Spring 4-12-2023

B-Cell Monoclonal Antibodies for Management of Relapse Remitting Multiple Sclerosis: A Cost Effectiveness Analysis

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by

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B.S., Biology, University of New Mexico, 2018

THESIS

Submitted in Partial Fulfillment of the
Requirements for the Degree of:

Master of Science
Pharmaceutical Sciences

The University of New Mexico
Albuquerque, New Mexico

May 2023

DEDICATION

To my other-half, Telesfor.

For the past decade, the love and support you have provided to me is unmatched.

Words cannot express my gratitude to you.

ACKNOWLEDGMENTS

I would like to begin by acknowledging my thesis advisor and mentor, Dr. Roberts, who has consistently supported my research endeavors since my first year of pharmacy school. Through her role as an instructor in the PharmD and MS courses, and in our research projects together, I have learned so much about Pharmacoeconomics, research design, data collection and analytics. It was also through these projects with Dr. Roberts, that I was able to observe her logical and systematic approach to working through a research question—something that I now attempt to reflect in my own research. Dr. Roberts was always readily available to answer questions and work with me on our projects, and we have spent many hours together both in zoom meetings and in on-campus classes. Her instruction and feedback have helped to shape the quality of my thinking and of my work. Dr. Roberts has always been patient and kind in her teachings, and allowed me the opportunity to progress from a naïve student with minimal research experience to one who has completed this master's thesis. Dr. Roberts has a brilliant mind and I am grateful for the time and effort she has dedicated to my education.

Next, I would like to acknowledge Dr. Borrego who served on the committee of this thesis and also instructed one of the first courses I took during my pharmacy program. It was in that course that I discovered my interest for what is best encapsulated by the Pharmacoeconomics, Epidemiology, Pharmaceutical Policy and Outcomes Research **(**PEPPOR) program at UNM. Dr. Borrego's passion for teaching is unquestionable. His lectures throughout the PharmD/MS program were always captivating and his feedback on assignments were both encouraging and educational. Dr. Borrego, like Dr. Roberts, has supported my research throughout my pharmacy education. He encouraged me to think of aspects in my research projects and assignments that I would have otherwise not considered and was always ready to educate and assist in my learning. I am thankful to Dr. Borrego for his contributions to my learning and support during both my PharmD and MS education.

I would also like to acknowledge Dr. Cunico who served as a committee member for this thesis. Dr. Cunico took time away from her full work schedule to consult and assist myself and the committee with this research. Her insight from a real-world and managed care perspective was invaluable. I am thankful for Dr. Cunico's time and contributions to this project.

Lastly, I would like to acknowledge my family and loved ones. My mother and father fostered a love of education in me and they have been supportive of all that I have done. From artistic to academic endeavors, my parents have always been in my corner. Without the love, attention, and intellectual stimulation they provided to me, none of this would have been possible. My fiancé, Telesfor, has been by my side since we were fourteen. He has stood by me through all the successes and failures of my academic career. Most importantly, he believed in me and was always there to build me up and motivate me to keep pushing forward.

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ABSTRACT

Multiple sclerosis (MS) is a neurodegenerative disease in which the central nervous system's myelin sheath is degraded by auto-immune cells. Relapse remitting multiple sclerosis (RRMS) is the most common MS phenotype, accounting for ~85% of new diagnoses. Disease modifying therapies (DMTs) are used in RRMS to reduce the frequency of relapses and prevent disability progression. The present study performed a cost effectiveness analysis of three B-cell depleting monoclonal antibody DMTs: ocrelizumab, ofatumumab and rituximab, in comparison to commonly utilized interferon beta-1a (IFN-B1a). A Markov model was created to determine the impact of selected DMTs on the number of relapses, progression to severe disability, severe adverse events and death over a 5-year time frame. Model results demonstrated that all B-cell DMTs retained more patients on therapy than IFN-B1a. In the base case analysis, ocrelizumab and rituximab were both cost-effective, while ofatumumab required a 5% cost reduction to reach cost effectiveness thresholds.

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CHAPTER 1: INTRODUCTION

Background of Multiple Sclerosis

Prevalence

Multiple sclerosis (MS) is a neurodegenerative autoimmune disease impacting the central nervous system (CNS).[1] The prevalence of MS within the United States (US) in 2017 was estimated between ~850,000 and 900,000 adults corresponding to an average case rate of 350 per 100,000 persons.[2] This estimate originates from a widely cited 2019 article that extrapolated claims data from 2010 to 2017.[2] The prevalence of MS appears to have increased in recent years. Estimates of case rates from 1976 and 1994 range from 50 to 85 per 100,000 respectively.[2] This increase in prevalence is consistent with trends observed for other autoimmune conditions in the US such rheumatoid arthritis, myasthenia gravis and lupus.[3] The onset of MS is observed most commonly in young adults between the ages of 20-40 years and affects females disproportionately in ~3:1 ratio to males.[1,4–7] Potential risk factors for MS beyond female sex include smoking, prior Epstein--Barr viral infection, and vitamin D deficiency.[4,5]

Pathophysiology

The pathophysiology surrounding MS involves a complex interplay between autoreactive T-cells and proinflammatory microglia and B-cells.[4,5] Infiltration of these immune cells into the CNS due to disruption of the blood brain barrier leads to demyelination of axons and sometimes neuron body damage.[4–7] The myelin sheath surrounds axons and helps to conduct signal transmission between neuron bodies in the CNS. Damage to the sheath results in impaired conduction and the neurological symptoms observed in MS.[4–7] Evidence of immune mediated damage within the CNS can be seen as T1 and T2 lesions on magnetic resonance imaging (MRI).[4] T1 and T2 refer to different methods of magnetic resonance imaging (MRI). The T1 technique is often paired with Gadolinium (Gd+) use and will highlight areas of active inflammation/disease activity.[8] The T2 technique provides the total number of lesions (new and old) over time.[8] Number and size of lesions are used as part of the diagnostic criteria as will be discussed further in following sections. [6,9]

Symptoms & Diagnosis

The hallmark symptoms of MS include unilateral optic neuritis (vision blurring or loss), painless dipoplia (double vision), brainstem or cerebellar syndrome (vertigo, facial numbness) and partial transverse myelitis.[5,9,10] The latter is associated with a host of symptoms such as weakness, paralysis, bladder and bowel issues, muscle spasms, numbness, tingling and burning.[11] These symptoms can be observed at disease onset and during periods of increased autoimmune activity.[5,9]

The McDonald Criteria, most recently revised in 2017, serves as the main diagnostic standard for MS. [9] Symptoms consistent with multiple sclerosis should warrant further investigation into symptom history and whether multiple episodes have occurred.[9] MRI of brain and spinal cord should be performed to determine presence of lesions.[9] Patients with $\geq$2 clinical attacks and $\geq$2 lesions require no additional criteria to be diagnosed with MS and should be started on treatment.[9] Other combinations of attacks and lesions may require further investigation and monitoring before a diagnosis of MS can be confirmed.[9]

Phenotypes

MS is often typified by its heterogenous presentation and progression between patients.[12–14] In an attempt to categorize the differences observed, MS phenotypes (subtypes) were established in 1996 and then revised in 2013 (see Figure 1).[12,13] These phenotypes include Clinically Isolated Syndrome (CIS), Relapse Remitting MS (RRMS), Primary Progressive MS (PPMS), and Secondary Progressive (MS).[12–15] CIS is the first clinical event that is suggestive that demyelinating damage has occurred.[12,13] Conversion to RRMS or PPMS is not absolute and ranges from 60-80% depending on the type of event/symptoms experienced and presence of lesions on MRI.[12]

RRMS is the most common phenotype seen at disease onset, accounting for ~85% of new cases.[12,14] As the name suggests, RRMS is characterized by periods of remission without disease activity and periods of relapses. Relapses are defined by emergence of new neurological symptoms (as described previously) lasting at least 24 hours in the absence of other causes.[12–15] At a physiological level, relapses are periods of increased disease activity

where autoimmune cells are causing demyelination and damage to CNS.[4] Residual effects of relapses will remain in 42% of patients, resulting in increased disability accumulation.[16] Emotional/physical stress and infections have both been correlated with an increase in relapse frequency.[12] Interestingly, pregnancy is associated with decreased disease activity and relapse number.[12]

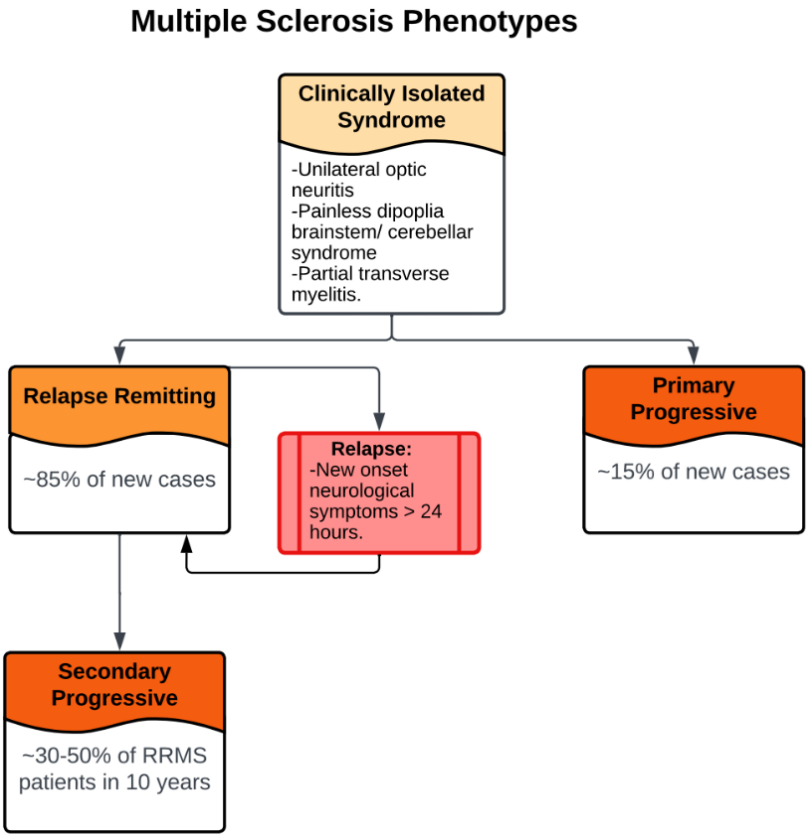


Figure 1: Multiple Sclerosis Phenotypes

PPMS is the least common phenotype, representing 10%-20% of new cases.[12–15] Disease progression occurs from the onset of the disease without intervals of remission.[12–15] Accumulation of disability is often faster in PPMS than in RRMS.[12–15] However, variability between patients exists and extent of disability accumulation is dependent on the level of disease activity.[12–15]

Unlike PPMS, SPMS does not originate at disease onset; instead, it is a progressive form of MS occurring after RRMS.[17–19] When conversion from RRMS to SPMS occurs, remission periods will cease, and patients will experience a decline in function/accumulation of disability in a more linear fashion.[17–19] Similar to PPMS, the rate at which a patient's disability advances is dependent on overall disease activity and varies between patients. Conversion rates from RRMS to SPMS are not consistent between studies but range from 2.5% per year and reach 30 to 50% in 10 years.[17–19] The median time from RRMS diagnosis to transition to SPMS is 19 years.[18] It is unclear how use of pharmacotherapy influences these transition rates. Part of the uncertainty in estimating SPMS conversion rates is due to a lack of definitive diagnostic criteria.[17,18] Diagnosis of SPMS is often done retrospectively as the boundary between RRMS and SPMS is unclear due to nonspecific/differentiating signs and symptoms.[12,17] This period of diagnostic uncertainty often lasts for ~ 3 years. [17]

As mentioned previously, patients with MS of all subtypes will likely experience disability of some kind. The Expanded Disability Status Scale (EDSS) was created in the 1950s by Dr. John Kurtzke specifically for use in patients with MS.[20] The scale ranges from 0 to 10, with 0 representing no disability and 10 corresponding to death.[20] The EDSS is frequently utilized by clinical drug trials and other MS related research. Determination of a patient's EDSS score is based on their gait/mobility and a sub functional system (FS) score.[20] The FS score is comprised of eight systems commonly impacted by MS: pyramidal motor function, cerebellar, brainstem, sensory, bowel & bladder, visual, mental, and other.[20] Depending on the FS score, patients can be categorized in between EDSS levels (ex: EDSS= 2.5).

Economic burden & Quality of Life

MS in all its phenotypes can detract significantly from quality of life and impose a high economic burden upon patients.[21,22] Total annual cost of care per patient ranges from $51,800 to $58,650 with higher EDSS levels corresponding to higher costs.[21] Direct medical costs account for ~77% of total costs with a large portion associated with costs of prescription medications.[21] These costs extrapolated to the most recent 2017 MS prevalence estimates result in a total cost of nearly $50 billion per year spent on MS in the US.

Pharmacotherapy Options

Disease modifying therapies (DMT) that suppress or alter immune function are the mainstay of RRMS management. As of 2022, there are currently 18 FDA approved DMTs for use in relapsing forms of MS (RRMS and SPMS). Approval in both phenotypes is likely due to the issues in distinguishing between the two previously discussed. These agents can be categorized based on their dosage form (injectable, oral and infusion) and vary by their relative efficacy, tolerability, and cost. Table 1 provides a list of available DMTs arranged by approval date. All cost estimates are from REDBOOK, and are wholesale acquisition cost. [23] If a generic formulation is available, cost is reported for generic to reflect real world preferences and utilization.

