Treatments for Multiple Sclerosis: Effectiveness and Value

Revised Background and Scope

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Background

Multiple sclerosis (MS) is a chronic, autoimmune disorder of the central nervous system (CNS) characterized by an inflammatory cascade of demyelination and axonal loss, which results in neurologic damage. The exact cause of MS is unknown, but genetic, environmental, and lifestyle factors may contribute to the development of the disease.[1] MS affects more than 900,000 people in the United States (US).[2] Women are affected almost 3 times more than men, and there are racial/ethnic differences in MS prevalence.[3] In the US, African Americans, particularly African American women, are at higher risk of developing MS compared with whites.[3,4] The total economic burden of MS is estimated to be $85 billion, with direct medical costs accounting for more than $63 billion.[5]

Symptoms of MS most commonly appear in the third decade of life, with symptoms correlating with areas of demyelination in the CNS. For example, demyelination of the optic nerve results in vision changes and eye pain (optic neuritis) and lesions in the spinal cord can lead to weakness, impaired sensation, and ataxia (partial myelitis).[1] Fatigue, pain, spasticity in muscles, balance problems, bowel and bladder dysfunction, insomnia, depression, and impaired memory and concentration are also possible symptoms.[6] Diagnosis of MS is based on the 2017 Revised McDonald Criteria, which involves a combination of clinical findings, imaging, and laboratory data, and requires the demonstration of MS disease characteristics in space (i.e., presence of lesions in distinct locations in the CNS) and time (development of new lesions over time).[7]

The most common form of MS is relapsing-remitting MS (RRMS), which affects 85% of persons and is characterized by periodic relapses with complete or near recovery. Disability accumulates over time with the median time for the need of a walking aid being approximately 20 years in untreated persons with MS (PwMS).[8] However, Black Americans with MS appear to have a more aggressive disease course, both with more severe initial symptoms and with faster disease progression.[9] Additionally, approximately 20% of persons with RRMS may develop progressive neurological decline and transition to secondary progressive MS (SPMS) around 15-20 years after diagnosis.[10] Life expectancy in PwMS is approximately 7 years shorter than average.[11]

Treatment of MS is focused on preventing relapses, disease progression, and worsening of disability. Comprehensive treatment of MS includes both supportive treatment, including symptom control, psychological support, management of comorbidities, lifestyle interventions, and rehabilitation, and disease-modifying therapies (DMTs) that reduce neuroinflammation. There are multiple classes of DMTs with a variety of delivery mechanisms, efficacy, and risk of adverse events, including injections (interferons, glatiramer), oral medications (sphingosine 1-phosphate [S1P] receptor modulators, fumarates, teriflunomide), and intravenous or subcutaneous monoclonal antibodies. Choice of initial therapy varies, with some clinicians and PwMS opting to begin treatment with medications that have moderate efficacy but a better safety profile such as the injectable or oral drugs and escalating as needed; other clinicians and PwMS opt to treat with monoclonal antibodies at diagnosis, which are more effective at suppressing disease activity but carry a higher risk of serious adverse events.[12] Treatment is generally lifelong, though the discontinuation of DMTs in older, stable PwMS with non-active disease and low risk of progression has been proposed[13] and the safety of such strategies is the subject of ongoing clinical trials (e.g., DISCOMS (NCT03073603), DOT-MS (NCT 04260711), STOP-I-SET (NCT03653273).

