of recently introduced therapies for RRMS
- Improved ability to identify patients at risk for PML.

Efficacy

- Large prospective head-to-head trials that address the outcome of long-term disability in RRMS
- Evidence for sequencing of therapy, specifically clinical trials comparing treatment strategies in patients with RRMS in whom treatment has failed or who are unable to tolerate initial therapy
- Clinical trials that specifically compare treatment strategies of “add-on” to “switch” therapies
- Clinical trials that capture outcomes of particular interest to patients, including fatigue, walking ability, cognitive function, and quality of life
- Evaluation of disease outcomes in patients stopping therapy after a prolonged course.

Patient Factors

- Well-designed and validated qualitative research methods, in conjunction with existing standard quality of life scales, would provide a much richer and clearer understanding of the impact of potential therapies on the lives of people living with MS, which quantitative data may miss.

CDEC Members:

Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani

Regrets:

One CDEC member was not available to participate in deliberations and voting.

Conflicts of Interest:

None.

One external Clinical Expert attended the meeting and participated in the discussion, but did not vote on the recommendations.

About This Document:

Cite as: Canadian Agency for Drugs and Technologies in Health. CADTH therapeutic review. Recommendations for drug therapies for relapsing-remitting multiple sclerosis [Internet]. Ottawa: The Agency; 2013 Oct. (CADTH Therapeutic Review vol.1, no. 2c). [cited yyyy mm dd]. Available from: http://www.cadth.ca/media/pdf/TR0004_RRMS_RecsReport_TR_e.pdf

The Therapeutic Review Recommendations or Advice are formulated following a comprehensive evidence-based review of the medication's efficacy or effectiveness and safety and an assessment of its cost-effectiveness. Therapeutic Review clinical and economic reports are based on published information available up to the time that CDEC made its recommendation. Input from stakeholders, such as drug manufacturers, patient groups, and health-related professional associations or organizations, is considered in the preparation of this recommendation document.

CDEC is a committee of the Canadian Agency for Drugs and Technologies in Health (CADTH). It makes recommendations and provides advice to Canadian jurisdictions to use in making informed decisions. It is made up of experts in drug evaluation and drug therapy, and public members.

The Final CDEC Therapeutic Review Recommendations or Advice neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

CADTH is not legally responsible for any damages arising from the use or misuse of any information contained in or implied by the contents of this document.

The statements, conclusions, and views expressed herein do not necessarily represent the view of Health Canada or any provincial, territorial, or federal government, or the manufacturer.

Production of this report is made possible through a financial contribution from Health Canada and the governments of Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Nunavut, Ontario, Prince Edward Island, Saskatchewan, and Yukon.

The Therapeutic Review Framework describes the Therapeutic Review process in detail.[44]