Injectable DMT

The first interferon (Betaseron) was approved for RRMS in 1993.[24] Three other interferons were approved in the following years. Given their early approval, interferons have been widely utilized and often serve as active comparators in newer DMT clinical trials. All interferon formulations for RRMS are injectables and pose significant tolerability issues for patients due to the occurrence of flu-like systemic reactions, local injection reactions and risk for suicidal thoughts ideation or psychosis.[25] Premedication is often used prophylactically to prevent injection related reactions. Glatiramer acetate (Glatopa/Copaxone) approved in 1996, is an amino-polymer mixture that resembles the structure of the myelin sheath.[26,27] Interactions between glatiramer acetate and T-cells modulate inflammatory processes and prevent damage to myelin sheath.[27] Glatiramer acetate is the preferred DMT for patients

planning to become pregnant and, in some cases, can be used during pregnancy for highly active disease.[28,29]

Oral DMT

Oral options began in 2010 with the approval of fingolimod (Gilenya) belonging to the sphingosine-1-phosphate receptor (S1PR) modulator class. [30] Fingolimod is the only DMT approved for use in children ≥10 years old.[30] Four other agents belonging to the S1PR modulator class have since become available. The S1PR modulators share similar pharmacodynamic properties and dosing regimens to one another. Other oral options include teriflunomide, cladribine, and the fumaric acid derivatives (dimethyl fumarate, diroximel fumarate, and monomethyl fumarate). Cladribine being a potent antimetabolite with origins in oncology is reserved for patients who have failed on previous therapies. [31]

Infusion DMT

All of the infused DMT are monoclonal antibodies (mAb). Natalizumab (Tysabri) an anti-alpha 4 integrin subunit mAb, received the earliest approval in 2004 and is a once monthly infusion. [32] Integrin molecules play a role in lymphocyte transport acting as points of adhesion when immune cells enter inflamed tissue.[33] Prevention of adhesion with natalizumab results in less lymphocytes present in the CNS.[33] Alemtuzumab (Lemtrada), an anti-CD52 mAB, gained approval in RRMS/SPMS in 2013[34]. However, alemtuzumab had prior FDA approval under the brand name of Campath for use in solid organ transplantation. Alemtuzumab binds to the CD52 antigen present on B and T cells resulting in antibody dependent destruction of the cells.[34] Given its highly immunosuppressive nature, it is reserved for treatment resistant RRMS.[34]

Table 1: Disease Modifying Therapies

Disease Modifying Therapy	Class/ Mechanism of Action	Approval Date	Monthly WAC	Administration Route & Frequency
Interferon beta-1b (BETASERON)	Interferon	1993 RRMS/SPMS	$8,593	Subcutaneous injection every other day
Interferon beta-1a (AVONEX)	Interferon	1996 RRMS/SPMS	$7,529	Weekly intramuscular injection
Glatiramer Acetate (generic available)	Amino-polymer mixture-similar to myelin sheath and interacts w/ T-cells	1996 RRMS/SPMS	$1,950	Once daily subcutaneous injection
Rituximab (RITUXAN)	Ant—CD20 monoclonal antibody	1997 Off-label RRMS	$1,565	Infusion every 6-12 months
Interferon beta 1a (REBIF)	Interferon	2002 RRMS/SPMS	$9,228	Subcutaneous injection 3 times weekly
Natalizumab (TYSABRI)	Infusion/Monoclonal Anti- alpha 4 integrin subunit	2004 RRMS/SPMS	$7,855	Once monthly intravenous infusion
Fingolimod (GILENYA)	S1PR modulators	2010 RRMS/SPMS + Pediatric approval	$9,550	Once daily oral tablet
Teriflunomide (AUBAGIO)	Pyrimidine Synthesis Inhibitor	2012 RRMS/SPMS	$8,518	Once daily oral tablet
Dimethyl Fumarate (generic available)	Fumaric Acid Derivative	2013 RRMS/SPMS	$225	Twice daily oral tablet
Peginterferon Beta-1a (PLEGDRIDY)	Interferon	2014 RRMS/SPMS	$7529.31x2	IM/SUBQ injection every 14 weeks
Alemtuzumab (LEMTRADA)	Infusion/Monoclonal Anti-CD52	2013 RRMS/SPMS reserved for treatment resistant	$26,502 per infusion (5 infusions per year) $11,042 per month	Annual (5 consecutive days) intravenous infusion
Ocrelizumab (OCREVUS)	Infusion/Monoclonal	2017 PPMS/RRMS/ SPMS	$37,550 (every 6 months) $6,258 per month	Biannual intravenous infusion
Diroximel Fumarate (VUMERITY)	Fumaric Acid Derivative	2019 RRMS/SPMS	$7825.32	Two oral capsules twice daily
Siponimod (MAYZENT)	S1PR modulators	2019 RRMS/SPMS	$8,460	Once daily oral tablet
Cladribine (MAVENCLAD)	Antimetabolite Purine Analog	2019 RRMS/SPMS Treatment resistant	$45,709.45 per cycle $1,905 per month	Two oral tablet five day cycles over 2 years
Ozanimod (ZEPOSIA)	S1PR modulators	2020	$7,718	Once daily oral tablet
Ofatumumab (KESIMPTA)	Injectable/ Monoclonal	2020 RRMS/SPMS	$7,480	Once monthly subcutaneous injection
Monomethyl Fumarate (BAFIERTAM)	Fumaric Acid Derivative	2020 RRMS/SPMS	$6,022	Two oral capsules twice daily
Ponesimod (PONVORY)	S1PR modulators	2021 RRMS/SPMS	$8,520	Once daily oral tablet

Three DMTs belonging to the Anti-CD20 mAb class (B-cell therapies): ocrelizumab, ofatumumab and rituximab are available. Ocrelizumab (Ocrevus) is the only DMT that has

approval (2017) in both RRMS and PPMS and is considered the first line for treatment of PPMS.[35,36] Ofatumumab (Kesimpta) was the most recently approved anti-CD20 mAb in 2020 and is the first mAb available as a subcutaneous injection for RRMS–though its previous uses in oncology were all infusion based.[37,38] Lastly, rituximab approved for oncology indications in 1997, has gained traction in recent times for a potential off-label treatment for RRMS. [39] Ocrelizumab, ofatumumab, and rituximab bind to the CD20 antigen present on B-cells and lead to antibody dependent destruction of B-cells.[36–38] The reduced number of circulating B-cells results in reduced if not halted disease activity. All three agents have demonstrated superiority over interferon beta-1a, teriflunomide, and dimethyl fumarate in their respective clinical trials. [40–42]

Efficacy

The 2018 American Academy of Neurology (AAN) and the 2019 Consortium of Multiple Sclerosis Center (CMSC) DMT guidelines discuss the selection and utilization of DMTs for MS.[28,29] The AAN 2018 guidelines do not currently provide a treatment algorithm or recommendations on which DMTs should be used first-line in management of RRMS, rather they provide a list of agents that have shown significant efficacy in clinical trials and a recommendation to providers on tailoring the medication choice to patient specific needs.[29] The sole exception to the above statement is the guideline recommendation to prescribe monoclonal antibodies alemtuzumab or natalizumab or S1PR modulator fingolimod in patients with highly active RRMS.[29] Similar recommendations are provided by the 2019 CMSC DMT guidelines stating that any approved DMT can be considered as initial therapy given the right patient circumstances.[28] The CMSC guidelines list the monoclonal antibody class of DMTs as high efficacy and recommended for patients with highly active RRMS.[28] These guidelines will be discussed in further detail in Chapter 2.

Several network meta-analyses (NMA) have been performed comparing the efficacy and safety of available DMT to one another.[41,43–46] Results from the studies are consistent and categorize the injectable medications (interferon formulations and glatiramer acetate) as low efficacy, the oral formulations teriflunomide and fumarate acid derivatives as low to medium efficacy, the S1PR modulators as medium efficacy and the monoclonal antibodies as high

efficacy. Tolerability comparisons generally followed the same order with interferons as the least tolerable and S1PR modulators and monoclonal antibodies as the most. [41,43–46] Chapter 2 will review these NMA in greater detail.

Utilization Trends and Formulary Coverage

Patterns of DMT utilization have changed in the last three decades. The injectable medications interferon and glatiramer acetate were the sole DMT utilized from the mid-1990s until around 2010 where there was a sharp increase in the use of oral DMT and in the infusion medication natalizumab.[47] During more recent years, 2016 to present, utilization of the injectable DMT appeared to decrease slightly while use of the oral and infusion medication increased.[47]

A review of a sample of formularies from the largest US health plans and their associated pharmacy benefit managers: Anthem, Cigna, Express scripts, Humana, Kaiser Permanente, United Healthcare, and the VA national formulary was performed using Clarivate's Fingertip Formulary Software.[48] The DMT most commonly covered under Tier 1 & 2 pharmacy benefits were dimethyl fumarate, teriflunomide, glatiramer acetate, fingolimod and interferon beta-1a. The mAb DMTs were either covered under medical benefit or were not covered.[48]

It is interesting that lower efficacy agents such as interferon beta-1a are still commonly covered as preferred agents on formularies. In general, older and less efficacious pharmaceutical agents can be obtained at lower costs. DMTs appear to be an exception to this trend with the oldest agents, interferon-beta 1a/1b, comparable in monthly cost (~$8,000) if not more expensive than with newly approved DMTs.

Given the number of available options, selection of a DMT can be difficult. Guidelines suggest that potentially any approved DMT can be appropriate given a patient's preferences and circumstances. While mAb DMTs are considered the highest efficacy agents, the B-cell therapies (ocrelizumab, ofatumumab, and rituximab), present a unique circumstance. All three share the same molecular target and mechanism of action but differ in their FDA approved indications, administration and cost. Rituximab, while off-label, is the least costly

option at ~$9,400 to $18,800 per year (depending on frequency) but requires administration at infusion centers and the associated fees. Ocrelizumab is priced at roughly $34,400 per year but has the additional approval in PPMS which suggests that it may have additional benefit in preventing disease/disability progression. Ofatumumab is the costliest option at $89,700 per year, yet offers the convenience of at-home injections.

The cost for all DMT is substantial. MS treatment guidelines, clinical trials, and network meta-analyses suggest that monoclonal antibodies are the most efficacious DMT and should be used in patients with high disease activity. However, lower efficacy agents are still utilized and incorporated frequently into formularies.

Value-Based Healthcare Framework

Value in healthcare has been defined as patient health outcomes achieved relative to the cost of care.[49–51] Value based healthcare ensures that healthcare resources are utilized in a manner that will improve patient and population health. Although the terms "value-based care" and "value-based contracting" are becoming more common amongst healthcare payers as shifts from fee-for-service models are made, the writing of a formal framework of value-based health care is attributed to Porter in 2010.[49]

In this framework, emphasis is placed on selecting patient centered outcomes. That is, health outcomes should be relevant and hold value to patients and should be reflective of both near and longer-term outcomes.[49] This study will center its outcomes based on a value-based healthcare framework and incorporate them into a cost-effectiveness analysis (CEA). A more in-depth discussion of this framework will be provided in Chapter 2.

While CEAs have been performed on the B-cell mAb DMTs, no CEAs have been reported that have compared ofatumumab, ocrelizumab and rituximab, to one another.[75-82] Additionally, significant limitations in these above-mentioned CEA methodologies exist. Short term efficacy data was often over extrapolated due to selection of lifetime time horizons. Additionally, handling of suboptimal response/treatment discontinuation was

inadequate and unreflective of treatment guidelines.[28,29] Methodologies and limitations of previous CEAs will be discussed further in Chapter 2.

In this study, a CEA will be performed in alignment with the value-based healthcare framework. This study will attempt to minimize the limitations of previous studies and model a more realistic progression through relapsing and disability states while on these therapies.

Aims of Study

This study will perform a cost-effectiveness analysis of the monoclonal antibody B-cell therapies versus the commonly utilized interferon-beta 1a. Rituximab, while not FDA approved as a treatment for MS, but has clinical evidence supporting its use, will be included among the B-cell comparator therapies.

AIM #1: To model a population of RRMS patients initiated on one of the three B-cell therapies ocrelizumab, ofatumumab and rituximab or on interferon-beta 1 using a Markov model to model how patients in a real-world setting may experience relapse(s), disease progression, clinical outcomes, and discontinuation from the treatments.

AIM #2: To determine the cost-effectiveness of ocrelizumab, ofatumumab, rituximab or interferon beta-1a in RRMS patients for preventing relapse(s), disease progression and discontinuation from the treatments from a societal perspective using a Markov model. Incremental cost-effective ratios (ICERs) will be calculated and reported as total cost per suboptimal response avoided (relapse, severe disability, severe adverse even and death). This corresponds directly to the number of patients remaining in the Markov model after the set time horizon has elapsed.

Significance

RMMS is a potentially debilitating disease that detracts from quality of life and places a substantial economic burden on the patient and the US healthcare system. The initiation of an appropriate DMT is crucial to a patient's wellbeing as increased disease activity and CNS

damage will occur when not managed sufficiently. Despite increasing evidence that highlights clinical superiority of newer agents such as the B-cell therapies, guidelines do not give preference to these therapies for all patients. The lack of algorithm-based guidelines in conjunction with the current formulary coverage trends suggests that patients are likely to be placed on less efficacious therapies first line. This places patients at risk for the occurrence of breakthrough relapses, disability accumulation and overall increases in healthcare utilization. Therefore, the question becomes whether it is worthwhile to initiate patients on lower efficacy medications if there is potential of disease breakthrough that will necessitate further therapy and increase healthcare costs. The goal of this study is to determine if it is more cost effective to use B-cell therapies or the common alternative interferon beta-1a in order to inform decision makers on the most cost-effective treatment options for this patient population and improve health outcomes.

Study Limitations

This study has several limitations. First, is the "memory less" assumption used in Markov models meaning past events have no bearing on the probability of current ones. An individual patient with high disease activity may have increased probability for future events, but the model will only capture the mean probability of an event occurring across a population. The model is to determine costs and effectiveness on average; the treatment experience of an individual with MS may vary from model assumptions. Adherence to DMTs of interest will not be incorporated into the model due to lack of data surrounding the impact of adherence on DMT efficacy. However, differences in adherence to the different dosage forms may exist and could have potential influence on efficacy in real world practice. Lastly, the cost of treatment switching after discontinuation from study DMTs will not be assessed.

CHAPTER 2: REVIEW OF THE LITERATURE

Introduction

This chapter is organized into two main sections. The first reviews concepts central to the design and structure of this study with a discussion of the value-based healthcare framework and cost effectiveness analyses.

In the second section, pertinent literature surrounding RRMS is reviewed. It begins with a thorough examination of the most current RRMS treatment guidelines. In the subsequent sections, clinical trials and network meta-analyses of the B-cell DMT are reviewed in order to establish the expected efficacy of these agents. Lastly, economic analyses that have been performed on the B-cell DMT are discussed in order to highlight where future research, particularly this study, could improve the methodological designs.

Value-Based Healthcare Framework

Value in healthcare has been defined as patient health outcomes achieved relative to the cost of care.[49–51] The principles of value based healthcare ensure that healthcare resources are utilized in a manner that will improve patient and population health. Value-based care has gained traction amongst healthcare payers as the realization that the fee-for-service models will no longer be sustainable with the continued release of specialty medications and high-cost personalized treatments. The Academy of Managed Care Pharmacy (AMCP) has made available a wide variety of resources to aid healthcare payers in understanding value-based care and how to implement value-based contracting into their current payment models.[51–53] AMCP has highlighted the various value assessment tools available including the ICER value assessment framework, NCCN evidence blocks, and the ASCO value framework.[54]

Though the terms “value-based care” and “value-based contracting” are becoming more common amongst healthcare payers as shifts from fee-for-service models are made, the writing of a formal framework of value-based health care is attributed to Porter 2010.[49]

In this framework, emphasis is placed on selecting patient centered outcomes. That is, health outcomes should be relevant and hold value to patients and should be reflective of both near and longer-term outcomes.[49] The framework recognizes that in a single disease state multiple outcomes may hold value to patients.[49] Outcomes are structured into three tiers. Tier 1 represents outcomes of most value to patients, while Tiers 2 and 3 represent outcomes patients may value should Tier 1 outcomes be met.[49] Figure 2 depicts the different health outcome tiers as described in the framework and examples of their relation to RRMS outcomes.

