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Convergence yet Continued Complexity: A Systematic Review and Critique of Health Economic Models of Relapsing-Remitting Multiple Sclerosis in the United Kingdom

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ABSTRACT

Objectives: Several disease-modifying therapies have marketing authorizations for the treatment of relapsing-remitting multiple sclerosis (RRMS). Given their appraisal by the National Institute for Health and Care Excellence, the objective was to systematically identify and critically evaluate the structures and assumptions used in health economic models of disease-modifying therapies for RRMS in the United Kingdom. **Methods:** Embase, MEDLINE, The Cochrane Library, and the National Institute for Health and Care Excellence Web site were searched systematically on March 3, 2014, to identify articles relating to health economic models in RRMS with a UK perspective. Data sources, techniques, and assumptions of the included models were extracted, compared, and critically evaluated. **Results:** Of 386 results, 26 full texts were evaluated, leading to the inclusion of 18 articles (relating to 12 models). Early models varied considerably in method and structure, but convergence over time toward a Markov model with states based on disability score, a 1-year cycle length, and a lifetime time horizon was apparent. Recent models also allowed for disability improvement within the natural history of the condition. Considerable variety remains, with increasing numbers of comparators, the need for treatment sequencing, and different assumptions around efficacy waning and treatment withdrawal. **Conclusions:** Despite convergence over time to a similar Markov structure, there are still significant discrepancies between health economic models of RRMS in the United Kingdom. Differing methods, assumptions, and data sources render the comparison of model implementation and results problematic. The commonly used Markov structure leads to problems such as incapability to deal with heterogeneous populations and multiplying complexity with the addition of treatment sequences; these would best be solved by using alternative models such as discrete event simulations.

Keywords: cost-effectiveness, health economics, multiple sclerosis, systematic review.

Introduction

Multiple sclerosis (MS) is a chronic immune-mediated disease characterized by inflammation in the central nervous system [1]. It affects more than 100,000 people in the United Kingdom and is the most common cause of disability in working-age adults [2]. For most of the patients, symptoms such as movement problems and sensory disturbances initially follow a relapsing-remitting pattern (relapsing-remitting multiple sclerosis [RRMS]), but over time disability progresses until the disease enters the secondary-progressive phase (secondary-progressive multiple sclerosis [SPMS]) [3]. MS has a significant impact on patients' health-related quality of life [4]. The economic burden of the disease is also substantial and increases with disease severity and during relapses [5]. A number of immunomodulatory drugs are now available for the treatment of RRMS. Because these reduce the number of relapses, and may reduce disability progression and/or slow down the observed changes on magnetic resonance imaging scans, these are collectively referred to as disease-modifying therapies (DMTs) [6].

A number of DMTs have marketing authorizations in the European Union for the treatment of RRMS, and the National Institute for Health and Care Excellence (NICE) in the United Kingdom has undertaken health technology appraisals of beta interferons and glatiramer acetate (2002), natalizumab (2007), fingolimod (2012), teriflunomide (2014), alemtuzumab (2014), and dimethyl fumarate (2014). NICE prefers that technology appraisals be conducted from the cost perspective of the National Health Service (NHS) and Personal Social Services (PSS), so the economic benefits of DMTs should be balanced against their direct costs. In

Conflict of interest: F. Allen and N. Adlard are employees of Novartis. J. Kusel, M. Maruszczak, and S. Montgomery are employees of Costello Medical Consulting, which was contracted by Novartis to undertake some of the work.

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addition, long-term clinical benefits in terms of health-related quality-of-life improvements over a patient's lifetime need to be taken into account by decision makers when deciding whether each DMT is to be reimbursed. The NICE appraisal process for beta interferons and glatiramer acetate in MS ran from August 1999 to February 2002, leading to controversy because NICE found all the economic models presented unsatisfactory. Appeals against the initial draft guidance were upheld, prompting NICE to commission a satisfactory model to inform its reconsideration of the initial proposed guidance. In the published final guidance, NICE was unable to recommend beta interferons and glatiramer acetate but these were subsequently made available on the NHS under a risk-sharing scheme. Natalizumab, fingolimod, teriflunomide, alemtuzumab, and dimethyl fumarate all received positive recommendations in the RRMS population, or subgroup(s) thereof.