In addition to DMTs already approved by the Food and Drug Administration (FDA), there are additional agents in development, including ublituximab, a monoclonal antibody which is currently undergoing FDA review, and Bruton's tyrosine kinase inhibitors. Additionally, for some persons, hematopoietic stem cell transplantation (HSCT) has shown promise as a treatment for MS, though the ideal treatment population and optimal timing for HSCT have not yet been established.[14]

Stakeholder Input

This revised scoping document was developed with input from diverse stakeholders, including patient organizations, clinicians, researchers, and manufacturers of the agents of focus in this review. This document incorporates feedback gathered during calls with stakeholders and open input submissions from the public; we have also incorporated patient perspectives that were discussed during a prior 2017 ICER review of MS treatments. Based on this feedback, we have made the following changes to the scope: 1) Added language to reflect that PwMS may have symptoms and disability that are not well-captured by standard outcome scales such as the EDSS; 2) Added language to reflect that the choice of DMT is affected by many patient-important factors and that shared decision-making is important; 3) Acknowledged that there may be limitations in including DMTs that do not currently have a FDA-approved indication for MS in our assessment; and 4) Added more specific information about the planned interventions and comparator for the comparative value analyses. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of DMTs for MS.

Because the onset of MS is early in life, the disease has impact not only on the physical and emotional health of PwMS, but can also affect family planning, work and educational productivity, and social and leisure activities. Economic hardship, including lost wages from missed work, the need to transition to part-time work, the inability to continue working, and the high cost of medications and medical equipment, is a major burden for PwMS.[15] There can also be impact on caregivers, particularly with progression of patient disability, and caregivers can experience high levels of distress and decreased quality of life.[16]

The primary goal for PwMS is to remain independent, including the ability to continue working and perform normal activities. Although ambulation is an important marker of disability, debilitating fatigue, comorbid mood disorders, urinary incontinence, and cognitive changes also have a great impact on one's daily life activities, particularly on the ability to work. Thus, early diagnosis and comprehensive treatment are critical to making the impact of MS on a person's life as minimal as possible. The most important issues for PwMS when considering treatment are how well a DMT delays onset of disability and prevents relapses or new MRI lesions, whether a treatment is oral or otherwise, and the risks for adverse events, particularly for serious adverse events that might accompany the higher efficacy therapies.[15] For PwMS of childbearing age, the impact of therapy on family planning is also an important consideration. However, it is important to note that DMTs do not necessarily have an impact on all patient-important outcomes (e.g., a DMT might have an impact on relapses but not necessarily on bladder dysfunction) and thus additional treatments besides DMTs may be necessary for symptom control. Additionally, the high cost of DMTs – even generic formulations – can lead to large out-of-pocket costs, and burden of prior authorization can also affect patient choice for therapy. Other factors associated with treatment – e.g., site of treatment, time needed off work and travel distance for infusions, response to COVID vaccines – were also mentioned as important factors in the decision-making process. With multiple choices for therapy with differing efficacy, tolerability, mode of delivery, and costs, shared decision-making to meet the patient's goals is an important part of choosing the appropriate DMT for each patient. Finally, patient groups identified that there is substantial practice variation in treatment of MS, particularly based on whether the physician is a MS specialist or general neurologist.

Clinical experts agreed that the main goal of treatment for MS is to prevent or delay progression of disability and noted that the choice of starting with moderate or high efficacy DMT is dependent on patient characteristics as well as patient and clinician preferences. Clinical trials such as TREAT-MS (NCT03500328) and DELIVER-MS (NCT03535298) are currently in progress to help ascertain what the best treatment strategies for MS treatment are. Additionally, clinical experts mentioned that there is both under- and over-treatment of the disease. For example, some patients would benefit from being treated with more aggressive therapies (i.e., under treatment); on other hand, older patients with non-MS-related life-limiting conditions may continue to be treated despite not having active disease (i.e., over treatment). Furthermore, clinicians advised that the Expanded Disability Status Scale (EDSS), the current standard for measuring disability in clinical trials, may not be

optimal for measuring all aspects of disability and quality of life for PwMS, particularly cognitive function.

Manufacturers noted some challenges in interpreting clinical trials, including the changing criteria for diagnosis and the changing standard of care over time, as well as the difficulty in identifying persons who have transitioned from RRMS to SPMS. Additionally, manufacturers discussed the limitations of trial outcomes such as the EDSS in characterizing the impact of treatments for MS. Finally, manufacturers cautioned against the inclusion of DMTs that do not have an FDA-approved indication for MS, as evidence of efficacy for such agents may be limited.