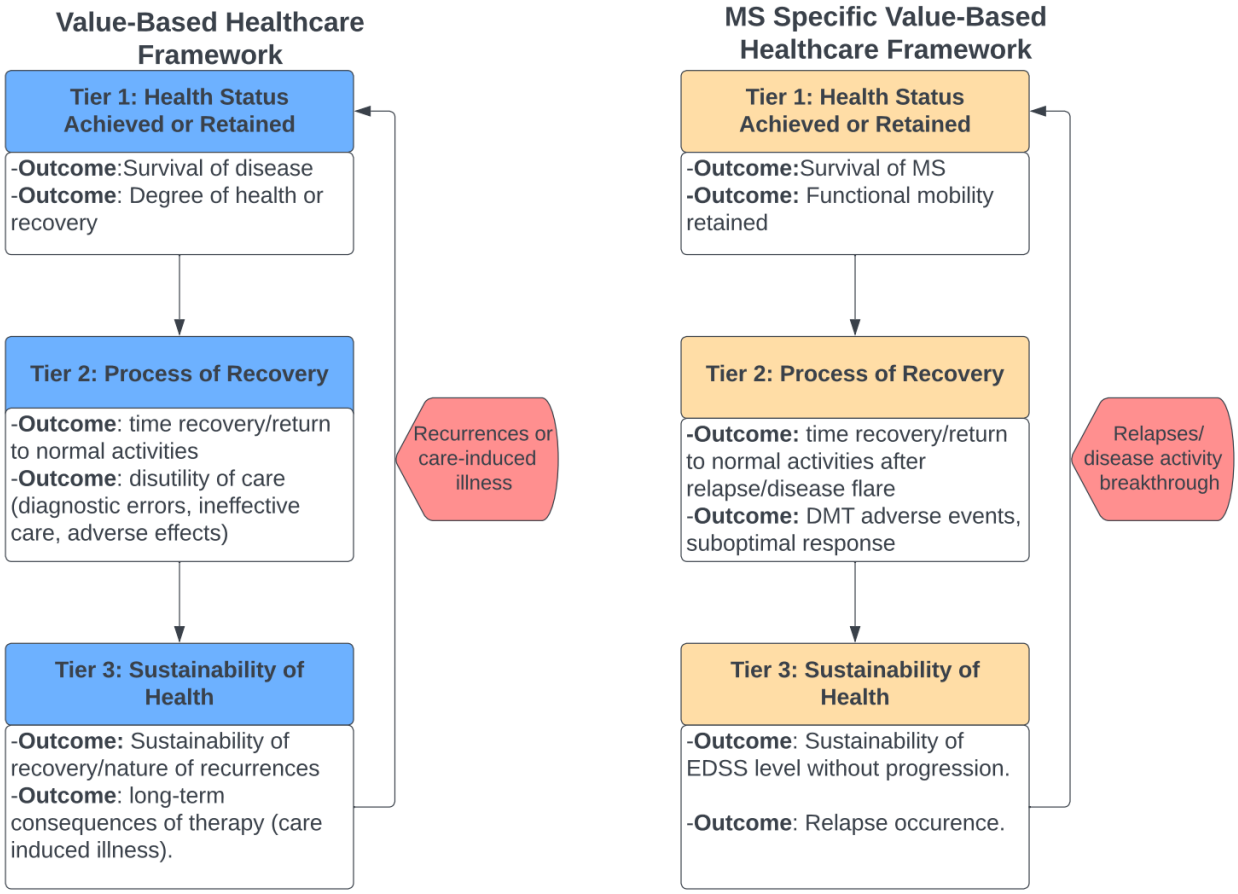


Figure 2: Value-Based Framework

Described in terms of RRMS, the outcome of DMTs impact on EDSS/disability level falls within Tier 1 as a patient's level of mobility/function is retained at a certain level. DMT associated adverse events and treatment failures could be categorized within Tier 2 outcomes. Relapse occurrence or disability accumulation and EDSS level progression would

fall within Tier 3 and could disrupt a patient's health state to a point of reentering Tier 1 health outcomes.

The similarities between value-based healthcare and the structure of CEAs have been noted in the literature.[55,56] Put simply, the equations for value (outcome/cost) and cost effectiveness ratios (cost/outcome) are reciprocals of one another. The institute for clinical and economic review (ICER) provides recommendations on performing value-based assessments in which incremental cost effectiveness ratios and comparative effectiveness are incorporated in conjunction with long-term value-based outcomes.[55] A recent article published in the ISPOR Value in Health journal proposes how CEAs can be used to achieve value-based health outcomes.[56] This article suggests that the value-based healthcare framework does not provide enough structure or guidance to be used in decision making on its own, but when combined with the robust methodology of a CEA could enhance the principles of value-based healthcare in resource distribution. [56]

Cost-Effectiveness Analyses

Amongst pharmacoeconomic assessments, cost-effectiveness analyses are the most widely performed.[57] CEAs are used to compare the cost and outcomes of a healthcare intervention (in this case pharmaceutical treatment) in order to inform decision makers on the coverage or implementation of the treatment(s).[57–59] Outcomes are measured in natural health units specific to the disease state.[57–59] In RRMS, examples of these include relapses avoided and disability progression prevented.

Two important aspects of outcomes used in CEAs should be noted. The first is in relation to the value-based framework discussed previously. Outcomes selected will always hold clinical relevance but may not be reflective of outcomes that patients value. Selection of the reduction of blood pressure units (mmHg) as the outcome of a CEA is clinically relevant as it has implications for future health events (myocardial infarctions, stroke) but it may not directly translate to an understandable nor valuable measure for patients. Solutions to this issue include selecting outcomes relevant to patients as outlined in the Value-Based

Healthcare Framework or utilizing a subtype of CEA, the cost utility analysis (CUA), where outcomes are based on impacts to patients' quality of life. [49,57]

The second aspect relates to comparability of outcomes. Interventions in which outcomes are measured in different health units are not comparable with a traditional CEA.[57] This can present a challenge when comparing multiple treatments that have had efficacy assessed in different ways. Cost benefit analyses (CBA) can circumvent such issues by converting outcomes into costs. [57]

The incremental cost effectiveness ratio (ICER) is the most common way of reporting the results of CEAs. [57–59] Figure 3 depicts the standard formula used. An ICER represents the cost to gain an additional unit of health compared to another option.[57] Whether or not a calculated ICER is cost effective is based on a predetermined cost effectiveness threshold. The monetary value of this threshold is a topic of much debate, but a common recommendation from the World Health Organization is to set it at twice the nation's per capita gross domestic product (GDP).[60,61]

$$ICER = \frac{Cost\ New\ Treatment - Cost\ of\ Old\ Treatment}{Outcome\ of\ New\ Treatment - Outcome\ of\ Old\ Treatment}$$

Figure 3: Incremental Cost Effectiveness Ratio Equation

A cost effectiveness grid can be used to visually depict when an ICER should be calculated or when it is apparent that a treatment is first order (outright) dominant or dominated by another treatment (see Figure 4). A treatment is considered first order dominant when it is both lower cost and provides either the same or higher effectiveness than a comparator. Conversely, a treatment is first order dominated when it provides the same or lesser effectiveness at a higher cost.

	Lower Cost	Same Cost	Higher Cost
Less Effectiveness	ICER	Dominated	Dominated
Same Effectiveness	Dominant	Indifferent	Dominated
Higher Effectiveness	Dominant	Dominant	ICER

Figure 4: Cost Effectiveness Grid

Decision tree and Markov models are tools commonly utilized by CEAs in order to calculate the occurrence and associated costs of the outcomes of interest given a certain intervention.[57] In a Markov model, patients are modeled over time in a cyclical fashion.[57] Cycle lengths are set to reflect the time frame in which outcomes of interest are expected to occur. Patients are placed into different health states and in each cycle have the ability to transition from one state to another.[57] Absorbing health states are events that patients cannot return to the model from such as death. Markov models provide the ability to model patient's experiences with an intervention over an extended time period and then quantify the associated costs.[57]

Clinical Guidelines

American Academy of Neurology (AAN) Guidelines

The 2018 AAN guidelines performed a literature review of systematic reviews and clinical trials. Given the year of publication, DMTs approved after 2018 were not included in this guideline. Seven clinical questions were posed to direct the review of the literature.[29] Of these, the questions that revolved around DMT efficacy of preventing relapses and disease progression will be summarized as they pertain to the topic of this study.

A consensus statement was provided for each agent reviewed on whether they demonstrated efficacy in clinical trials and systematic reviews on the specified outcomes.[29] All formulations of interferons, dimethyl fumarate, teriflunomide and cladribine were found to be superior to placebo for preventing relapses and disability progression. Glatiramer acetate demonstrated superiority to placebo and equivalence to interferon beta-1a for relapse

prevention, but guidelines found insufficient evidence supporting use for progression prevention. Fingolimod demonstrated superior efficacy to interferon beta-1a for relapse prevention but equivalency to interferon beta-1a for progression prevention. Guidelines found the mAb DMTs alemtuzumab and ocrelizumab were superior to interferon beta-1a for relapse and progression prevention, while natalizumab demonstrated superiority over only placebo on both outcomes. Natalizumab did pose significant safety risks for progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain. Rituximab, though off-label, was assessed for relapse prevention and reported as superior to placebo. Mitoxantrone, while reported as efficacious for both outcomes, was not recommended for use due to risk of severe AE.

The remaining sections of the 2018 guideline provided recommendations for initiating, switching and stopping DMT. All patients meeting diagnostic criteria for RRMS should be initiated on a DMT. Those meeting criteria for CIS are eligible to be initiated on DMT given the risk of progression to MS. The DMTs listed by the AAN guidelines that met specified efficacy outcomes without significant safety risks (mitoxantrone), are considered options to select from. No algorithm is provided for first line vs second line DMT use; rather, recommendations are centered around patients' education on options and expectations. Patients should be informed on the different regimens, administration routes, benefits and risks of DMT. Adherence to therapy is a major concern for DMT efficacy and therefore, assessing barriers to adherence including pre-existing mental health concerns is recommended. In patients with highly active RRMS, the guidelines recommend initiation of alemtuzumab, fingolimod or natalizumab. The definition of highly active disease is not specified in detail but is generally associated with a higher number of relapses and lesions.

The time until clinical effectiveness is variable between DMT but is generally between 3-6 months. DMT switching should be considered if sufficient time since initiation has elapsed and patient has experienced $\geq$1 or more relapses, $\geq$2 new MRI-detected lesions, or increased disability on examination over a 1-year period. Assessment of adherence should always be performed before the decision to switch is made. Switching to a DMT with a different mechanism of action or alemtuzumab, fingolimod, natalizumab, or ocrelizumab is recommended.

Consortium of Multiple Sclerosis Center (CMSC) Guidelines

The CMSC 2019 Guidelines are divided into six sections. Section 1, 2, and 6 will be reviewed here as they pertain to this study.[28] Section 1 provides recommendations on the selection of DMT in RRMS. The CMSC guidelines state that initiation of DMT should begin as early as possible in patients with clinically confirmed RRMS or those with CIS demonstrating high risk signs/symptoms. Analysis of each agent's efficacy is not discussed, rather available DMTs are provided in a table and categorized by mode of administration (oral, injection, infusion). Given the publication date, the sole S1PR modulator incorporated is fingolimod. Ofatumumab and rituximab are not included within the infusion DMT class due to approval date and off-label use, respectively. A stepwise approach is not recommended and therefore, terms like first- and second-line therapy are avoided. Similar to the 2018 AAN guidelines, the CMSC recommends an individualistic approach to DMT selection taking into account efficacy, safety, cost, mode of administration and patient specific factors (dexterity to administer injections, transportation to infusion centers). The guidelines emphasize that efficacy can only be truly established via trial of a DMT for each patient and that clinical trials only provide efficacy data for cohorts of patients. That said, mAb DMT are still discussed within guidelines under the context of being high efficacy, while fingolimod and cladribine are listed as moderately high efficacy amongst oral agents.

Section 2 discusses the selection of DMT in highly active RRMS. CMSC guidelines defines highly active RRMS on the basis of relapses, disability worsening, and MRI changes. Demographic risk factors for increased disease activity include being male, >40 years old at disease onset, and African American. Clinical factors associated with highly active disease include:

- Frequent relapses ($\geq$2 per year) or severe relapses resulting in EDSS progression/ incomplete recovery are associated with highly active disease.
- Reaching EDSS 4 within 5 years of RRMS onset, or change in EDSS $\geq$2 points in 1 year
- Accumulation of $\geq$2 T1 lesions or $\geq$3 T2 lesions

In these patients, initiation of mAB DMTs ocrelizumab, alemtuzumab or natalizumab should be considered. The CMSC guidelines make a specific point to mention the PML risk with natalizumab as well.

Section 3 examines switching between therapies. Reasons for switching include suboptimal response, safety/tolerability issues, and patient specific preferences. Suboptimal response is defined as**:**

- 1 significant relapse with or without full recovery
- $\geq$ 1 relapse (mild or significant) within a year of starting therapy
- $\geq$ 2 or more MRI lesions in a year
- Initial response followed by breakthrough disease
- Persistent neutralizing antibodies for natalizumab

A period of 3-6 months is required for most DMTs to become clinically active, and assessment of response should not be made until that trial period has passed. That said, CMSC guidelines suggest the first 1 to 2 years after initiating DMT are the most important to assess patients for suboptimal response. If switching DMT is decided upon, one option is switching to a DMT with a different mechanism of action. Escalation to higher efficacy mAb DMT can be considered if patients meet criteria for highly active disease or have trialed 2 lower efficacy agents.

Clinical Trials of B-cell Agents

A literature search was performed for clinical trials of B-cell DMT in PubMed utilizing standard Boolean Operator conventions. Key search terms included combinations of: “clinical trials”, “ocrelizumab”, “ofatumumab”, “rituximab”, and “relapsing multiple sclerosis”. Studies were filtered for clinical trials. For ofatumumab and ocrelizumab, only original phase 3, phase 3 extension trials, or phase 3 sub-analysis pertaining to efficacy or safety were included. Due to the paucity of data surrounding rituximab in RRMS, trials were included if they were phase 1-3 or observational and rituximab was used as monotherapy in RRMS. All studies evaluating efficacy must report outcomes based on relapses or disability

progression via the EDSS in order to support this study's focus. Trials were excluded if they were phase 1 or 2 trials (except rituximab), if they did not include agents of interest as monotherapy or if they were conducted in phenotype other than RRMS. Tables 2-4 provide a summary of studies.

Efficacy

Ocrelizumab search terms generated 22 results, and seven trials were included in this review making ocrelizumab the most studied agent amongst the mAb DMTs. OPERA I & II were the main phase 3 trials conducted for ocrelizumab in RRMS.[40] There were several subgroup analyses published based on the results of these trials.[62–64] OPERA I & II evaluated ocrelizumab against the subcutaneous formulation of interferon beta-1a in 1,656 participants with relapsing forms of MS for 96 weeks.[40] On the outcome of relapses, ocrelizumab was superior to interferon-beta 1a with an annualized relapse rate (ARR) of 0.16 and hazard ratio (HR) of 0.54 (46% reduction in relapses).[40] As for disability progression measured at week 24 of the trials, a smaller percentage of patients treated with ocrelizumab (6.9%) progressed on the EDSS scale versus interferon beta-1a (10.5%); HR= 0.60 (40% reduction in likelihood of disability progression).[40] Subgroup analyses revealed that in patients >40 years old at baseline the difference between ocrelizumab and IFN-B1a was not statistically significant.[62] Patients that were male, had a BMI >25, had prior DMT within 2 years, or had >2 relapses in a year prior to trial did not have statically significant differences on disability progression outcomes.[49] Patients of African American descent, 2% of OPERA participants, have comparable outcomes to non-African participants on the basis of relapses.[63] However, differences between treatment groups were not statistically significant for African American participants at week 24 progression.[51]

The CASTING and CHORDS trials were both 96-week, single arm trials evaluating ocrelizumab use in patients with suboptimal previous response.[53,54] Suboptimal response was defined as experience/development of $\geq$1 relapses or $\geq$ 1 lesions after 6 months of DMT therapy.[53,53] The most common previous DMTs were interferon formulations, glatiramer acetate, dimethyl fumarate, and fingolimod.[53,54] The primary outcome in both trials was no evidence of disease activity (NEDA) defined as either proportion of patients with absence of

relapse or absence of relapses and lesions during treatment period. Absence of relapses occurred in 74-89% of patients by week 96.[53,54] Week 24 confirmed disability progression (CDP) occurred in 2- 10% of patients. [53,54]

Table 2: Ocrelizumab Clinical Trials

Search Terms **Ocrelizumab AND relapsing multiple sclerosis**	**Filters Applied** **Clinical Trials**	**Search Results** **22 results, 7 included**			
Trial Name	**Length/Methods**	**Population Demographics/ Sample Size**	**Relapse Rate Outcomes**	**EDSS Progression Outcomes**	**Safety/ Tolerability**
Hauser SL, Bar-Or A, Comi G, et al. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. *N Engl J Med.* 2017;376(3):221-234. [40] **(OPERA I & II)**	**Design:** Concurrent RCTs; Active Comparator, Double-Blind **Length:** 96-week **Intervention:** 1:1 **OCR:** 600mg Q6 months + methylprednisolone 100mg pre-infusion VS. **IFN:** Interferon beta-1a SUBQ (Rebif) 3x weekly **Inclusion Criteria:** -18 to 55 years with RMS -Evidence of disease activity -EDSS score of 0 to 5.5 - >1 relapse in the year before screening, >2 relapses in the 2 years before screening -Neurologically stable before screening	**Sample Size:** ***OPERA I:*** OCR: 410 IFN: 411 ***OPERA II:*** OCR: 417 IFN: 418 **Demographics:** Age: ~37 Female ~66% US ~26% ROW ~74% Time since symptom onset:6.5years Time since diagnosis: 4.9 years No. Relapses prior 12 months Treatment Naive: 73% Previous treatment: 27% -IFN 19% -Glatiramer Acetate 9% Mean EDSS 2.8 Prior Lesions: -0 lesions: 59% -1 lesion: 14%	**Primary Outcome:** Ocrelizumab: ARR: 0.16 IFN-beta 1a: ARR: 0.29 HR: 0.54 (0.4-0.7) P <0.001	**Secondary Outcome:** Disability Progression Wk 12 ***Ocrelizumab*** Patients: 9.1% ***IFN beta-1a*** Patients: 13.6% 0.60 (0.45-0.81) P <0.001 **Disability Progression Wk 34** ***Ocrelizumab*** Patients: 6.9% ***IFN beta-1a*** Patients: 10.5% 0.60 (0.43-0.84) P <0.001 **Disability Improvement:** OPERA I SS OPERA II- NS ***Ocrelizumab*** 20.7% ***IFN beta 1a:*** 15.6% (33% improvement rate) p =0.02	Any AE: OCR: 83% IFN:82% AE w/ discontinuation: OCR: 3.5% IFN:6% Infusion related reaction: OCR: 35% IFN: 10% Infection OCR: 58% IFN:53% Serious Infection: OCR: 1.3% IFN:2.9% Neoplasm: OCR: 0.2% IFN: 0.2% Death OCR: 0.2% IFN: 0.2%

Table 2 (cont.)

