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Commentary

Health Canada Drug Approval Process: A Barrier to Personalized Care in Multiple Sclerosis

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Introduction

Multiple sclerosis is a chronic neurological disorder characterized by inflammation, demyelination and axonal loss in the central nervous system (CNS). It is most commonly diagnosed in people aged 20–40 years and is associated with progressive neurodegeneration and disability during the lifelong course of the disease. Accumulating science in recent years suggests that MS is a disease continuum and that current subtypes of MS are insufficient to reflect underlying disease biology[1].

The first disease-modifying therapy (DMT) for MS was approved by Health Canada in 1995, and 18 DMTs have now received marketing authorization. All therapies target varying aspects of the dysregulated immune response in MS with significant differences in the relative efficacy of individual DMTs. Therapies considered to be of higher efficacy include oral agents that sequester T cells in secondary lymphoid organs (fingolimod, ozanimod, ponesimod, siponimod) or deplete T and B cells (cladribine); and monoclonal antibodies administered by infusion or injection that target B cells (ocrelizumab, ofatumumab) and T and B cells (alemtuzumab) or block lymphocyte entry into the CNS (natalizumab).

While the number of treatment options would appear to offer clinicians and persons with MS (PwMS) a plethora of choices, Health Canada's approach to approving drugs only for specific subtypes of MS and as first- or second-line therapy has imposed onerous restrictions on how clinicians may prescribe treatments necessary to improve clinical outcomes. Choices are further limited by government-mandated bodies such as the Canadian Agency for Drugs and Technologies in Health (CADTH) and the Institut national d'excellence en santé et services sociaux (INESSS), which evaluate and recommend how these medications should be used, as well as by provincial and private payors, who may further constrain prescribing based on the government's recommendations and seemingly arbitrary corporate policies.

The net result of this prescribing process might be termed Procrustean, named for the figure in Greek mythology who stretched or amputated his victims to fit the length of a bed. MS clinicians must force-fit PwMS into predetermined categories (e.g., MS phenotype, disease activity, age) to access DMTs and obtain reimbursement as the cost of most DMTs is prohibitive for most pwMS without reimbursement. The alternative for clinicians is to prescribe a suboptimal therapy until the PwMS worsens sufficiently to meet the criteria for a more effective treatment, which can often result in irreversible neurological disability accumulation, poor quality of life and long-term personal and professional consequences.

This issue, which is one of the greatest challenges encountered in MS clinical practice in Canada, was addressed at a meeting of an MS expert panel, held on September 29, 2023, in Toronto. The following outlines the group's discussions on how Health Canada's outdated process of drug approval infringes on current efforts to personalize and optimize care in pwMS and how such restrictions may contribute to suboptimal clinical outcomes.

Pathophysiology and clinical course of MS

The Lublin-Reingold classification scheme described several subtypes of MS, which were later consolidated into three clinical courses: relapsing-remitting (RRMS), in which acute attacks were

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followed by periods of remission; primary-progressive (PPMS), characterized by gradual disability worsening from the outset; and secondary-progressive (SPMS), in which RRMS transitions to a progressive course[2]. These descriptions, based on clinical observations from a physician survey rather than from rigorous biological evidence, were intended primarily to standardize patient groups for epidemiologic studies and clinical trials.

The classification system subsequently added clinically isolated syndrome (CIS), a form of inflammatory demyelination not meeting the full diagnostic criteria for MS, as well as the phenotype modifiers of disease activity and progression. "Disease activity" referred to inflammatory activity (i.e., relapses and inflammatory lesions detected as new gadolinium-enhancing or new/enlarging lesions observed on T2-weighted sequences on magnetic resonance imaging [MRI]); this was intended as a means of identifying PwMS who were more likely to respond to a DMT, all of which target inflammation via various mechanisms. "Progression" referred to worsening neurological disability during relapse-free periods (now termed progression independent of relapse activity [PIRA]); by definition, progression was only considered in PwMS in progressive phases of the disease (SPMS, PPMS)[3].

These descriptions conformed to a two-stage hypothesis of MS, which posited that an initial inflammatory phase eventually progressed to a secondary neurodegenerative phase of the disease. However, it is now apparent that MS is a single disease entity in which inflammation and neurodegeneration co-occur from the earliest stages; indeed, evidence of neurodegeneration has been identified even before MS onset[4].

Key pathological features during the clinical course of MS are the development of peripheral immune activation, in which activated lymphocytes and monocytes enter the CNS and cause focal white-matter lesions; diffuse inflammation that is compartmentalized within the CNS and characterized by activation of macrophages/microglia and astrocytes; and demyelination and axonal loss resulting from innate and acquired immune activation, redistribution of sodium ion channels, accumulation of calcium ions and mitochondrial failure that damages neurons and impedes remyelination (reviewed in[1]). Patient-specific factors, such as genetics, environmental exposures and age, will influence the clinical expression of the disease. Thus, disability progression is not the result of a single disease mechanism. Rather, it is due to a combination of several mechanisms that act to varying degrees in individual PwMS throughout their clinical course, making current disease subtyping inadequately reflective of clinically relevant biological processes in pwMS.