Report Aim

This project will evaluate the health and economic outcomes of oral agents (fumarates, S1P receptor modulators, teriflunomide) and monoclonal antibody treatments (intravenous and subcutaneous) for relapsing forms of MS. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from PwMS and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see ICER's grey literature policy).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the revised scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Populations

The population of focus for the review is adults with relapsing forms of MS, including clinically isolated syndrome (CIS), relapsing-remitting disease (RRMS), and active secondary progressive disease (SPMS).

Data permitting, we intend to examine the following subgroups including, but not limited to:

1. Race/ethnicity
2. Age
3. Pregnant or planning a pregnancy
4. CIS subgroup
5. RRMS subgroup
6. Active SPMS subgroup
7. No previous use of disease-modifying therapy/treatment naïve

Interventions and Comparators

We intend to compare agents within the monoclonal antibodies class to one another as well as against leading oral therapies using head-to-head and placebo-controlled trials. We also plan to compare all the agents to one another though network meta-analysis. We note that rituximab does not include an FDA label for persons with relapsing forms of multiple sclerosis. However, given past and ongoing randomized MS trials that include rituximab,[17,18] observational data that suggest effectiveness of rituximab,[19,20] and hearing from clinical experts, we decided to keep rituximab within the scope of our assessment. To our knowledge, biosimilar forms of Rituxan® have not been studied in populations of patients with MS. Therefore, biosimilar forms of Rituxan® are not currently being considered for the comparative clinical effectiveness assessment. Additionally, agents which are generally not used as first-line treatment due to safety concerns (e.g., alemtuzumab, cladribine) are excluded from this assessment.

The full list of interventions is as follows:

- Monoclonal antibodies
    - natalizumab (Tysabri®, Biogen)
    - ofatumumab (Kesimpta®, Novartis)
    - ocrelizumab (Ocrevus®, Genentech)
    - rituximab (Rituxan®, Genentech)
    - ublituximab (TG Therapeutics)
- Oral therapies
    - Fumarates:
        - dimethyl fumarate (Tecfidera®, Biogen, and generics)

        - diroximel fumarate (Vumerity®, Biogen)
        - monomethyl fumarate (Bafiertam®, Banner Life Sciences)
    - S1P receptor modulators:
        - fingolimod (Gilenya®, Novartis)
        - ozanimod (Zeposia®, Bristol Myers Squibb)
        - ponesimod (Ponvory®, Janssen)
        - siponimod (Mayzent®, Novartis)
    - teriflunomide (Aubagio®, Sanofi)

Outcomes

The outcomes of interest are described in the list below. We recognize not all outcomes will be measured consistently across disease-modifying therapy clinical trials.

- Patient-important outcomes
    - Disability improvement or progression as measured by
        - Expanded Disability Status Scale (EDSS)
        - Multiple Sclerosis Functional Composite measure (MSFC)
    - Relapse
    - Cognitive function
    - Fatigue
    - Depression
    - Manual dexterity
    - Visual acuity
    - Health-related quality of life outcomes
    - Need for caretaker/health aide
    - Treatment adherence
    - Mobility
    - Ability to maintain employment
    - Adverse events including
        - Serious adverse events (SAEs)
        - Adverse events (AEs) leading to discontinuation of therapy
        - AEs unique to specific drugs
- Other Outcomes
    - Magnetic resonance imaging (MRI) outcomes (T2, T1, brain volume changes)
    - No evidence of disease activity (NEDA 3 and/or 4)
    - Caregiver impact
        - Caregiver quality of life
        - Caregiver health
        - Caregiver productivity

Timing

Evidence on intervention effectiveness will be derived from studies of at least one year's duration and evidence on harms from studies of at least three month's duration.

Settings

All relevant settings will be considered, with a focus on outpatient settings in the United States.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements (i.e., not specific to a given disease) are listed in the table below.