REFERENCES

1. Alonso A, Hernan MA. Temporal trends in the incidence of multiple sclerosis: a systematic review. Neurology. 2008 Jul 8;71(2):129-35.
2. Koch-Henriksen N, Sorensen PS. The changing demographic pattern of multiple sclerosis epidemiology. Lancet Neurol. 2010 May;9(5):520-32.
3. Ramagopalan SV, Sadovnick AD. Epidemiology of multiple sclerosis. Neurol Clin. 2011 May;29(2):207-17.
4. Richards RG, Sampson FC, Beard SM, Tappenden P. A review of the natural history and epidemiology of multiple sclerosis: implications for resource allocation and health economic models. Health Technol Assess (Winch Eng) [Internet]. 2002 [cited 2013 Feb 28];6(10):1-73. Available from: http://www.hta.ac.uk/execsumm/summ610.htm
5. Zintzaras E, Doxani C, Mprotsis T, Schmid CH, Hadjigeorgiou GM. Network analysis of randomized controlled trials in multiple sclerosis. Clin Ther. 2012 Apr;34(4):857-69.
6. Trojano M, Paolicelli D, Tortorella C, Iaffaldano P, Lucchese G, Di Renzo V, et al. Natural history of multiple sclerosis: have available therapies impacted long-term prognosis? Neurol Clin. 2011 May;29(2):309-21.
7. Olek MJ. Treatment of relapsing-remitting multiple sclerosis in adults. 2013 [cited 2013 Feb 28]. In: UpToDate [Internet]. Waltham (MA): UpToDate. Available from: www.uptodate.com Subscription required.
8. O'Connor P, Devonshire V, Canadian Network of MS Clinics. The use of disease-modifying agents in multiple sclerosis--by the Canadian Network of MS Clinics. Can J Neurol Sci [Internet]. 2008 May [cited 2013 Feb 28];35(2):127-9. Available from: http://cjns.metapress.com/content/ex21864q62217889/fulltext.pdf
9. Common Drug Review. CDEC final recommendation: fingolimod (Gilenya - Novartis Pharmaceuticals Canada Inc.). Indication: multiple sclerosis [Internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH); 2011 Nov 16. [cited 2013 Jul 18]. Available from: http://www.cadth.ca/media/cdr/complete/cdr_complete_Gilenya_Nov-18-11_e.pdf
10. Freedman MS, Selchen D, Arnold DL, Prat A, Banwell B, Yeung M, et al. Treatment Optimization in MS: Canadian MS Working Group Updated Recommendations. Can J Neurol Sci. 2013 May;40(3):307-23.
11. Canadian Agency for Drugs and Technologies in Health. CADTH therapeutic review. Comparative clinical and cost-effectiveness of drug therapies for relapsing-remitting multiple sclerosis [Internet]. Ottawa: The Agency; 2013 Oct. (CADTH Therapeutic Review vol.1, no. 2b). [cited 2013 Oct 30]. Available from: http://www.cadth.ca/en/products/therapeutic-reviews/relapsing-remit-multiple-sclerosis/reports
12. Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 2006 Mar 2;354(9):899-910.
13. Cadavid D, Wolansky LJ, Skurnick J, Lincoln J, Cheriyan J, Szczepanowski K, et al. Efficacy of treatment of MS with IFN b-1b or glatiramer acetate by monthly brain MRI in the BECOME study. Neurology. 2009 Mar 11;72(23):1976-83.
14. O'Connor P, Filippi M, Arnason B, Comi G, Cook S, Goodin D, et al. 250 microg or 500 microg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study. Lancet Neurol. 2009 Oct;8(10):889-97.

15. Calabrese M, Bernardi V, Atzori M, Mattisi I, Favaretto A, Rinaldi F, et al. Effect of disease-modifying drugs on cortical lesions and atrophy in relapsing-remitting multiple sclerosis. Mult Scler. 2012 Apr;18(4):418-24.

16. The CAMMS223 Trial Investigators, Compston DAS, Selmaj KW, Lake SL, Moran S, Margolin DH, et al. Alemtuzumab vs. interferon b-1a in early multiple sclerosis. N Engl J Med. 2008;359(17):1786-801.

17. 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 Oct 31.

18. Coles AJ, Twyman CL, Arnold DL, Cohen JA, Confavreux C, Fox EJ, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet. 2012 Oct 31.

19. Clanet M, Radue EW, Kappos L, Hartung HP, Hohlfeld R, Sandberg-Wollheim M, et al. A randomized, double-blind, dose-comparison study of weekly interferon b-1a in relapsing MS. Neurology. 2002 Nov 26;59(10):1507-17.

20. Comi G, Filippi M, Wolinsky JS. European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging--measured disease activity and burden in patients with relapsing multiple sclerosis. European/Canadian Glatiramer Acetate Study Group. Ann Neurol. 2001 Mar;49(3):290-7.

21. 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 Sep 20;367(12):1087-97.

22. Gold R, Kappos L, Arnold DL, Bar-Or A, Giovannoni G, Selmaj K, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med. 2012 Sep 20;367(12):1098-107.

23. Etemadifar M, Janghorbani M, Shaygannejad V. Comparison of Betaferon, Avonex, and Rebif in treatment of relapsing-remitting multiple sclerosis. Acta Neurol Scand. 2006 May;113(5):283-7.

24. Panitch H, Goodin DS, Francis G, Chang P, Coyle PK, O'Connor P, et al. Randomized, comparative study of interferon b-1a treatment regimens in MS: The EVIDENCE Trial. Neurology. 2002 Nov 26;59(10):1496-506.

25. Kappos L, Radue EW, O'Connor P, Polman C, Hohlfeld R, Calabresi P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med. 2010 Feb 4;362(5):387-401.