Health Canada approval of MS treatments

Health Canada approvals of DMTs limit the use to specific disease phenotypes (RRMS, SPMS, PPMS); in some instances, inflammatory disease activity (relapses, MRI lesions) must be present. In addition, some treatments are designated as second-line agents, that is, after ≥1 prior treatment has been shown to produce an inadequate response or has been poorly tolerated.

Drug indications are ostensibly based on clinical trial data, although this evidence-based approach is applied inconsistently. For example, the phase III trials for all of the drugs approved as second-line agents (fingolimod, natalizumab, cladribine) primarily enrolled previously untreated PwMS. The only pivotal trial of second-line use was for alemtuzumab, which is indicated by Health Canada as a third-line agent.

Another example of the inconsistency of drug indications can be observed with the labeling for sphingosine 1-phosphate receptor (S1PR) modulators, a class of drugs that sequesters activated T cells in secondary lymphoid organs that has been found to be beneficial in pwMS. Two of these drugs (ozanimod, ponesimod) are indicated for any RRMS patient; one (fingolimod) is recommended in RRMS after prior treatment failure, and one (siponimod) is limited to active SPMS.

Such a regulatory approach contrasts with that adopted in 2019 by the US Food and Drug Administration (FDA), which permitted the approval of all higher-efficacy DMTs for a wide range of MS indications, specifically, the treatment of all relapsing forms of MS, which includes CIS, RRMS and active SPMS. Although this approach was welcomed by MS neurologists as it greatly simplified prescribing, it was not necessarily evidence-based. Most DMTs have not been studied in CIS and SPMS populations. However, the FDA likely adopted this approach as there is growing recognition of the need to revisit MS disease subtyping. The FDA does not designate DMTs as first- or second-line therapies; the sole exception is alemtuzumab, which is labeled as a third-line agent.

The limitations imposed by Health Canada's emphasis on phenotypes are further complicated by the heterogeneity of provincial and private payors with differing criteria for PwMS to access specific DMTs. An example is ocrelizumab, an anti-CD20 monoclonal antibody that depletes B cells, which is currently approved in Canada for RRMS and PPMS. In Quebec, the Régie de l'assurance maladie du Québec (RAMQ) specifies that it may only be prescribed in PwMS with an Expanded Disability Status Scale (EDSS) score <7.0 (the disability level when at least a wheelchair is required to ambulate short distances). In Ontario, the Exceptional Access Program requires an EDSS score <6.0 (the disability level when at least a unilateral walking aid is required to ambulate short distances). In British Columbia, the PharmCare program does not reimburse ocrelizumab in RRMS, opting to reimburse rituximab, another anti-CD20 agent that is not approved in Canada for the treatment of MS.

Evolution of MS research

Current drug authorizations and reimbursements support a stepwise approach in which a highly effective therapy is generally employed only after one or more treatment failures. This does not take into account how rapidly evolving MS research has led to new treatment strategies. It is now generally accepted that the benchmark of relapse activity is an inadequate indicator of long-term outcome, which has required the recognition of other determining factors. Progression that occurs during relapse-free periods, also known as PIRA, is now viewed as the main driver of accumulating disability, blurring the distinction between relapsing and progressive forms of the disease[5]. Accordingly, the new treatment paradigm is to use higher-efficacy therapy early in the disease course to limit the neurodegeneration that results in progression of disability.

The concept of progression itself is undergoing expansion to supplement the limitations of the EDSS by including additional indicators of disability worsening, such as those obtained with novel MRI techniques, neurocognitive testing and patient-reported outcomes. Numerous imaging, fluid and digital biomarkers now in development also have the potential to refine prognosis and more precisely monitor the therapeutic response of individual PwMS, further enabling clinicians and PwMS to personalize therapy based

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on the individual's risk profile, underlying disease mechanisms and personal preferences.