Trial Name	Length/Methods	Population Demographics/ Sample Size	Relapse Rate Outcomes	EDSS Progression Outcomes	Safety/ Tolerability
Turner B, Cree BAC, Kappos L, et al. Ocrelizumab efficacy in subgroups of patients with relapsing multiple sclerosis. J Neurol. 2019;266(5):1182-1193. doi:10.1007/s00415-019-09248-6[62]	see OPERA 1 &2	**Subgroups:** **OCR Arm:** # participants ROW: 610---------- USA: 217---------- <40: 496---------- >40: 331---------- Female: 541---------- Male: 266---------- BMI <25: 406---------- BMI >25: 41---------- No prior DMT w/in 2 years: 604---------- Prior DMT w/in 2 years: 223---------- **Prior relapse:** ≤1 585---------- ≥ 241---------- **Baseline EDSS** <4 629---------- ≥4 198---------- <2.5 310---------- ≥2.5 517---------- **Baseline Lesions** 0 lesions: 485---------- ≥1 lesions: 333----------	**OCR arm** **Relapses; ARR; RR** 143; 0.15; (0.52) ---- 51; 0.17; (0.58) ------ 103;0.15;0.41--------- 91;0.17;0.76- **NS**---- 130;0.16;0.53--------- 64;0.14;0.56---------- 98;0.16;0.52---------- 94;0.15;0.55---------- 137;0.16;0.57--------- 57;0.15;0.46---------- 122;0.0.14;0.57------ 72;0.20;0.53---------- 118;0.11;0.49--------- 76;0.23;0.67---------- 52;0.10;0.46---------- 142;0.16;0.57--------- 124;0.18;0.74--------- 70;0.13;0.36----------	**OCR arm 6mon.** **Progression: HR** 36; 0.54 21; 0.76-NS 27; 0.59 30; 0.62 33; 0.57 24;0.66-NS 18;0.37 38;0.88-NS 39;0.57 18;0.67-**NS** 37;0.56 20;0.69-**NS** 47;0.65 10;0.44 24;0.73 33;0.54 31;0.60 26;0.58	N/A

Table 2 (cont.)

Trial Name	Length/Methods	Population Demographics/ Sample Size	Relapse Rate Outcomes	EDSS Progression Outcomes	Safety/ Tolerability
Barkhof F, Kappos L, Wolinsky JS, et al. Onset of clinical and MRI efficacy of ocrelizumab in relapsing multiple sclerosis. Neurology. 2019;93(19):e1778-e1786. doi:10.1212/WNL.0000000000008189 [65]	see OPERA 1 &2	**Subgroups by Time in Trial:** Week 0-8 Week 0-12 Week 0-24 Week 0-48 Week 0-96	**OCR Arm** **ARR; reduction** 0.121;54.9% 0.166; 48.8% 0.181;40.4% 0.156; 48.7% 0.156;46.5% **Probability of first relapse** Wk 8 2% Wk 16 4% Wk 24 7% Wk 48 12% Wk 72 15% Wk 96 19%	N/A	N/A
Cree BAC, Pradhan A, Pei J, Williams MJ; OPERA I and OPERA II clinical investigators. Efficacy and safety of ocrelizumab vs interferon beta-1a in participants of African descent with relapsing multiple sclerosis in the Phase III OPERA I and OPERA II studies. Mult Scler Relat Disord. 2021;52:103010. doi:10.1016/j.msard.2021.103010 [63]	see OPERA 1 &2	**OCR Arm- African Descent (n=40)** -Age 35.8 -Female 72.5% -Time since MS symptom onset 5.6 years -No prior DMT in 2 years: 65% -EDSS score: 2.9 -No. relapses in last year 1.3 -No. relapses in last 2 years 1.8	**OCR Arm**: ARR African: 0.13 RR 0.50 ARR Non-african 0.14 RR 0.54	**OCR Arm:** 12 week **Progression; HR** -African: 15%; 0.82- NS -Non-African: 8.8%; 0.59 **OCR Arm:** 24 week -African 12.5%;0.69-**NS** -Non-African 7.0%;0.60	N/A

Table 2 (Cont.)

Trial Name	Length/Methods	Population Demographics/ Sample Size	Relapse Rate Outcomes	EDSS Progression Outcomes	Safety/ Tolerability
Mayer L, Kappos L, Racke MK, et al. Ocrelizumab infusion experience in patients with relapsing and primary progressive multiple sclerosis: Results from the phase 3 randomized OPERA I, OPERA II, and ORATORIO studies. Mult Scler Relat Disord. 2019;30:236-243. doi:10.1016/j.msard.2019.01.044[66]	see OPERA 1 &2	see OPERA 1 &2	see OPERA 1 &2	see OPERA 1 &2	-IRR: 34% -Pruritus: 10.3% -Rash: 10.3% -Throat irritation: 8.1% -Flushing: 5.5% -Urticaria 3.0% -Oropharyngeal pain 2.9% -Headache 3.3% -Tachycardia 1.6% -Nausea 1.2% -Hypotension 1.1% -Myalgia 1.0%
Weinstock-Guttman B, Bermel R, Cutter G, et al. Ocrelizumab treatment for relapsing-remitting multiple sclerosis after a suboptimal response to previous disease-modifying therapy: A nonrandomized controlled trial. *Mult Scler.* 2022;28(5):790-800. doi:10.1177/13524585211035740 [67]	**Design:** Prospective, multicenter, open-label, single-arm **Length:** 96 weeks **Intervention:** OCR 600mg Q6 months **Inclusion Criteria:** 18-55YO EDSS 0-5.5 Trialed ≤3 DMTs trialed for >6 months & had suboptimal response: > 1 relapse >1 T1 lesion > 2 T2 lesion	Participants: 608 Age: 37.2 Female: 72% White: 81% BMI: 28.58 Years since diagnosis: 4.2 Duration of last DMT: 26y **No. prior of DMTs**: 1: 55% 2: 36.2% ≥3 8.8% **Prior DMT used:** Glatiramer acetate 30% Dimethyl fumarate 29% Fingolimod 15% Teriflunomide 9.0% IFN B-1a SC 7.6% IFN B-1a IM 4.1%	Primary outcome (no evidence of disease activity)= free from relapse, 24 week CDP, or new lesions **NEDA** 0-96: 48% 0-48: 51.2% 0-24: 59% **No relapse**: 0-96: 89.6% 0-48: 92.3% 0-24: 94.1% **Relapses:** 0-96: 10.4% 0-48: 7.7% 0-24: 5.9%	**No 24 week CDP** 0-96: 89.6% 0-48: 90.8% **24 week CDP:** 0-96: 10.4% 0-48: 9.2%	-Patients w/ ≥1 AE: 525/608 -Eye disorders 6.4% -GI disorders 19.7% -Nausea 5.3% -IRR 43.3% -Fatigue 9.5% -Infections 50.5% -UTI 14.8% -URI 9.4%

Table 2 (cont.)

Trial Name	Length/Methods	Population Demographics/ Sample Size	Relapse Rate Outcomes	EDSS Progression Outcomes	Safety/ Tolerability
Vermersch P, Oreja-Guevara C, Siva A, et al. Efficacy and safety of ocrelizumab in patients with relapsing-remitting multiple sclerosis with suboptimal response to prior disease-modifying therapies: A primary analysis from the phase 3b CASTING single-arm, open-label trial. Eur J Neurol. 2022;29(3):790-801. doi:10.1111/ene.15171[64]	**Design:** Single-arm; open-label **Length:** 96 weeks **Intervention:** OCR 600mg Q6 months **Sub-Group Enrollment Criteria:** -18-55YO -RRMS -EDSS 0-4 -Prior suboptimal response to DMTs defined by: ≥1 lesions ≥1 relapses *After being on DMT for ≥6 months	**Participants**: 680 Age: 34 Female: 64% White: 92% BMI 25 Reason for Enrollment: -MRI activity 24% -Relapse activity 35% -MRI+ relapse 40% -Duration since MS symptom onset 5 year: -No relapses in past year 1.2 -Baseline EDSS 2.1 -Patients w/0 lesion 85.9% -Patients w/1 lesion 9.4% -Duration of last DMT: 26.5 months -Duration of last DMT and OCR: 1.9 months -**Last prior DMT:** • IFN: 29.1% • Dimethyl 24.7% • Fingolimod 19% • Glatiramer 17% • Teriflunomide 9.6%	**Primary Outcome:** No evidence of disease activity (NEDA) **Proportion of patient's w/absence of relapse during 96 week treatment periods:** Overall: 74.8% EDSS <2.5 77.2% EDSS ≥2.5 70.8% ≤1 previous relapse:78.2% >1 previous relapse: 66% Age ≤40 yrs 74.7% Age >40 yrs 75% Females 72% Males 79.7% One prior tx: 77.6% 2 prior tx: 70.3% IFN 81% Glatiramer 73.9% Dimethyl 73.8% Teriflunomide 69.8% Fingolimod 68.9%	**Confirmed Disability Progression (CDP):** **Week 24 CDP** 2% **Week 48 CDP** 4.75% **Week 96 CDP** 11.6%	-Any AE 89% -AEs leading to DC 7% -IRR 43.2% -Nasopharyngitis 30.9% -Headache 22.6% -Flu 13.5% -UTI 10.3% -Serious AE 7.2% -Serious Infection 1.6% -Malignancies 0.4%

Abbreviations: AE: adverse event; ARR: annualized relapse rate; BMI: body mass index; CDP: confirmed disability progression; DC: discontinuation; DMT disease modifying therapy; EDSS: expanded disability status scale; GI: gastrointestinal; IFN: interferon beta-1a; IM: intramuscular; IRR: infusion/injection related reaction; MRI: magnetic resonance imaging; NS: not significant; NEDA: no evidence of disease activity; OCR: ocrelizumab; RR: rate ratio; ROW: rest of world; SC: subcutaneous; UTI: urinary tract infection; URI: upper respiratory tract infection

Ofatumumab search terms generated seven results, and three were included. ASCLEPIOS I & II, named after the Greek god of medicine, were the main phase 3 trials conducted for ofatumumab in RRMS.[41] A subgroup analysis and a phase 3 extension trial examining long-term safety were also identified.[68,69] ASCLEPIOS I & II evaluated ofatumumab against oral teriflunomide in 1,882 participants in a 30-month double blind, double dummy trial.[41] On the primary outcome of relapse rates, ofatumumab demonstrated superiority to teriflunomide with an ARR range of 0.10-0.11 versus 0.22-0.25, respectively.[41] Rate ratios ranged from 0.42 to 0.49 between ASCLEPIOS I & II (relapse reduction of 51% to 58%). At month 3, ofatumumab was superior to teriflunomide for disability progression (HR 0.66).[41] However, at month 6, only ofatumumab in ASCLEPIOS I, HR 0.61, was statistically superior to teriflunomide.[41] In the subgroup analysis, 314 participants were considered treatment naive and ofatumumab retained its superiority for ARR (0.09), 3 month CDP (HR 0.62) and 6 month CDP (HR 0.54).[68]

Table 3: Ofatumumab Clinical Trials

Search Terms **Ofatumumab** **AND relapsing multiple sclerosis**	**Filters Applied** **Clinical Trials**	**Search Results: 7 results, 3 included**			
Trial Name	**Length/Methods**	**Population Demographics/ Sample Size**	**Relapse Rate Outcomes**	**EDSS Progression Outcomes**	**Safety/ Tolerability**
Hauser SL, Bar-Or A, Cohen JA, et al. Ofatumumab versus Teriflunomide in Multiple Sclerosis. *N Engl J Med*. 2020;383(6):546-557. doi:10.1056/NEJMoa1917246 **(ASCLEPIOS I & II)** [41]	**Design:** Concurrent RCTs Active Comparator, Double-Blind, Double Dummy **Length**: 30 months **Intervention:** Ofatumumab 20mg Q6 months VS. Teriflunomide 14mg daily **Inclusion Criteria:** -18 to 55 years with RMS -Evidence of disease activity -EDSS score of 0 to 5.5 - >1 relapse in the year before screening, >2 relapses in the 2 years before screening -Neurologically stable before screening	**Demographics:** Participants: 1,882 (85% completed) -ASPECLIOS I: 927 -ASPECLIOS 2: 955 Mean Age 38 Female 68% Male: 32% Mean EDDS 2.9 Race: not reported	**Primary: Relapse Rate** **ASCLEPIOS I** Relapses: Ofa: 90 Teri: 177 ARR: Ofa:0.11 Teri: 0.22 RR 0.49 (0.37 to 0.65) **ASCLEPIOS II** Relapses: Ofa: 95 Teri: 198 ARR Ofa: 0.10 Teri: 0.25 RR 0.42 (0.31 to 0.56).	**Secondary:** **3-month disability progression** **ASCLEPIOS I** HR 0.65(0.45-0.96) **ASCLEPIOS II** HR 0.66 (0.50-0.86) **6-month disability progression** **ASCLEPIOS I** HR 0.61 (0.40-0.93) **ASCLEPIOS II**- NS Disability improvement at 6 months -NS	Any Adverse Event: Ofa: 82-85% Teri: 82-86% AE leading to DC: Ofa: 5.8-5.6% Teri: 5.2-5.3% Infection: Ofa: 49.2%-53.8% Teri: 51%-53.8% IRR: Ofa: 16-24% Teri: 13-16% Serious AE: Ofa: 7.9-10.3% Teri: 7.6-8.2% Death : 0%

Table 3 (Cont.)