26. The IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. Neurology. 1993 Apr;43(4):655-61.

27. De Stefano N, Curtin F, Stubinski B, Blevins G, Drulovic J, Issard D, et al. Rapid benefits of a new formulation of subcutaneous interferon beta-1a in relapsing-remitting multiple sclerosis. Mult Scler. 2010 Jul;16(7):888-92.

28. Durelli L, Verdun E, Barbero P, Bergui M, Versino E, Ghezzi A, et al. Every-other-day interferon beta-1b versus once-weekly interferon beta-1a for multiple sclerosis: results of a 2-year prospective randomised multicentre study (INCOMIN). Lancet. 2002 Apr 27;359(9316):1453-60.

29. Johnson KP, Brooks BR, Cohen JA, Ford CC, Goldstein J, Lisak RP, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. Neurology. 1995 Jul;45(7):1268-76.

30. Jacobs LD, Cookfair DL, Rudick RA, Herndon RM, Richert JR, Salazar AM, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. Ann Neurol. 1996;39(3):285-94.

31. O'Connor PW, Li D, Freedman MS, Bar-Or A, Rice GP, Confavreux C, et al. A Phase II study of the safety and efficacy of teriflunomide in multiple sclerosis with relapses. Neurology. 2006 Mar 28;66(6):894-900.
32. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. Lancet. 1998 Nov 7;352(9139):1498-504.
33. Mikol DD, Barkhof F, Chang P, Coyle PK, Jeffery DR, Schwid SR, et al. Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the REbif vs Glatiramer Acetate in Relapsing MS Disease [REGARD] study): a multicentre, randomised, parallel, open-label trial. Lancet Neurol. 2008 Oct;7(10):903-14.
34. Saida T, Kikuchi S, Itoyama Y, Hao Q, Kurosawa T, Nagato K, et al. A randomized, controlled trial of fingolimod (FTY720) in Japanese patients with multiple sclerosis. Mult Scler. 2012;18(9):1269-77.
35. O'Connor P, Wolinsky JS, Confavreux C, Comi G, Kappos L, Olsson TP, et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. N Engl J Med. 2011 Oct 6;365(14):1293-303.
36. 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 Feb 4;362(5):402-15.
37. Kappos L, Li D, Calabresi PA, O'Connor P, Bar-Or A, Barkhof F, et al. Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial. Lancet. 2011 Nov 19;378(9805):1779-87.
38. Lublin FD, Cofield SS, Cutter GR, Conwit R, Narayana PA, Nelson F, et al. Randomized study combining interferon & glatiramer acetate in multiple sclerosis. Ann Neurol. 2013 Feb 19.
39. Freedman MS, Wolinsky JS, Wamil B, Confavreux C, Comi G, Kappos L, et al. Teriflunomide added to interferon-b in relapsing multiple sclerosis: a randomized phase II trial. Neurology. 2012 Jun 5;78(23):1877-85.
40. Goodman AD, Rossman H, Bar-Or A, Miller A, Miller DH, Schmierer K, et al. GLANCE: results of a phase 2, randomized, double-blind, placebo-controlled study. Neurology [Internet]. 2009 Mar 3 [cited 2012 Nov 16];72(9):806-12. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2821836/pdf/6342.pdf
41. Rudick RA, Stuart WH, Calabresi PA, Confavreux C, Galetta SL, Radue E-W, et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. N Engl J Med. 2006 Mar 2;354(9):911-23.
42. Weinshenker BG, Bass B, Rice GP, Noseworthy J, Carriere W, Baskerville J, et al. The natural history of multiple sclerosis: a geographically based study. I. Clinical course and disability. Brain. 1989 Feb;112 (Pt 1):133-46.
43. Tremlett H, Zhu F, Petkau J, Oger J, Zhao Y, BC MS Clinic Neurologists. Natural, innate improvements in multiple sclerosis disability. Mult Scler. 2012 Oct;18(10):1412-21.
44. Canadian Agency for Drugs and Technologies in Health. Therapeutic review framework [Internet]. Ottawa: The Agency; 2012 Jan. [cited 2013 Oct 29]. Available from: http://www.cadth.ca/media/pdf/TR_Framework.pdf