Table 1.1. Categories of Contextual Considerations and Potential Other Benefits or Disadvantages

Contextual Consideration*
Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability
Magnitude of the lifetime impact on individual patients of the condition being treated
Other (as relevant)

*Contextual considerations refer to social or ethical priorities that shape to some extent how the value of any effective treatments for a particular condition will be judged.

Potential Other Benefit or Disadvantage*
Patients' ability to achieve major life goals related to education, work, or family life
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life
Patients' ability to manage and sustain treatment given the complexity of regimen
Society's goal of reducing health inequities
Other (as relevant)

*Potential other benefits or disadvantages are meant to reflect the broader effects of a specific treatment on patients, caregivers, and society.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop an economic model to assess the lifetime cost effectiveness of treatment initiation of each monoclonal antibody as compared to at least one market leading oral DMT. An emphasis of the comparative value analysis will be on ublituximab, a monoclonal antibody which is currently undergoing FDA review. The other interventions within the same category as ublituximab, the monoclonal antibodies, will also be considered as interventions within the cost-effectiveness analysis to provide supporting context in addition to the comparative clinical assessment. Dimethyl fumarate, assuming the lowest cost generic pricing, is a leading candidate for the base-case comparator following conversations with stakeholders suggesting it is a market leader, effective, and currently the lowest cost oral DMT. Each monoclonal antibody will also be compared against rituximab in a separate scenario analysis because rituximab is within the same treatment category as the interventions of interest and is known to be the lowest treatment cost option.

The model structure will be based in part on a literature review of prior published models of relapsing forms of MS, including models developed for prior ICER reviews related to MS.[15,21-25] The base-case analysis will take a health care sector perspective (i.e., focus on direct medical care costs only). Data permitting, productivity impacts and other indirect costs will be considered in a separate analysis. This modified societal perspective analysis will be considered as a co-base case when the societal costs of care are large relative to direct health care costs, and the impact of treatment on these costs is substantial. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than $200,000 per quality-adjusted life year (QALY), and/or when the result crosses the threshold of $100,000-$150,000 per QALY gained.

The target population will consist of adults ages 18 years and older in the US with relapsing forms of MS. The model will consist of health states defined by EDSS and death. A cohort of patients will transition between these health states during predetermined cycles of one year over a lifetime time horizon, modeling patients from treatment initiation until death. If a patient discontinues the initial therapy, they will transition to a subsequent DMT treatment basket with an annual cost representative of the average cost of a market basket of DMTs and treatment effectiveness equivalent to the least effective of the therapies evaluated. Key model inputs will include clinical probabilities, quality of life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between interventions. Treatment effectiveness, measured by annualized relapse rates (ARR) and disability progression, will be estimated using planned network meta-analysis.

Health outcomes will be dependent on time spent in each health state (defined by EDSS category), clinical events, and AEs. The health outcome of each intervention will be evaluated in terms of the

life-years (LY), QALYs, equal value of life years (evLY), and years able to walk without an aid. Quality of life weights will be applied to each health state, including quality of life decrements for serious adverse events. The model will include direct medical costs, including but not limited to costs related to drug administration, drug monitoring, condition-related care, and serious adverse events. In addition, productivity changes and other indirect costs will be included in a separate analysis if available data allow. All future costs and consequences will be discounted at 3% per year. Results will be expressed in terms of the marginal cost per QALY gained, cost per evLY gained, cost per LY gained, and cost per additional year able to walk without an aid.

In separate analyses, we will explore the potential health care system budgetary impact of ublituximab, a monoclonal antibody which is currently undergoing FDA review, over a five-year time horizon, utilizing published or otherwise publicly available information on the potential population eligible for ublituximab and results from the economic model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact and will allow assessment of any need for managing the cost of such interventions. More information on ICER's methods for estimating potential budget impact can be found here.

Identification of Low-Value Services

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see ICER's Value Assessment Framework). These services are ones that would not be directly affected by treatments for MS (e.g., cost of nursing care or physical therapy), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of MS beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

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