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Comparative Clinical and Cost-Effectiveness of Drug Therapies for Relapsing-Remitting Multiple Sclerosis — Project Protocol

Supporting Informed Decisions

This report is prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). This report contains a comprehensive review of existing public literature, studies, materials, and other information and documentation (collectively the "source documentation") available to CADTH at the time it was prepared, and it was guided by expert input and advice throughout its preparation.

The information in this report is intended to help health care decision-makers, patients, health care professionals, health systems leaders, and policy-makers make well informed decisions and thereby improve the quality of health care services. The information in this report should not be used as a substitute for the application of clinical judgment in respect to the care of a particular patient or other professional judgment in any decision-making process, nor is it intended to replace professional medical advice. While CADTH has taken care in the preparation of this report to ensure that its contents are accurate, complete, and up-to-date, CADTH does not make any guarantee to that effect. CADTH is not responsible for any errors or omissions or injury, loss, or damage arising from or as a result of the use (or misuse) of any information contained in or implied by the information in this report. CADTH takes sole responsibility for the final form and content of this report. The statements, conclusions, and views expressed herein do not necessarily represent the view of Health Canada or any provincial or territorial government.

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1 INTRODUCTION AND RATIONALE

Multiple sclerosis (MS) is a chronic inflammatory disease associated with central nervous system demyelination, with an age of onset commonly between 20 to 40 years, and which predominantly affects women.[1] In Canada, the prevalence of MS has been reported to be 240 per 100,000 persons.[2]

Approximately 85% of patients will follow a relapsing-remitting course of disease after onset; relapsing-remitting MS (RRMS) is characterized by periodic acute attacks followed by full or partial recovery.[3] Other patients follow a primary progressive course of disease, lacking relapses, but with progressive worsening of neurologic deficits over time. The benefit of disease-modifying agents have been primarily demonstrated in patients with RRMS.[4]

In Canada, the first available disease-modifying agents for MS included interferons (interferon beta-1a and interferon beta-1b) and glatiramer acetate approved by Health Canada in the 1990s. Natalizumab was approved by Health Canada in 2006 for the treatment of RRMS; however, there are safety concerns with natalizumab due to its association with progressive multifocal leukoencephalopathy (PML), a rare demyelinating neurological disorder caused by the reactivation of the John Cunningham virus.[5] More recently (in 2011), Health Canada approved fingolimod, the first oral agent for treatment of RRMS. However, the price of fingolimod is considerably higher than either the interferons or glatiramer acetate. The Health Canada- approved monograph for natalizumab (Tysabri) indicates that the drug "is generally recommended in MS patients who have had an inadequate response to, or are unable to tolerate, other therapies for multiple sclerosis." The Health Canada-approved monograph for fingolimod (Gilenya) indicates that the drug "is generally recommended in MS patients who have had an inadequate response to, or are unable to tolerate, one or more therapies for multiple sclerosis."

Currently, a number of new disease-modifying agents (both oral and injectable) are in development for the treatment of MS. The emergence of novel oral and injectable drug therapies will necessitate consideration of their place in therapy based on both clinical and cost-effectiveness. Further considerations include the potential for combination therapy in the future.

The Canadian Agency for Drugs and Technologies in Health (CADTH) will undertake a systematic review to compare the efficacy and safety of disease-modifying agents for patients with RRMS, and will examine their cost-effectiveness. The review will include disease-modifying agents that are currently available in Canada (interferon beta-1a and -1b, natalizumab, glatiramer acetate, fingolimod), and a number of agents that are newly emerging and not yet approved in Canada (teriflunomide, dimethyl fumarate, and alemtuzumab).

The systematic review and cost-effectiveness evidence will be reviewed by the Canadian Drug Expert Committee (CDEC) for the purpose of making recommendations. Recommendations and advice provided by CDEC are provided to CADTH to inform participating jurisdictions.

2 DELIVERABLES

The following deliverables are planned:

- Science Report, including both a systematic review of comparative efficacy and safety of currently available and emerging disease-modifying agents for RRMS, and an examination of their cost-effectiveness based on a cost-utility analysis.
- CDEC Recommendations and/or advice based on the Science Report and stakeholder feedback; recommendations and/or advice will be limited to disease-modifying agents for RRMS that are approved by Health Canada.

3 RESEARCH QUESTIONS

1. What is the comparative efficacy and safety between individual disease-modifying agents in RRMS?
2. What is the comparative cost-effectiveness between individual disease-modifying agents in RRMS?
3. What is the comparative efficacy and safety of combination therapy (two or more disease-modifying agents compared with individual agents or other combinations) in RRMS?
4. What is the comparative cost-effectiveness of combination therapy (two or more disease-modifying agents compared with individual agents or other combinations) in RRMS?

4 METHODS

4.1 Literature Search Strategy

The literature search will be performed by an information specialist using a peer-reviewed search strategy. Published literature will be identified by searching the following bibliographic databases: MEDLINE (1946) with In-Process records & daily updates via Ovid; Embase (1980) via Ovid; Cochrane Central Register of Controlled Trials through Ovid; and PubMed. The search strategy will consist of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts are Relapse-Remitting Multiple Sclerosis and interferon beta-1a and -1b, natalizumab, glatiramer acetate, fingolimod, teriflunomide, dimethyl fumarate, and alemtuzumab.