Trial Name	Length/Methods	Population Demographics/ Sample Size	Relapse Rate Outcomes	EDSS Progression Outcomes	Safety/ Tolerability
Gärtner J, Hauser SL, Bar-Or A, et al. Efficacy and safety of ofatumumab in recently diagnosed, treatment-naive patients with multiple sclerosis: Results from ASCLEPIOS I and II. Mult Scler. 2022;28(10):1562-1575. doi:10.1177/13524585221078825 [68]	**Subgroup Inclusion Criteria:** -RRMS -0 ≤36 YO -Treatment Naïve.	**Demographics:** Participants: 314 Treatment Naive Ofatumumab ARM ASCLEPIOS I & II: Mean age 36.8 Female 69.1 RRMS 99% SPMS 1% Time since diagnosis 0.63 yrs Relapses in previous year 0.7 EDSS score 2.3	**Total no. relapses:** 45 ARR 0.09 RR 0.50 p<0.001	**3-month CDP:** 7.7% HR 0.62 (0.37-1.03) p=0.065 **6-month CDP:** 5.4% HR: 0.54 (0.30-0.98) p=0.044	AE 94.7% AE w. DC: 6.1% Nasopharyngitis 24.8% IRR 20.1% Headache 14.3% URI 12.7% Fatigue 8.9% Alopecia 5.1% Infections 56.1%
Hauser SL, Cross AH, Winthrop K, et al. Safety experience with continued exposure to ofatumumab in patients with relapsing forms of multiple sclerosis for up to 3.5 years. *Mult Scler.* 2022;28(10):1576-1590. doi:10.1177/13524585221079731 **(ALITHIOS)**[69]	**Design:** Phase 3b, open-label, single-arm, extension of ASCLEPIOS I&II; Safety data **Length**: on-going; currently at 3.9 years; end 5 years **Inclusion Criteria:** Patients randomized to ofatumumab in previous trial or who switched from teriflunomide	**Demographics:** Participants: 1969 Age: 38.7 Female: 68.3% RRMS 94.9% SPMS 5.1% Time since MS symptom onset: 9.0 EDSS: 2.9 Time on ofa therapy median: 21 months -35 months continuous -18 months new switch	N/A	N/A	≥1 AE 83.8% Grade 3/4: 9.0% Serious: 9.7% AE w/ DC: 5.8% IRR; 24.8% (systemic) Injection site reaction: 11.5% Infections 54.3% Nasopharyngitis 16.8% URI 10.3% UTI 9.8% COVID-19 5.8%

Abbreviations: AE: adverse event; ARR: annualized relapse rate; CDP: confirmed disability progression; DC: discontinuation; DMT disease modifying therapy; EDSS: expanded disability status scale; IM: intramuscular; IRR: infusion/injection related reaction; MRI: magnetic resonance imaging; NS: not significant; OFA: ofatumumab; RR: rate ratio; SC: subcutaneous; TERI: teriflunomide; UTI: urinary tract infection; URI: upper respiratory tract infection

Rituximab search terms generated 20 results, and four trials were included. Three of these were clinical trials (phase 1-3) and one was a retrospective observational study.[42,70–72] The phase 1 trial was a single arm 72 week open label trial evaluating rituximab in 26 RRMS patients.[72] By week 72, 80% of patients had not experienced a relapse (ARR=0.18).[59] The phase 2 placebo controlled trial, was conducted in 104 patients for 48 weeks.[70] Rituximab was superior to placebo with relapses occurring in 20% of participants versus 40% with placebo at week 48 (ARR=0.4).[57] In a 24 month phase 3 trial conducted in Sweden, rituximab was compared against dimethyl fumarate in 197 RRMS patients.[42] By month 24, participants had a lower relapse rate with rituximab (3%) versus dimethyl fumarate (16%); RR=0.19 (81% relapse risk reduction).[42] However, rituximab did not demonstrate superiority to dimethyl fumarate on the basis of disability progression as findings were not statistically significant.[42] Lastly, a retrospective analysis was performed comparing patients initiated on either rituximab or fingolimod after failure on natalizumab.[71] The primary outcome assessed occurrence of relapses after 1.5 years of treatment. Rituximab had a relapse rate of 0.02 while fingolimod had a relapse rate of 0.16 (HR 0.10).[58] Participant numbers in all rituximab studies were notably much smaller than in the ocrelizumab and ofatumumab trials which may lead to skewed results.

Safety

The most common adverse events occurring amongst the B-cell DMT were systemic injection/infusion related reactions (IRR) and infection.[40–42,66,69,70] IRR occurred in 30-40% of patients receiving ocrelizumab and rituximab infusions and onset is typically within the first 24 hours following infusion. From a sub-analysis performed on OPERA I & II data on patient's infusion experiences, pruritus, rash, urticaria, flushing and throat irritation are amongst the common symptoms associated with a systemic infusion response.[66] For that reason, premedication (antihistamines, corticosteroids) are used before infusion with ocrelizumab and rituximab. IRR occurred in ~20% of patients receiving ofatumumab, and local injection site reactions occurred in ~11%.[41,69] Infections occurred in roughly 50% of patients on all DMT (B-cell mAbs and comparators).[40–42,66,69,70] Upper respiratory infections (nasopharyngitis) were the most frequently occurring infection (~30%). No cases of PML were reported.[40–42,66,69,70] This is notable as natalizumab carries a well-known risk for PML.

Table 4: Rituximab Clinical Trials

Search Terms **Rituximab AND relapsing multiple sclerosis**	**Filters Applied** **None**	**Search Results: 20 results, 4 included**			
Trial Name	**Length/Methods**	**Population Demographics/ Sample Size**	**Relapse Rate Outcomes**	**EDSS Progression Outcomes**	**Safety/ Tolerability**
Hauser SL, Waubant E, Arnold DL, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. *N Engl J Med.* 2008;358(7):676-688. doi:10.1056/NEJMoa0706383 [70]	**Design:** Phase 2: Randomized Control Trial **Length:** 48 week (~12 month) **Intervention:** Rituximab 1000mg IV days 1 & 15 VS placebo **Inclusion Criteria:** -18-50 YO -RRMS -EDSS 0-5 - >1 relapse in prior year	**Participants:** **Ritux**: 69 participants Age: 39.6 Female: 52% Disease Duration: 9.6 EDSS Score: 2.5 EDSS baseline: 0: 5.8% 1.0-1.5: 13% 2.0-2.5%: 34.8% 3.0-3.5: 29% 4.0-4.5: 15.9% 5.0: 4.3% No. previous relapses: 0 5.8% 1: 75.4% 2: 11.6% 3: 5.8% Treatment Naive: Ritux 64%; Previous therapy: IFN or glatiramer acetate 36% **Placebo**: Participants: 35 Age: 41.5 Female: 82% Mean EDSS: 2.5 Treatment Naive: 60% Previous therapy: IFN or glatiramer 40%	Relapses @Week 48 Patients w/ Relapse: Ritux: 14(20.3%) Placebo: 14 (40%) RR: 0.5 **ARR:** Placebo: 0.7 Ritux: 0.4 Number of relapses: Placebo; Ritux 0 relapses: 60%;79.7% 1 relapse: 31.4%;11.6% 2 relapses: 2.9%;7.2% ≥3 relapses: 5.7%; 1.4%	N/A	**Discontinuation before wk 48:** Placebo: 40% Ritux: 15.9% **Reason for DC:** ***Death:*** Placebo: 0% Ritux: 1.4% ***Adverse Events:*** Placebo: 0% Ritux: 1.4% Pregnancy Placebo: 2.9% Ritux: 0 ***Lost to follow***: Placebo: 5.7% Ritux: 2.9% ***Patients Decision***: Placebo: 11% Ritux: 0% ***Physicians Decision***: Placebo: 8.6% Ritux: 4.3% ***Relapse:*** Placebo: 5.7% Ritux: 2.9%

Table 4 (cont.)

Trial Name	Length/Methods	Population Demographics/ Sample Size	Relapse Rate Outcomes	EDSS Progression Outcomes	Safety/ Tolerability
Svenningsson A, Frisell T, Burman J, et al. Safety and efficacy of rituximab versus dimethyl fumarate in patients with relapsing-remitting multiple sclerosis or clinically isolated syndrome in Sweden: a rater-blinded, phase 3, randomised controlled trial. Lancet Neurol. 2022;21(8):693-703. doi:10.1016/S1474-4422(22)00209-5 **RIFUND-MS[42]**	**Design:** Phase 3-Randomized Control Trial --> multicenter Sweden **Length:** 24 months (2 years) **Intervention:** Ritux: 600mg Q6 months VS. Dimethyl Fumarate 240mg BID **Inclusion Criteria:** -18-50 YO -RRMS or CIS - EDSS 0-5.5 - ≥1 relapse in prior year	**Demographics:** **Rituximab:** Participants: 99 Age: 33 Female: 68% Duration of mS: 1.6 years Treatment Naive: 98% IFN prior: 1% EDSS: 1.6 Relapses prior year: 0: 23% 1: 55% >1: 22% **Dimethyl Fumarate (DF):** Participants: 98 Age: 33 Female: 65% Duration of MS: 1.8yrs Treatment Naive: 95% IFNeron prior 4% EDSS: 1.7 Relapses prior year: 0: 31% 1: 59% >1: 10%	**Primary: Patients w/ Relapse:** Ritux: 3% DF: 16% RR: 0.19	**Patients w/confirmed EDSS worsening:** Ritux: 10% DF: 5% RR: 1.98-NS NEDA-3: no relapses and no disability worsening Patients that did not meet NEDA-3: Ritux: 32% DF: 46% RR: 0.68	DC Ritux: 3% DF: 49% Infections: URI Ritux: 61.5% DF: 59.9% UTI: Ritux: 8.6% DF: 5.1% Abdominal Pain Ritux: 3.9% DF: 21.9% Nausea: Ritux: 3.5% DF: 10.9% Infusion reactions: Ritux: 40% DF: N/A Arthralgia Ritux: 4.3% DF: 1.5% Headache: Ritux: 9.3% DF: 3.6%

Table 4 (cont.)

Trial Name	Length/Methods	Population Demographics/ Sample Size	Relapse Rate Outcomes	EDSS Progression Outcomes	Safety/ Tolerability
Alping P, Frisell T, Novakova L, et al. Rituximab versus fingolimod after natalizumab in multiple sclerosis patients. *Ann Neurol*. 2016;79(6):950-958. doi:10.1002/ana.24651[71]	**Design**: Retrospective- patients recorded in Swedish MS register w/ RRMS, JCV+, ending Tx w/ natalizumab & switching to either rituximab or fingolimod **Inclusion:** Tx with natalizumab > 6 months	**Rituximab** Age: 40 Participants: 114 Male 41% MS duration: 8yrs EDSS 2.0 Time on NTZ 3.49yrs Follow up time 1.45yrs **Fingolimod** Participants 142 Age: 40 MS duration: 10.4 EDSS: 2.5 Time of NTZ 3.16 yrs Follow up time: 1.82yrs	**Relapse in 1.5 years** **Rituximab** 2 patients Incidence per year: 0.02 **Fingolimod** 25 patients Incidence per year: 0.16 HR 0.10 (0.02-0.43)	**N/A**	**First Dosing AE**: Rituximab: 30 (26%) Fingolimod: 10 (7%) **Discontinuation**: Rituximab 2 (2%) Fingolimod 40 (0.24%)
Bar-Or A, Calabresi PA, Arnold D, et al. Rituximab in relapsing-remitting multiple sclerosis: a 72-week, open-label, phase I trial [published correction appears in Ann Neurol. 2008 Jun;63(6):803. Arnlod, Douglas [corrected to Arnold, Douglas]]. Ann Neurol. 2008;63(3):395-400. doi:10.1002/ana.21363[72]	**Design:** phase 1, open label; single arm **Length:** 72 weeks (18 month) **Intervention:** Rituximab 1000mg IV Week 1;Week 2; Week 24; Week 26 **Inclusion Criteria:** 18-55 YO RRMS EDSS 0-5	**Rituximab**: Participants: 26 Mean age: 40.4 Female: 73% White 80.8% EDSS: 2.3 Time since MS diagnosis: 5.4 yrs No. of relapses in prior year: 1.3 ≥1 relapse in year prior 73% Previous IFN beta-1a use 75%	**Baseline** 0 relapses: 1 (3.8%) 1 relapses: 19 (73.1%) 2 relapses: 5 (19.2%) ≥3 relapses: 1 (3.8%) **Weeks 0-24** 0 relapses: 23 (88.5%) 1 relapses: 3 (11.5%) 2 relapses: 0 ARR: 0.25 **Weeks 0-72** 0 relapses: 21 (80.8%) 1 relapses: 4 (15.4%) 2 relapses: 1 (3.8%) ARR: 0.18	N/A	AE reported : 100% Mild-moderate: 77% Severe: 23% IRR:65% Infection: 61%

Abbreviations: AE: adverse event; ARR: annualized relapse rate; CDP: confirmed disability progression; DF: dimethyl fumarate; DC: discontinuation; DMT: disease modifying therapy; EDSS: expanded disability status scale; IM: intramuscular; IRR: infusion/injection related reaction MRI: magnetic resonance imaging; NEDA: no evidence of disease activity; NS: not significant; RITUX: rituximab; RR: rate ratio; SC: subcutaneous; UTI: urinary tract infection; URI: upper respiratory tract infection;

Network Metanalyses

A literature search was performed for network meta-analyses (NMA) of B-cell DMT in PubMed. Key search terms included combinations of: “disease modifying therap*” “comparative effectiveness” “efficacy” “network meta analyses” “relapsing multiple sclerosis” and the individual drug names. A filter for the year 2019 and forward was applied to increase likelihood that ofatumumab was included in the analyses. Table 5. presents information on the DMTs included in NMAs, the efficacy measures analyzed, and broad reporting of the most efficacious therapies.

Search terms generated 15 studies, six of which were suitable for inclusion in this review. All of the studies included mAb ocrelizumab, natalizumab, and alemtuzumab.[43-46,60,61] Four of the studies included ofatumumab.[44,45,60,61] Two of the studies included daclizumab, which was removed from the market due to safety concerns in March of 2018.[46,61] None of the studies included rituximab in the network meta-analyses, likely due to its off-label status in RRMS. ARR and CDP at varying time frames were the main efficacy outcomes assessed across studies.

MAb DMTs were consistently superior to the other DMTs on pairwise/mixed comparisons and highest ranked on SUCRA analyses. [43-46,60,61] Oral agents such as cladribine, dimethyl fumarate, and S1PR modulators (fingolimod, ponesimod) were often ranked with moderate to high efficacy. [43-46,60,61] The different formulations of interferons and glatiramer acetate were consistently dominated by the other DMTs. [43-46,60,61] A similar trend was observed throughout all NMAs.

When comparing an agent's efficacy on ARR versus CDP, statistical significance was more often achieved for ARR. [43-46,60,61] This is consistent with trends seen in clinical trials. No single MAb was found to demonstrate statistically significant efficacy over the others and the highest SUCRA ranked agent alternated between alemtuzumab, ocrelizumab and ofatumumab.