Barriers to optimal treatment selection

In conforming to outdated models of MS pathophysiology, health regulators and provincial payors create a Procrustean prescribing environment: MS specialist neurologists are not free to select a drug that best meets the requirements of a given PwMS, but rather the PwMS must conform to the drug's labeling and reimbursement requirements. Common examples are when a newly diagnosed PwMS plans to become pregnant but cannot start with an intermittent therapy (e.g., cladribine, ocrelizumab, ofatumumab) that would allow for safe family planning without fetal exposure to a DMT or a PwMS with a rapidly evolving disease cannot receive a highly effective DMT (e.g., natalizumab); in both instances, these drugs are not considered first-line agents. PwMS with a worsening disability may not meet reimbursement criteria due to disability level (e.g., EDSS ≥6.0) or age (e.g., ≥55 years) despite the variability of an individual's disease and drug response. With siponimod, one of the few DMTs to demonstrate efficacy in SPMS, active disease must be demonstrated to access this DMT after the transition to SPMS – even if a prior treatment has effectively suppressed disease activity. Moreover, if treatment is ineffective, the PwMS, now recorded as having the SPMS phenotype in medical records so as to access siponimod, may no longer be eligible for another higher-efficacy treatment since the alternative options are indicated only for RRMS.

The path to personalized care in MS

The path to personalized care in MS is evolving from a focus on outdated disease phenotypes to a multifactorial approach that incorporates an assessment of the individual PwMS's pathobiology at different stages of their disease, genetic and environmental risks, physical and cognitive disability, comorbidities, life stage (including family planning) and patient-reported measures, such as symptomatology, quality of life and treatment satisfaction. Such assessments will become further refined with the ongoing advances in neuroimaging (MRI, positron emission tomography, optical coherence tomography), fluid biomarkers (including neurofilament-light chain, a marker of neuronal damage and glial fibrillary acidic protein, a marker of astrocyte activation, among others) and digital biomarkers (e.g., for gait analysis, eye tracking, wearable devices).

As these technologies become the new standard of care, regulators may consider adding additional criteria utilizing these new biomarkers before a treatment will be reimbursed. However, this would only further complicate access to necessary DMTs and lose sight of the overall goal: to employ a treatment that will optimally control an individual PwMS's disease to improve long-term outcomes. Achieving this goal would necessitate clinicians having a freer hand in prescribing so as to develop a personalized treatment regimen that may often include new/emerging DMTs according to their best clinical judgment. In MS, clinical and research data are constantly expanding and evolving, and arguably only a neurologist with expertise in MS has the knowledge and experience to interpret the many sources of clinical, imaging and laboratory data to make an informed decision about an individual PwMS. This same complexity of decision-making would likely require that DMT prescribing be limited to MS neurologists at MS clinics and community neurologists with expertise in MS, a situation that already exists in several Canadian provinces. MS clinics would need to expand community outreach programs (which might include virtual care options) and increase fellowship training and preceptorship programs to ensure equitable access to DMTs in rural and other underserved communities.

Cost considerations

Higher-efficacy DMTs are generally more costly than first-line oral and injectable therapies. However, enabling neurologists with expertise in MS and PwMS to have greater access to these medications, notably as first-choice agents, would be expected to reduce the overall cost of MS care over the disease course, which spans decades. Many PwMS on a higher-efficacy DMT remain relapse-free, which could translate to considerable savings on this measure alone. The Canadian Prospective Cohort Study to Understand Progression in Multiple Sclerosis (CanProCo) estimated that the annual excess cost of one relapse requiring hospitalization was CDN$10,543 per patient[6]. Similarly, a US cost-effectiveness analysis comparing ocrelizumab with a modest-efficacy injectable beta-interferon found that improved disease control was associated with substantial savings relating to relapse prevention, drug monitoring and adverse event-related costs[7].

There would be additional economic benefits associated with the judicious use of higher-efficacy DMTs according to the MS specialist's clinical judgment. Head-to-head trials have demonstrated that high-efficacy DMTs outperform modest-efficacy agents in reducing short- and long-term disability and slowing the rate of brain volume loss[8–10]. Improved care would lower costs associated with worsening disability, such as hospitalizations, physician visits and symptomatic medications, and reduce the economic cost of MS on a societal level related to employment disability. A recent Canadian study demonstrated that even in the earliest stages of MS, there is a substantial loss of workplace productivity, and allowing pwMS to have access to DMTs that minimize disability accrual over time has the potential to substantially reduce MS-related disability that may eventually result in the inability to remain employed[11]. While payors' drug budgets tend to focus narrowly on drug costs rather than overall savings to the health care system ("siloing"), it is noteworthy that drug acquisition costs were lower for ocrelizumab versus beta-interferon in the above-cited US study, although it should be noted that drug pricing differs in the USA.

MS care is a rapidly changing therapeutic environment requiring complex decision-making to optimize treatment based on the needs of the individual PwMS as they evolve during the clinical course. The goal of personalized medicine cannot be achieved if neurologists with expertise in MS do not have the freedom to act in the best interest of PwMS due to the inflexible restrictions imposed by regulators and payors. We believe it is time for regulators – starting with Health Canada – and payors to consider these points for current and future DMT approvals and indications so that clinical outcomes can be maximized for PwMS in Canada and beyond.

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