Methodological filters will be applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, and randomized controlled trials. In addition, an economic filter will be applied to identify economic studies. Where possible, retrieval will be limited to the human population. Retrieval will not be limited by date but will be limited to English language results. Conference abstracts will be excluded from the search results. Regular alerts will be established to update the search until recommendations by CDEC, based on this review, are finalized. Regular search updates will be performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) will be identified by searching relevant sections of the *Grey Matters: A Practical Search Tool for Evidence-Based Medicine* checklist (http://www.cadth.ca/resources/grey-matters), which includes the websites of regulatory agencies, health technology assessment agencies, clinical trial registries, and

professional associations. Google and other Internet search engines will also be used to search for additional web-based materials. These searches will be supplemented by reviewing the bibliographies of key papers and through contacting appropriate experts.

4.2 Selection Criteria

4.2.1 Clinical

Two reviewers will independently screen titles and abstracts relevant to the clinical research questions regarding available and emerging drug therapies for treatment of patients with RRMS. Full texts of potentially relevant articles will be retrieved and independently assessed for possible inclusion based on the predetermined selection criteria (Table 1). The two reviewers will then compare their chosen included and excluded studies; disagreements will be discussed until consensus is reached. The study selection process will be presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart.

Table 1: Inclusion and Exclusion Criteria for Primary Studies

Inclusion Criteria	
Study Design	Published RCTs
Patient Population	Patients diagnosed with RRMS*
Interventions	• Disease-modifying agents ▪ Currently available (formulations and doses approved and available in Canada only will be included) o fingolimod — oral o interferon-β-1a — injectable o interferon-β-1b — injectable o natalizumab — injectable o glatiramer acetate — injectable ▪ Emerging o teriflunomide — oral o dimethyl fumarate — oral o alemtuzumab — injectable • Placebo
Outcomes	• Relapse • Disability • MRI changes • Quality of life • Deaths • Serious adverse events • Withdrawals due to adverse events • Adverse events
Exclusion Criteria	
Studies will be excluded if they: are in languages other than English, do not meet the above-mentioned selection criteria, provide results of a qualitative or a non-comparative study, are follow-up or extension studies, or present preliminary results in abstract form. Duplicate publications, narrative reviews, and editorials will also be excluded.	

interferon-β = interferon beta; MRI = magnetic resonance imaging; MS = multiple sclerosis; RCT = randomized controlled trial; RRMS = relapsing- remitting multiple sclerosis.

*RCTs having a mixed population (i.e., persons with primary progressive or secondary progressive MS, in addition to persons with RRMS) will be included for completeness if the RRMS population is greater than 50% of the total population.

4.2.2 Economic

One reviewer will screen titles and abstracts relevant to the economic research questions on the use of available and emerging drug therapies for the treatment of patients with RRMS that might inform data inputs in the health economic model. Full papers will be obtained for those that appeared to be potentially relevant.

4.2.3 Data Extraction and Critical Appraisal of Clinical Studies

One reviewer will perform data extraction for each article using a pre-drafted data extraction form covering the following items:

- Baseline characteristics of trial participants
- Interventions evaluated, including dose, duration, and relevant concomitant medication
- Efficacy and safety results for specified outcomes
- Type of analysis (intention-to-treat [ITT] or per-protocol).

All extracted data will be checked for accuracy by a second reviewer. Any disagreements will be resolved through discussion until consensus is reached. Quality assessment of randomized controlled trials (RCTs) will be performed independently by two reviewers using a standardized table based on major items from the Scottish Intercollegiate Guidelines 50 (SIGN 50) instrument for internal validity. Further critical appraisal will be performed based on input from clinical experts.

4.3 Data Analysis and Synthesis

4.3.1 Clinical

Included studies will be classified based on trial populations and relevant comparisons. Prior to quantitative pooling of study-specific outcomes, a thorough qualitative analysis will be undertaken to assess clinical heterogeneity. If substantial heterogeneity exists in certain comparisons or subset of studies, then only narrative reviews of findings will be reported. Where appropriate, meta-analysis of direct comparisons and indirect/mixed treatment comparisons employing a network meta-analysis may be performed. Subgroup analyses will be conducted where appropriate; these include age (≤ 40 years or > 40 years), baseline Extended Disability Status Scale (EDSS) score (0 to 3, or > 3), gadolinium-enhancing lesions at screening (0, ≥ 1), gender (female or male), and number of relapses in the previous year before screening (1, 2, or ≥ 3).

4.3.2 Economic

An economic model will be constructed and the primary analysis will be in the form of a cost-utility analysis. The primary outcome will be the number of quality- adjusted life-years (QALY), with treatments compared in terms of the incremental cost per QALY (incremental cost utility ratio [ICUR]). The parameter uncertainty will be assessed through both deterministic and probabilistic sensitivity analysis. In addition, value of information analysis will be conducted for the expected value of perfect information (EVPI).

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