Considerable complexity in modeling is required to adequately capture the natural history of MS, and, as such, models presented to decision makers to this point have been highly variable in their characteristics. Four recent review articles have considered aspects of economic modeling in RRMS. Guo et al. [7] reviewed the methodological challenges of modeling the cost-effectiveness of DMTs in MS, focusing on long-term ($\geq$10 years) cost-effectiveness analyses with homogeneous contexts of analysis, published over the previous decade. They included 12 studies and identified several major issues associated with the included studies, including great variations in model designs and assumptions; repetitive use of an old data source for the natural history of disease progression; infrequent use of comparative efficacy data from head-to-head clinical trials or network meta-analyses; and no consideration of switching to other DMTs after initial treatment discontinuation. Thompson et al. [8] discussed the methodological challenges in modeling the cost-effectiveness of treatments for MS. Their review included 36 published models and analyses and found that the greatest source of uncertainty was the absence of head-to-head randomized controlled trials (RCTs). Major drivers of results included the time horizon modeled and DMT acquisition costs. Hawton et al. [9] conducted a review to identify all published economic evaluations of MS treatments to suggest practical recommendations for future research to aid decision making. They included 37 articles; estimates for utilities, costs, and impact of treatment on the course of MS varied considerably between studies. They identified issues concerning the wide variation in costs and outcomes from different sources, from potentially unrepresentative samples, and the modeling of disease progression from natural history data from over 30 years ago. Yamamoto and Campbell [10] evaluated the quality of recent cost-effectiveness studies. They included 22 articles in their review and found that most studies (68%) achieved the highest quality category. To continue to improve the cost-effectiveness evidence for DMTs, several recommendations were made, including using lifetime horizons; the development of modeling and input standards for comparability; head-to-head RCTs between DMTs and long-term prospective studies; and comprehensive cost-effectiveness studies that compare all appropriate DMTs.

Taking these reviews as a whole, several clear topline themes emerge, especially around the variety in model structure, the problems of comparability of results, the limited data available with a lack of head-to-head RCTs, and the repeated use of a natural history data set from many decades ago. One specific complication that was not extensively considered in these reviews is that in the European Union some DMTs have different licensed indications and are used in specific patient subpopulations; the available RCT data, however, do not always reflect these licensed indications. Since 2013, the launch and economic appraisal of teriflunomide, alemtuzumab, and dimethyl fumarate has resulted in further proliferation of models and data sources. The availability of manufacturers' submissions to NICE provides a rich set of contemporaneous, detailed, model reports in English, all taking a UK perspective. However, none of the reviews discussed above included NICE submissions within their remit or identified any other published reports of the cost-effectiveness of teriflunomide, alemtuzumab, or dimethyl fumarate. Therefore, there is a need to consider how models have further developed in the light of these significant new therapeutic options.

Exploration of how the techniques used in modeling RRMS in the United Kingdom have evolved over time, and critically evaluating these techniques with a focus on methodology, is important to inform the methodological development of future models. This will allow these future models to address issues and meet the challenges facing decision makers appraising DMTs. By restricting the perspective to one health system, problems of comparability are reduced and it becomes clearer which methodological points need to be addressed by the model builder and considered by the decision maker for any new DMT. Furthermore, given the globally influential nature of NICE and the impact of its decisions as one of the leading health technology appraisal bodies, a review focused on UK models will draw out modeling insights of global relevance. Therefore, this review seeks to systematically identify and critically evaluate the model structures and assumptions used to date in health economic models of DMTs for RRMS from a UK perspective. The review also aims to propose practical recommendations for future modeling that address the underlying drawbacks of models to date, with the recommendations being of particular interest to both model developers and decision makers.

Methods

A systematic review was conducted following the Cochrane Handbook for Systematic Reviews of Interventions for methods and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting, where appropriate [11,12]. The protocol for the systematic review was developed by the authors and is described fully in this article. The inclusion/exclusion criteria are listed in Table 1, along with the rationale for how each relates to the objectives stated above.

Information Sources and Search Strategy

Literature searches were carried out using both MeSH/Emtree and free text terms for MS, terms relating to treatment, terms relating to economic models, and terms relating to the United Kingdom. MEDLINE, MEDLINE In-Process, and Embase databases were searched on March 3, 2014, *via* OVID. The Cochrane Library platform was used to search the following databases: Cochrane Database of Systematic Reviews, NHS Economic Evaluation Database, and Health Technology Assessment database. Full details of all search terms and time periods used for each database are provided in Supplemental Material found at http://dx.doi.org/10.1016/j.jval.2015.05.006. The NICE Web site was also searched to identify economic models used in manufacturers' submissions of MS treatments. In addition, reference lists of relevant systematic reviews were checked to identify any further publications of interest.

Initially, a single reviewer screened the title and abstract of each result against predefined eligibility criteria. This was followed by the same reviewer assessing potentially relevant full texts against inclusion and exclusion criteria; decisions on full texts were then checked by a second reviewer. A full list of excluded full-text articles is given in Supplemental Material found at http://dx.doi.org/10.1016/j.jval.2015.05.006.

Changes Made during the NICE Appraisal Process

An inherent part of the NICE appraisal process is that manufacturers' models are critiqued and changes are often requested. For the included NICE submissions, the changes made during the process