Table 5: Network Meta-Analyses

Search Terms: **Disease modifying therapies OR B-cell therapies AND meta-analysis AND multiple sclerosis AND relaps***	**Filters Applied:** **2019-Present**	**Search Results (HIT):** **15 studies; 6 included**	
Trial Name	**DMTs Included**	**Efficacy Measures Analyzed**	**DMTs Demonstrating Superiority**
Liu Z, Liao Q, Wen H, Zhang Y. Disease modifying therapies in relapsing-remitting multiple sclerosis: A systematic review and network meta-analysis. *Autoimmun Rev*. 2021;20(6):102826. doi:10.1016/j.autrev.2021.102826[44]	Glatiramer Acetate Betaseron (50ug,250ug, 500ug) Avonex 30ug Rebif 22 ug Natalizumab 300 mg Avonex + natalizumab Cladribine 3.5mg/kg; 5.25mg/kg Fingolimod 0.5mg;1.25mg Teriflunomide 7mg, 14mg Alemtuzumab 12mg Dimethyl Fumarate 240 mg BID Ocrelizumab 600mg Ozanimod 0.5mg, 1mg Ofatumumab 20mg	**Mixed Comparisons via Random Effects Model:** -Annualized Relapse Rate -3 Month CDP **Surface Under the Cumulative Ranking Curve (SUCRA):** -Annualized Relapse Rate	**Lowest ARR on Mixed Comparison:** 1.Ofatumumab 20mg 2. Ozanimod (0.5mg,1mg) 3. Ocrelizumab 600mg 4. Dimethyl Fumarate 5. Alemtuzumab **Highest SUCRA Score:** 1.Ofatumumab 2. Natalizumab 3. Alemtuzumab 4. Avonex + Natalizumab 5. Ocrelizumab

Table 5 (cont.)

Trial Name	DMTs Included	Efficacy Measures Analyzed	DMTs Demonstrating Superiority
Samjoo IA, Worthington E, Drudge C, et al. Comparison of ofatumumab and other disease-modifying therapies for relapsing multiple sclerosis: a network meta-analysis. J Comp Eff Res. 2020;9(18):1255-1274. doi:10.2217/cer-2020-0122[45]	Ofatumumab vs. Teriflunomide 7mg, 14mg Interferon beta-1a IM Interferon beta-1a SC Glatiramer acetate 20mg Dimethyl fumarate Fingolimod Cladribine 3.5mg/kg; 5.25mg/kg Ocrelizumab Natalizumab Alemtuzumab	**Mixed Comparisons via Bayesian Random Effects Model: ofatumumab vs comparator** -Annualized Relapse Rate -3 Month CDP -6 Month CDP	**ARR:** Ofatumumab superior to all DMT except: -Cladribine 3.5mg/kg; 5.25mg/kg -Ocrelizumab -Natalizumab -Alemtuzumab **3 Month CDP:** Ofatumumab superior to all DMT except: -Interferon beta-1a SC -Cladribine 3.5mg/kg; 5.25mg/kg -Dimethyl fumarate -Ocrelizumab -Natalizumab -Alemtuzumab **6 Month CDP:** Ofatumumab only superior to teriflunomide (7mg,14mg)
Li H, Hu F, Zhang Y, Li K. Comparative efficacy and acceptability of disease-modifying therapies in patients with relapsing-remitting multiple sclerosis: a systematic review and network meta-analysis. J Neurol. 2020;267(12):3489-3498. doi:10.1007/s00415-019-09395-w [43]	Teriflunomide 7mg, 14mg Interferon beta-1a IM Interferon beta-1a SC Peg-interferon beta-1a Glatiramer acetate 20mg Dimethyl fumarate Fingolimod Cladribine 3.5mg/kg; 5.25mg/kg Ocrelizumab Natalizumab Alemtuzumab Mitoxantrone	**Pairwise Comparisons using Fixed and Random Effects Model:** -≥1 relapse in 24 months -Disability worsening over 24 months **Surface Under the Cumulative Ranking Curve (SUCRA):** ≥1 relapse 24 months	**Lowest Relapse Rates:** 1. Alemtuzumab 2. Ocrelizumab 3. Mitoxantrone 4. Natalizumab 5. Fingolimod **Highest SUCRA Score:** 1.Alemtuzumab 2.Ocrelizumab 3. Mitoxantrone 4. Natalizumab 5. Fingolimod **Lowest 24 Month Disability Progression:** 1. Alemtuzumab 2. Ocrelizumab 3. Natalizumab 4. Dimethyl Fumarate 5. Interferon- beta 1a (rebif)

Table 5 (Cont.)

Trial Name	DMTs Included	Efficacy Measures Analyzed	DMTs Demonstrating Superiority
McCool R, Wilson K, Arber M, et al. Systematic review and network meta-analysis comparing ocrelizumab with other treatments for relapsing multiple sclerosis. Mult Scler Relat Disord. 2019;29:55-61. doi:10.1016/j.msard.2018.12.040[46]	Ocrelizumab vs Teriflunomide 7mg, 14mg Interferon beta-1a IM (30ug) Interferon beta-1b (250uq) Pegylated Interferon beta-1a (125ug) Interferon beta-1a SC (44ug) Glatiramer acetate 20mg Dimethyl fumarate (240mg) Fingolimod (0.5mg) Cladribine 3.5mg/kg; 5.25mg/kg Ocrelizumab (600mg) Natalizumab (300mg) Alemtuzumab (12mg) Daclizumab (150mg)	**Mixed Comparisons via Bayesian Random Effects Model: ocrelizumab vs comparator** Annualized Relapse Rate 12-Week Disability Progression **Surface Under the Cumulative Ranking Area (SUCRA):** Annualized Relapse Rate 12-Week Disability Progression	**Annualized Relapse Rates:** Ocrelizumab superior to all DMT except: -Alemtuzumab -Cladribine 3.5mg/kg; 5.25mg/kg -Natalizumab **12 Week Disability Progression:** ocrelizumab superior to DMT except: -Alemtuzumab -Cladribine 3.5mg/kg; 5.25mg/kg -Natalizumab -Pegylated interferon -Daclizumab -Dimethyl Fumarate **SUCRA Annualized Relapse Rate** 1. Alemtuzumab 2. Natalizumab 3. Ocrelizumab 4. Cladribine 5. Fingolimod **SUCRA 12 Week Disability Progression:** 1. Ocrelizumab 2. Alemtuzumab 3. Natalizumab 4. Daclizumab Pegylated interferon beta-1a

Table 5 (Cont.)

Trial Name	DMTs Included	Efficacy Measures Analyzed	DMTs Demonstrating Superiority
Chen C, Zhang E, Zhu C, et al. Comparative efficacy and safety of disease-modifying therapies in patients with relapsing multiple sclerosis: A systematic review and network meta-analysis [published online ahead of print, 2022 Aug 1]. *J Am Pharm Assoc (2003)*. 2022;S1544-3191(22)00241-2. doi:10.1016/j.japh.2022.07.009[73]	Alemtuzumab Natalizumab Ofatumumab Ocrelizumab Siponimod Cladribine Ozanimod Fingolimod Dimethyl Fumarate Ponesimod Dimethyl Fumarate Pegylated Interferon Teriflunomide Glatiramer Acetate Interferon Beta-1a: SC Interferon Beta-1a IM	**Pairwise Meta-Analyses Fixed & Random Effects:** -Annualized relapse rate -12 week: confirmed disease progression **Surface Under the Cumulative Ranking Curve (SUCRA):** -Annualized relapse rate -12 week: confirmed disease progression	**Lowest Relapse Rates:** 1.Alemtuzumab 2.Natalizumab 3.Ofatumumab 4. Ocrelizumab 5. Siponimod **Lowest 12 Week CDP:** 1. Ofatumumab 2. Dimethyl Fumarate **SUCRA:** 1.Ofatumumab 2. Dimethyl Fumarate 3.Cladribine 4. Pegylated-interferon beta-1a 5. Teriflunomide
Hennessy B, Zierhut ML, Kracker H, Keenan A, Sidorenko T. Comparative Efficacy of Relapsing Multiple Sclerosis Therapies: Model-Based Meta-Analyses for Confirmed Disability Accumulation and Annualized Relapse Rate. Mult Scler Relat Disord. 2022;64:103908. doi:10.1016/j.msard.2022.103908[74]	Alemtuzumab Natalizumab Ofatumumab Ocrelizumab Daclizumab Siponimod Cladribine Ozanimod Fingolimod Dimethyl Fumarate Ponesimod Dimethyl Fumarate Pegylated Interferon Teriflunomide Glatiramer Acetate Interferon Beta-1a: SC Interferon Beta-1a IM	**Model Based Meta-Analysis:** -Annualized Relapse Rate -12 Week CDP	**Lowest Relapse Rates:** 1.Ofatumumab 2. Alemtuzumab 3.Ocrelizumab 4. Natalizumab 5. Daclizumab **Lowest 12 Week CDP:** 1.Alemtuzumab 2.Ofatumumab 3.Ocrelizumab 4. Natalizumab 5. Daclizumab
Abbreviations: ARR: annualized relapse rate; CDP: confirmed disease progression; DMT: disease modifying therapy; SUCRA: surface under cumulative ranking area			

Economic Studies of DMTs in MS

A literature search was performed for economic analyses of B-cell DMTs in PubMed. Search terms included: “cost effectiveness analysis” “economic” “multiple sclerosis” and B-cell DMT names (ocrelizumab, ofatumumab, rituximab). All economic studies that included the B-cell DMTs of interest in treatment of RRMS were included. In addition, a special emphasis was placed on the structure of Markov models identified. Table 6 presents the search terms used for each B-cell DMT, the type of economic analysis, key results, and, if applicable, details of the Markov model structure.

Following the trend seen with clinical trials, ocrelizumab-related search terms produced the most results at 26. Only five articles met the inclusion criteria of being an economic analysis of ocrelizumab use in RRMS. Four out of the five included articles were CEAs utilizing Markov Models.[77-81] In two studies, ocrelizumab was compared against interferon beta-1a and in the remaining three against other mAb DMT. In studies comparing against interferon beta-1a, ocrelizumab was found to be more cost effective.[77,78] However, mixed results are reported for the economic analyses including other mAb DMT.[79-81]

Ofatumumab-related search terms produced 7 results and two studies were included. Both studies utilized a Markov model.[75-76] In a Canadian study, ofatumumab was found to have an ICER dominant to ocrelizumab and natalizumab was well as other DMT.[75] In an analysis conducted in Germany, results projected that ofatumumab would be associated with lower EDSS scores after 10 years as compared to treatment with dimethyl fumarate or glatiramer acetate.[76] This corresponds to 299,498 euros per 10 years of treatment with ofatumumab which was a 6.8% reduction in costs compared to 10 years of Dimethyl Fumarate therapy.[76]

Rituximab search terms generated 16 results. Of those, a single CEA utilizing a Markov model was included.[82] In this study, rituximab was compared against natalizumab, and model results suggested that rituximab’s ICER was dominant to natalizumab.[69] No economic analyses were identified that included all three B-cell mAb together.

The majority of the identified studies (5/6) utilized a Markov model in their economic analysis. The Markov model framework aligns well with the presentation and disease progression observed in RRMS, with EDSS levels logically serving as transition states. The

structure/health states of the Markov models for the identified economic analyses were similar to one another. All models used the EDSS levels as transition states with a chance of relapses in each cycle. Depending on the model, patients could either remain on DMT therapy until death or discontinue to best supportive care due to progression to high EDSS levels, AE discontinuation rates, or conversion to SPMS. Death served as the common Markov absorbing states across all analyses. During each cycle, relapses could occur, and patients could remain in the same EDSS level or transition to a higher (worse) one. The majority of the Markov models (4/5) included were set for extended time periods ($\geq$20 years) or lifetime time horizons.

Common limitations posed by authors centered around the validity of data extrapolation from short term clinical trials to lifetime horizons used in the Markov models.[75,77-79,80] Additionally, the handling of treatment discontinuation and treatment waning effects were often listed as potential model shortcomings.

Interestingly, despite the recommendations of the AAN and CMCS for treatment evaluation and potential switch after $\geq$1 relapse occurrence, relapses were allowed to continuously occur throughout the duration of the models. This is contradictory to how the majority of RRMS patients would be treated in a real-world setting. Suboptimal responses as defined by guidelines and in sub-analyses of clinical trials require intervention. Several models had mandatory transitions to best supportive care for patients reaching higher EDSS levels, in an attempt to model the treatment discontinuation or switch that would ensue from suboptimal response on the basis of disability progression. It is curious that the same consideration was not applied to incidence of relapses.

Table 6: Ofatumumab Economic Analyses

Search Terms **Cost effectiveness analysis OR economic AND ofatumumab AND multiple sclerosis**	**Filters Applied:** **none**	**Search Results:** **7 results; 2 included**		
Study Name	**DMTs Analyzed**	**Methods:** **Study Type/ Data Sources/ Time Horizon**	**Markov Structure**	**Key Results**
Baharnoori M, Bhan V, Clift F, et al. Cost-Effectiveness Analysis of Ofatumumab for the Treatment of Relapsing-Remitting Multiple Sclerosis in Canada. Pharmacoecon Open. 2022;6(6):859-870. Doi:10.1007/s41669-022-00363-1[75]	**Base-Case First Line:** Ofatumumab vs. Ocrelizumab Teriflunomide Dimethyl Fumarate Glatiramer Acetate Avonex Rebif 22, 44ug Betaseron Extavia Best supportive care (BSC) **Second Line:** Cladribine Natalizumab Fingolimod	-CEA -Markov Model -Time Horizon: 65 years -Data Source: Samjoo et.al NMA, OPERA, -ASCLEPIOS -Data was applied from clinical trials and NMA to natural history data -Direct & indirect costs and utility impact assessed	**Cycle Length:** 1 year **Transition States:** 1.EDSS 0-9 2.Relapse (occur continually) 3.Discontinue to BSC (EDSS and relapse transitions still occur) **Absorbing States:** Death *EDSS>7 = discontinue to BSC *Discontinuation rates from NMA were used *All patient after DMT use for 10 years= discontinuation to BSC	**ICER ($ per QALY):** Ofatumumab dominant over: -Ocrelizumab -Teriflunomide -Dimethyl fumarate -Avonex -Rebif 22,44 -Betaseron -Extavia -Natalizumab -Fingolimod Ofatumumab vs BSC ICER= $28,014

Table 6 (Cont.)

Study Name	DMTs Analyzed	Methods: Study Type/ Data Sources/ Time Horizon	Markov Structure	Key Results
Koeditz D, Frensch J, Bierbaum M, et al. Comparing the long-term clinical and economic impact of ofatumumab versus dimethyl fumarate and glatiramer acetate in patients with relapsing multiple sclerosis: A cost-consequence analysis from a societal perspective in Germany. *Mult Scler J Exp Transl Clin*. 2022;8(1):20552173221085741. Published 2022 Mar 29. Doi:10.1177/20552173221085741[76]	**Base Case**: 1.Ofatumumab vs Dimethyl Fumarate Glatiramer Acetate 2.Ofatumumab vs Dimethyl Fumarate + Glatiramer Acetate **Switch Scenarios:** 1.Early switch: switch to Ofatumumab after 1 year with dimethyl fumarate or glatiramer acetate 2.Late switch: switch to Ofatumumab after 5 years with dimethyl fumarate or glatiramer acetate	-Cost Consequence Analysis -Markov model -Time horizon: 10 years -Data source: Samjooet al. NMA -Data was applied from NMA to natural history data -Direct and indirect costs assessed -Time spent in different health states assessed.	**Cycle Length:** 1 year **Transition States:** 1.EDSS 0-9 2.Relapse (occur continually) 3.Discontinue to BSC (EDSS and relapse transitions still occur) **Absorbing States:** Death *EDSS>6 = discontinue to BSC *Discontinuation rates from NMA were used	**Base Case:** -Lower EDSS scores after 10 years with ofatumumab than with dimethyl fumarate and glatiramer acetate **Switch Scenario:** Early switch to ofatumumab was associated with lower EDSS scores than late switch **Base Case Cost of Ofatumumab only:** 299,498 euros per 10 years Vs DMF -6.8% Vs. glatiramer acetate +4.0%
Abbreviations: DMT: disease modifying therapy; EDSS: expanded disability status scale; ICER: incremental cost effectiveness ratio; RRMS: relapse remitting multiple sclerosis; QALY: quality adjusted life year;				

Table 7: Ocrelizumab Economic Analyses

Search Terms: **Cost effectiveness analysis OR economic AND ocrelizumab AND multiple sclerosis**	**Filters Applied:** **None**	**Search Results:** **26 results; 5 included**		
Study Name	**DMTs Analyzed**	**Methods:** **Study Type/ Data Sources/ Time Horizon**	**Markov Structure**	**Key Results**
Yang H, Duchesneau E, Foster R, Guerin A, Ma E, Thomas NP. Cost-effectiveness analysis of ocrelizumab versus subcutaneous interferon beta-1a for the treatment of relapsing multiple sclerosis. *J Med Econ*. 2017;20(10):1056-1065. Doi:10.1080/13696998.2017.1355310[77]	Ocrelizumab Interferon Beta-1a	-CEA -Markov Model -Time horizon: 20 years -OPERA 1&2 trials. ARR applied directly. -Direct costs and utilities assessed	**Cycle Length:** 1 year **Transition States:** 1.EDSS 0-7 Treated 2. EDSS 0-9 Untreated 3.EDSS 0-9 SPMS 4. Relapses occur continually **Absorbing State:** -Death *Treated discontinue to untreated >7 EDSS	Ocrelizumab dominant to interferon beta-1a: cost per LY gained, cost per QALY gained Ocrelizumab total cost savings: $63,822 over 20 years
Frasco MA, Shih T, Incerti D, Diaz Espinosa O, Vania DK, Thomas N. Incremental net monetary benefit of ocrelizumab relative to subcutaneous interferon β-1a. *J Med Econ*. 2017;20(10):1074-1082. Doi:10.1080/13696998.2017.1357564[78]	Ocrelizumab Interferon Beta-1a	-CEA -Markov Model -Time Horizon: 30 years -OPERA trials and interferon clinical trials RR/HR applied to natural history data -Direct, indirect, and utilities assessed	**Cycle Length:** 1 year **Transition States:** 1.EDSS 0-9 2. Relapse (occurs continually) **Absorbing State:** -Death *Natural history progression was not modeled, was used to apply treatment event reductions to.	**Incremental Net Monetary Benefit of Ocrelizumab**: $413,611

Table 7 (Cont.)

Study Name	DMTs Analyzed	Methods: Study Type/ Data Sources/ Time Horizon	Markov Structure	Key Results
Espinoza MA, Rojas R, Zaupa A, Balmaceda C. A Model-Based Economic Evaluation of Cladribine Versus Alemtuzumab, Ocrelizumab and Natalizumab for the Treatment of Relapsing-Remitting Multiple Sclerosis with High Disease Activity in Chile. *Pharmacoecon Open*. 2021;5(4):635-647. Doi:10.1007/s41669-021-00282-7[79]	-Cladribine vs -Ocrelizumab -Natalizumab -Alemtuzumab	-CEA -Markov Model -Time horizon: 45 years -Clinical trials ARR (ARR x number of patients alive each cycle) -NMA HR applied to natural history data for EDSS progression -Direct costs and utilities assessed	**Cycle Length:** 1 year **Transition States:** 1.EDSS 0-9 on DMT 2. EDSS 0-9 off DMT 3.Relapses **Absorbing States:** 1.Death 2.Discontinuation SPMS/EDSS progression	Natalizumab dominant to all comparators Base-Case ICER: -Natalizumab $0 -Ocrelizumab $58,062 -Cladribine $32,504 -Alemtuzumab -$6,052
Chirikov V, Ma I, Joshi N, et al. Cost-Effectiveness of Alemtuzumab in the Treatment of Relapsing Forms of Multiple Sclerosis in the United States [published correction appears in Value Health. 2019 Jun;22(6):750]. *Value Health*. 2019;22(2):168-176. Doi:10.1016/j.jval.2018.08.011[80]	Alemtuzumab vs Ocrelizumab Natalizumab Fingolimod Glatiramer Acetate Best Supportive Care (BSC)	-CEA -Markov Model -Time Horizon: 20 years -NMA and OPERA clinical trials RR/HR applied to natural history data -Direct costs and utilities assessed	**Cycle Length:** 1 year **Transition States:** 1.EDSS 0-9 on treatment 2. EDSS 0-9 BSC 3.Relapse **Absorbing States:** -Death *Treatment waning: after 10 years DMT efficacy reduced to 50%	Alemtuzumab vs ocrelizumab, natalizumab, fingolimod, glatiramer acetate: dominated Alemtuzumab vs BSC ICER: $103,895
Nicholas J, Halpern R, Ziehn M, Peterson-Brandt J, Leszko M, Deshpande C. Real-world cost of treatment for multiple sclerosis patients initiating and receiving infused disease-modifying therapies per recommended label in the United States. *J Med Econ*. 2020;23(8):885-893. Doi:10.1080/13696998.2020.1761821[81]	Ocrelizumab Natalizumab Alemtuzumab	-Claims retrospective study -Optum research database 2016-2018 -Patient characteristics assessed -Relapses occurred -Annual real-world costs	N/A	**Primary Cohort:** Ocrelizumab: 123 patients Relapses: 31% Mean Cost: $80,582 Alemtuzumab: 18 patients Relapses: 22% Mean Cost: $121,053 Natalizumab: 48 patients Relapses: 47.9% Mean Cost: $93,807
Abbreviations: DMT: disease modifying therapy; EDSS: expanded disability status scale; ICER: incremental cost effectiveness ratio; RRMS: relapse remitting multiple sclerosis; QALY: quality adjusted life year;				

Table 8: Rituximab Economic Analyses

Search Terms: **Cost effectiveness analysis OR economic AND rituximab AND multiple sclerosis**	**Filters Applied:** **None**	**Search Results :** **16 results; 1 included**		
Study Name	**DMTs Analyzed**	**Methods:** **Study Type/ Data Sources/ Time Horizon**	**Markov Transition & Absorbing States**	**Key Results**
Rezaee M, Morowvat MH, Poursadeghfard M, Radgoudarzi A, Keshavarz K. Cost-effectiveness analysis of rituximab versus natalizumab in patients with relapsing remitting multiple sclerosis. *BMC Health Serv Res*. 2022;22(1):118. Published 2022 Jan 28. Doi:10.1186/s12913-022-07495-4[82]	Rituximab Natalizumab	CEA Markov Model Time Horizon: lifetime Modeled after RRMS treated at MS Unit of University of Medical Sciences in 2020 Direct, indirect costs and utilities assessed	**Cycle Length:** 1 year **Transition States:** 1.EDSS 0-5.5 on DMT 2. EDSS 6-9.5 SPMS 3. Relapse **Absorbing State:** Death	**Base-Case Analysis:** Rituximab dominant to Natalizumab Incremental cost= -$295,867 Incremental QALY= 0.125
Abbreviations: DMT:disease modifying therapy; EDSS: expanded disability status scale; ICER: incremental cost effectiveness ratio; RRMS: relapse remitting multiple sclerosis; QALY: quality adjusted life year;				

Conclusion

Two clinical guidelines, AAN (2018) and CMSC (2019) were reviewed. In summary, both guidelines recommend the tailoring of DMT to patient specific characteristics and preferences. CMSC guidelines refrain from using terms such as “first-line” therapy and state that any DMT can be considered as initial therapy given the appropriate patient circumstances. Both guidelines regard mAb DMT as higher efficacy options and recommend these for patients presenting with highly active RRMS. The risk of PML with natalizumab is recognized in both guidelines, particularly in patients positive for JCV. Suboptimal response to therapy is addressed in both guidelines and shared characteristics include occurrence $\geq$1 relapse or formation of $\geq$2 MRI detected lesions in a one-year period. Six months of therapy is required before suboptimal response can be determined. Patients with criteria meeting suboptimal response should be considered for treatment switching.

A total of 14 studies evaluating efficacy of ocrelizumab, ofatumumab and rituximab were identified which were comprised of clinical trials and subpopulation analyses. Ocrelizumab had the largest number of studies supporting its use in RRMS. While ofatumumab and rituximab had three and four, respectively. Trial lengths ranged from 48-120 weeks (12-30 months) and comparators included placebo, teriflunomide, interferon beta-1a, fingolimod, and dimethyl fumarate. The most common efficacy measures assessed with annualized relapse rate and confirmed disability progression at specified time points. All B-cell DMTs demonstrated superiority to comparators on specified efficacy outcomes. ARRs ranged from 0.13-0.16 (ocrelizumab), 0.09-0.11 (ofatumumab), and 0.18-0.4 (rituximab).

Six NMAs were identified that included either or both ofatumumab and ocrelizumab. Rituximab was not included, likely due to its lack of approval for RRMS as an indication. Efficacy trends were consistent across NMAs, with mAb DMT ranked as the highest efficacy therapies. Oral agents such as fingolimod and dimethyl fumarate were ranked as moderate to high efficacy, while interferon formulations glatiramer acetate were ranked as lower efficacy agents.

Eight economic analyses were found for B-cell DMTs; however, rituximab was not compared against ofatumumab or ocrelizumab. All studies, except one, performed the economic analyses using a Markov model. Model structures were similar between analyses and based transition states on EDSS levels, relapses, and discontinuation. Death served as the primary absorbing state across studies. Time horizons ranged from 10 to 65 years, with the majority assuming a lifetime perspective, despite using clinical data that was collected for at most 30 months. Data sources utilized included clinical trials and NMAs. B-cell DMTs were found to be the most cost-effective option in five of the seven studies. Major limitations of economic analyses included short-term data (24-30 months) extrapolated to long-term outcomes (20 years-life) and handling of discontinuation/treatment switching. Patients reaching higher EDSS (>7) were often discontinued from therapy due to disability progression to a point where clinical intervention would usually occur. While this was reflective of real-life practices, relapses were allowed to continually occur throughout all models. This approach is contradictory to guidelines recommendations for suboptimal response and likely unreflective of real-world practices.

This review of the literature provides evidence of B-cell mAbs being amongst the highest efficacy DMTs available. While economic analyses exist, none have compared all three B-cell DMTs to one another. Preliminary evidence from these economic studies suggests that B-cell DMTs may be cost effective options, but limitations in methodology surrounding extrapolation of short term data to long-term outcomes and handling of treatment discontinuation due to suboptimal response detract from real-world application.

CHAPTER 3: METHODS

Introduction

Previous chapters have described the available disease modifying therapy (DMT) options for management of relapsing remitting multiple sclerosis (RRMS) as well as multiple sclerosis (MS) guidelines, clinical trials and previously conducted economic analyses of B-cell DMTs in MS. This chapter describes the methods used to conduct the proposed research.

Study Design

A cost-effectiveness analysis (CEA) will be conducted for the B-cell DMTs, ocrelizumab, ofatumumab, and rituximab versus the commonly utilized interferon beta-1a subcutaneous injection. A Markov model constructed in Excel will be utilized to model a population of patients with RRMS over a five-year period. Unlike previously reported or published CEAs of DMTs, the time frame used in this study is intentionally shorter in order to avoid over-extrapolating efficacy data from clinical trials due to concerns of waning treatment efficacy. The lengths of B-cell DMT clinical trials reported in the literature ranged from 1-2.5 years. Reducing the time over which results from the clinical trials are extrapolated may reduce the degree to which extrapolation assumptions influence CEA findings. Additionally, results of previously published lifetime economic studies may not be applicable to commercial payers and decision makers who generally provide coverage to patients for much shorter periods of time and therefore, may be concerned with near-future economic impacts. This CEA will assume a societal perspective and assess both direct and indirect costs. Incremental cost-effective ratios (ICERs) will be calculated and reported as total cost per suboptimal response avoided (relapse, severe disability, death, and severe adverse event).

Markov Model Structure

Figure 5 provides a visual representation of the Markov model. The two main categories of health states are: “On-DMT” and “Off-DMT.” Within these, specific health states will be structured based on the expanded disability scale (EDSS). Upon entering the model, all patients will be placed into the “On-DMT” category and distributed among EDSS levels 0-5 in a manner reflective of clinical trial demographics. Cycle lengths will be one year,

consistent with previously conducted economic analyses. In each one-year cycle, patients may remain at the same EDSS level or progress to a higher EDSS level. Regression to a lower disability state is not included as a possibility in the model. As the majority of clinical trials excluded patients with EDSS levels of ≥6 and efficacy data of B-cell DMT in these higher disability states of ≥6 is not well defined, patients reaching EDSS levels 6-9 (severe disability) will be discontinued from the treatment due to suboptimal response as modeled in previous economic analyses.[75-82] Patients will enter the Markov health state of "Off-DMT" after EDSS ≥6 is reached and will continue to transition through EDSS levels for the remaining model cycles. The occurrence of a single severe adverse event or relapse will also result in patient discontinuation to the "Off-DMT" health state. Death (EDSS 10) will serve as the absorbing state.

In order to reflect the clinical guidelines and real-world clinical practice, suboptimal response to DMT is defined as i) occurrence of a relapse over a 1-year period (cycle) or ii) progression into EDSS ≥6. As stated previously, rather than allow for continued relapses, patients will transition to the "Off-DMT" health state. In the "Off-DMT" health state patients may progress to a higher EDSS level, experience a relapse, or die. Since there is no treatment to switch off from in the "Off-DMT" health state, relapses and disability progression will occur continuously until the end of the time horizon. Costs that occur related to progression, relapse, adverse event and death will be quantified for both "On-DMT' and "Off-DMT" health states. The purpose of incorporating an "Off-DMT" health state category is to quantify events and costs associated with switching off of the DMTs of interest due to suboptimal response. Without this health state, patients that remained on therapy would inevitably accrue more costs than those who had a suboptimal response and exited the model, presenting an unrealistic scenario and potentially biasing the final results to favor treatments that result in higher numbers of patients exiting the model.

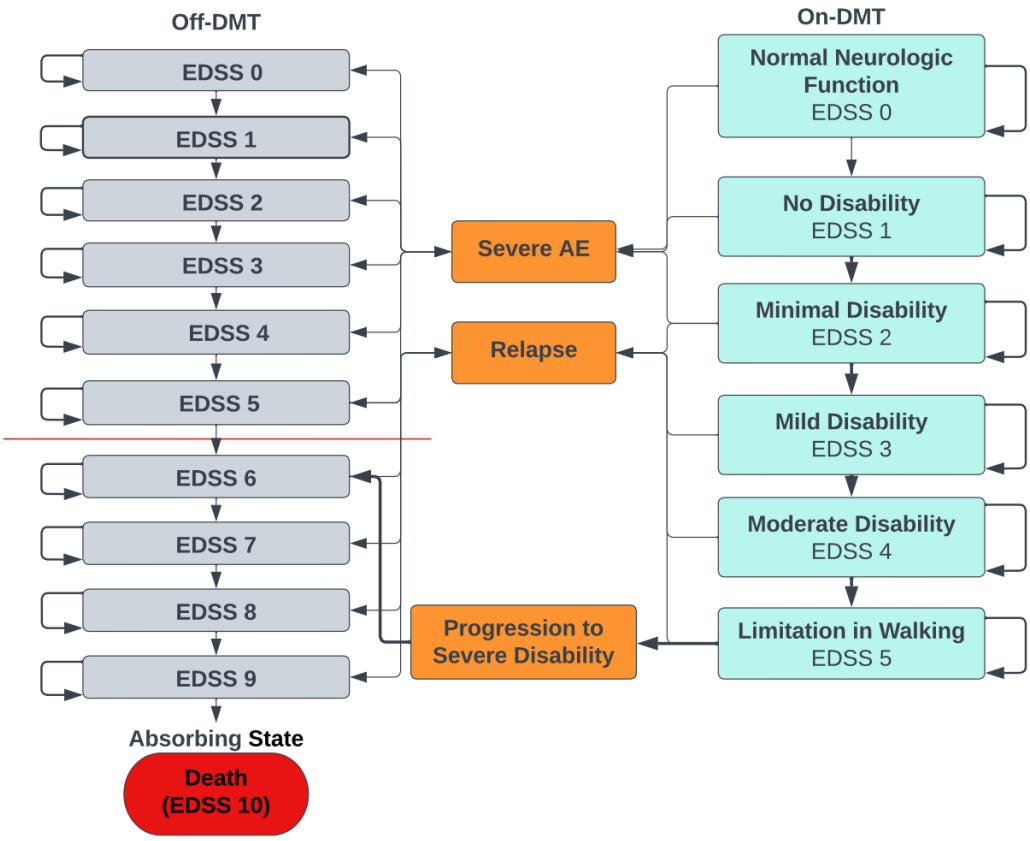


Figure 5: Markov Model Structure

EDSS: expanded disability status scale.

Intervention

Four medication treatment scenarios/model iterations will be performed based on the FDA approved dosages or in the case of rituximab, from clinical trials. In each, patients will be initiated on either ocrelizumab 600mg six-month infusions, rituximab 1,000mg six-month infusions, ofatumumab 20mg monthly subcutaneous injections or interferon-beta 1a subcutaneous injections (rebif) 44 mcg three times weekly. While a once weekly intramuscular formulation of interferon beta-1a is available, OPERA 1&2 trials used the subcutaneous formulation as the comparator.[40] It will be assumed that in a single cycle, patients will receive: two doses of ocrelizumab or rituximab, 12 doses of ofatumumab and 156 doses of interferon-beta 1a. Loading doses at treatment initiation will not be modeled.

Base Case Analysis

A population of 1,000 patients will be simulated through the Markov model. In the base case analysis, patients entering the "On-DMT" health states will be distributed across EDSS levels. The reported baseline EDSS distributions of patients in the clinical trials for ocrelizumab, ofatumumab and rituximab will be averaged to determine the initial starting distributions for the model. Other patient characteristics such as age and sex will also be determined by the averages across clinical trials.

For patients in the "On-DMT" health states, probability of transition to higher EDSS state will be based on the confirmed disability progression (CDP) hazard ratios (HR), reported in a network meta-analysis by Samjoo et al., that are then applied to natural history progression data.[45] The CDP HRs from the network meta-analysis are being used as they provide an estimate of the respective DMT's efficacy against placebo, whereas HRs from the respective DMT clinical trials were calculated against active comparators. Since rituximab was not included in the network meta-analysis, it's CDP HR was estimated by comparing the average difference between the other DMTs' HRs from clinical trials (against active comparators) to HRs from the network meta-analyses (calculated against placebo). HRs of B-cell DMTs against active comparators ranged from 0.60 (ocrelizumab) to 0.68 (rituximab). In network meta-analyses, HRs calculated for ocrelizumab and ofatumumab against placebo were 0.43 to 0.47 respectively, corresponding to an average difference of 0.18 from HRs calculated against active comparators. Therefore, applying this 0.18 reduction to rituximab's HR of 0.68 (calculated against dimethyl fumarate), the HR estimation of 0.51 against placebo was determined. Natural history data on disease progression was obtained from a 2013 analysis of MS patients in the British Columbia Multiple Sclerosis (BCMS) database from 1980–1995 (see Table 9).[83] For those that transition to "Off-DMT" health states, the probability of continued progression through EDSS levels will be based on the natural history progression rates alone.

Annualized relapse rates (ARR) from OPERA (ocrelizumab), ASCELPIOS (ofatumumab) and rituximab clinical trials will be used to determine the occurrence of relapses for patients

within "On-DMT" health states by multiplying the relapse rate by the number of patients alive in each cycle as seen in Espinoza et al.[79] Based on published data on relapse severity, three levels of relapses are modeled: severe requiring hospitalization (21%), moderate requiring an emergency department visit (46%), and mild only requiring outpatient management (33%).[84] As stated previously, the occurrence of a single relapse will transition the patient to the "Off-DMT" health states. Once a patient reaches the "Off-DMT" health state, relapses can occur continuously but at a maximum rate (based on natural history relapse rate data) of one relapse per cycle.[85]

The rates of severe adverse events leading to treatment discontinuation as reported in the ocrelizumab, ofatumumab, and rituximab clinical trials are used to model patients that exit the "On-DMT" treatment states due to adverse events. Other adverse events, that may necessitate treatment but may not lead to DMT discontinuation, such as mild to moderate infections or infusion reactions are not modeled as there is a paucity of data quantifying how often such events would reoccur over a set time frame, and these are expected to have minimal impact on the overall cost estimates for the MS treatments. Mortality will be modeled by applying MS specific mortality multipliers obtained from literature to the death rate for the overall US population in 2021 (see Table 10). [77,85]

Table 9: EDSS Transition Rates

	To EDSS									
From EDSS	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
0	0.69537	0.20294	0.07251	0.0217	0.00422	0.00137	0.00175	0.00011	0.00003	0
1	0.05826	0.69501	0.15783	0.06088	0.01638	0.00458	0.00643	0.00048	0.00013	0.00001
2	0.01586	0.12133	0.60789	0.16796	0.04458	0.01849	0.02159	0.00174	0.00052	0.00004
3	0.00594	0.0496	0.12006	0.54422	0.09109	0.05845	0.11649	0.013	0.00355	0.0003
4	0.00165	0.02214	0.0666	0.11519	0.48935	0.10388	0.16811	0.0258	0.00671	0.00056
5	0.00052	0.00533	0.02942	0.05866	0.08736	0.48695	0.2731	0.0388	0.01883	0.00102
6	0.00012	0.00133	0.00444	0.02497	0.03069	0.0408	0.74069	0.10897	0.04377	0.00423
7	0.00001	0.00015	0.00052	0.00247	0.00727	0.00385	0.11684	0.69269	0.16061	0.01559
8	0	0.00001	0.00004	0.00029	0.00055	0.0005	0.01881	0.05574	0.9034	0.02066
9	0	0	0	0.00002	0.00004	0.00003	0.00176	0.00568	0.17414	0.81832

Palace J, Bregenzer T, Tremlett H, et al. UK multiple sclerosis risk-sharing scheme: a new natural history dataset and an improved Markov model. BMJ Open. 2014;4(1):e004073. doi:10.1136/bmjopen-2013-004073[83]

Table 10: MS specific Mortality Rates

	Value	Source
US 2022 Mortality Rate per 1,000	0.84%	[85]
MS Specific Mortality Rate		
EDSS 0	0.0084	[77,85]
EDSS 1	0.012	[77, 86]
EDSS 2	0.013	[77, 86]
EDSS 3	0.014	[77, 86]
EDSS 4	0.014	[77, 86]
EDSS 5	0.015	[77, 86]
EDSS 6	0.019	[77, 86]
EDSS 7	0.026	[77, 86]
EDSS 8	0.037	[77, 86]
EDSS 9	0.054	[77, 86]

Direct Medical Costs

DMT treatment costs are based on wholesale acquisition cost (WAC) drug costs obtained from Micromedex Redbook database. Infusion costs for ocrelizumab and rituximab are based on the CMS physician fee schedule. Annual drug costs will be applied each cycle that a patient remains in an "On-DMT" health state. Costs for healthcare utilization (office visits, MRIs) are based on published cost data and are stratified based on a patient's EDSS level.[86] Higher EDSS levels are associated with higher utilization costs. Each cycle, EDSS level specific healthcare utilization costs will be applied. Relapses experienced will be weighted by their severity as discussed above and the corresponding management costs by severity level obtained from literature will be applied.[84,87]. In order to quantify the cost of severe adverse event management, the most common types of severe adverse events (severe infections, severe infusion reactions) and their associated treatment costs were identified. The final overall cost associated with a severe adverse event leading to discontinuation was weighted by the probabilities of occurrence of the types of severe adverse events and their respective average costs of management. [88–91]

Indirect Medical Costs

Missed-work time and unemployment due to MS will be estimated for each EDSS level .[86] The percentage of missed-work time will be multiplied by the average annual earnings for patients based on their age. Therefore, this value will represent pay the patient did not receive due to missed work time associated with their EDSS level. An MS-specific unemployment rate is used to determine how many patients will not receive the entire average annual earnings for that given cycle. For EDSS levels <3, due to the minimal disability present at these levels, the unemployment rate is equal to that of the national unemployment rate.[92] Higher EDSS levels are associated with higher missed-work times and unemployment rates.

Each relapse experienced will have an associated missed-work time applied and lost earnings will be quantified using the methods described above. Early mortality due to MS will be quantified by a patient's remaining lifetime productivity based on age at death. Estimates of annual earnings and remaining lifetime productivity will be obtained from literature.[93]

Table 11 provides a summary of base case parameters and costs. All costs will be standardized to US 2022 values using the annual Medical Consumer Price Index (M-CPI).[94]

Table 11: Model Parameters and Costs

Health State Parameter	Value	Source	Cost Parameter	Value	Source
Mean Age	37	[40,41,70,72]	Annual DMT Costs		
Female Sex	65%	[40,41,70,72]	Ocrelizumab	$75,100	[23,95]
Male Sex	35%	[40,41,70,72]	Ofatumumab	$91,548	[23]
EDSS Initial Distribution			Rituximab	$19,106	[23,95]
EDSS 0	3%	[40,41,70,72]	IFN-B1a	$110,748	[23]
EDSS 1	18%	[40,41,70,72]	Relapse Management Costs		
EDSS 2	31%	[40,41,70,72]	Severe	$25,866	[87]
EDSS 3	24%	[40,41,70,72]	Moderate	$2,306	[87]
EDSS 4	17%	[40,41,70,72]	Mild	$488	[87]
EDSS 5	7%	[40,41,70,72]	Worktime Missed Cost	$2,196	[86]
Annualized Relapse Rate			Adverse Event Costs (weighted)		
Ocrelizumab	0.16	[40]	Ocrelizumab	$1,647	[88–91]
Ofatumumab	0.11	[41]	Ofatumumab	$1,163	[88–91]
Rituximab	0.18	[72]	Rituximab	$1,663	[88–91]
IFN-B1a	0.29	[40]	IFN-B1a	$2,734	[88–91]
Off-treatment	0.54	[96]	Healthcare Utilization Costs		
Relapse Severity			EDSS < 3	$4,000	[86]
Severe	21%	[84]	EDSS 3-5	$10,937	[86]
Moderate	46%	[84]	EDSS >5	$20,963	[86]
Mild	33%	[84]	EDSS Missed Work Costs		
Confirmed Disability Progression HR			EDSS 3-5	$2,881	[86]
Ocrelizumab	0.47	[45]	EDSS > 5	$1,235	[86]
Ofatumumab	0.43	[45]	EDSS Unemployment		
Rituximab	0.51	[45]	EDSS <3	3.7%	[92]
IFN-B1a	0.77	[45]	EDSS 3-5	9.6%	[86,92]
Adverse Events Leading to DC Rate			EDSS >5	38.5%	[86,92]
Ocrelizumab	3.50%	[40]	Annual Earning Age Group	$68,616	[93]
Ofatumumab	5.7%	[41]	Remaining Productivity	$2,705,395	[93]
Rituximab	3.0%	[72]			
IFN-B1a	6.0%	[40]			

Abbreviations: DC: Discontinuation; EDSS: expanded disability status scale; HR: Hazard ratio; IFN-B1a: Interferon Beta-1a

Outcomes of interest

Outcomes of interest will include comparisons of both clinical and economic endpoints between B-cell DMTs and interferon beta-1a. Clinical outcomes include i) the number of patients within each EDSS level <6 after 5 years, and ii) the number of patients that discontinued due to disability progression to EDSS $\geq$6, adverse events, relapses, and death after 5 years. Economic outcomes include total costs between treatment options with costs reported by sub-type (direct, indirect, EDSS associated, relapse associated, etc.). Incremental cost-effective ratios (ICERs) will be calculated and reported as total cost per suboptimal

response avoided (i.e., relapse, EDSS ≥6, death, and severe adverse event avoided). Suboptimal response corresponds directly to the number of patients remaining in the model after 5 years. A cost effectiveness threshold of $138,576 per suboptimal response avoided will be utilized – a value that is twice the 2021 US per capita GDP ($69,288), based on the 2001 recommendations from the World Health Organization.[60]

Sensitivity Analyses

One-way sensitivity analyses will vary annualized relapse rates and confirmed disability hazard ratios to determine what efficacy difference is needed between agents to establish cost effectiveness/dominance over one another. Upper and lower estimates of ARR and CDP will be based on the bounds of the confidence intervals reported in the network meta-analyses and clinical trials. For rituximab, the ARR in the phase 2 trial was 0.4 which varies considerably from the rates in Phase 1 & 3 trials of 0.18 and 0.19, respectively. Therefore, to assess the impact of ARR clinical trial variability on results, 0.4 was used as the ARR upper estimate in the sensitivity analyses. Table 12 provides the ARR and CDP parameters used in the sensitivity analyses. DMT WAC prices will be discounted by 25%, 50% and 75% to model the impact of DMT cost reductions that may occur as a result of varying market prices or biosimilar/generic formulation releases. If a particular DMT is not cost effective in the base case analysis, the exact drug cost discount required to reach the cost effectiveness threshold will be calculated. Variation of the key parameters will allow for improved estimation of DMT's efficacy in a simulated population.

Table 12: Sensitivity Analyses Parameters

	Ocrelizumab	Source	Ofatumumab	Source	Rituximab	Source	IFN-B1a	Source
HR CDP Lower Estimate	0.25	[45]	0.33	[45]	0.41	[45]	0.48	[45]
HR CDP Mean (Base Case)	0.47	[45]	0.43	[45]	0.51	[45]	0.77	[45]
HR CDP Higher Estimate	0.89	[45]	0.86	[45]	0.90	[45]	1.30	[45]
ARR Higher Estimate	0.20	[40]	0.14	[41]	0.40	[70]	0.36	[40]
ARR Mean (Base Case)	0.16	[40]	0.11	[41]	0.18	[72]	0.29	[40]
ARR Lower Estimate	0.12	[40]	0.09	[41]	0.11	[72]	0.23	[40]
Acronyms: ARR: annualized relapse rate; CDP: confirmed disability progression; HR: hazard ratio								

Limitations

The use of a Markov model presents certain limitations. Health states of Markov models are considered to be "memory less" meaning that events in prior cycles have no influence on the probability of events in the current one. Certainly, in a real patient cohort, past events have the potential to influence future ones. Given the heterogeneity of RRMS, some patients would likely progress through EDSS states at faster rates than others based on disease activity. Only the average disability progression/relapse rates across a population are modeled here.

DMT adherence within this study is assumed to be 100%. In reality, adherence to DMT is known to be suboptimal, yet data surrounding the impacts of poor adherence on DMT efficacy is lacking. Though the structure of this CEA attempts to model suboptimal response in a manner more reflective of clinical practice than previous analyses, guidelines do recommend that adherence to DMT be assessed before definitively establishing efficacy of DMT is reduced and switching to an alternative treatment. Additionally, differences in adherence based on administration route may exist. Patients living in rural areas may miss infusion appointments due to lack of transportation, while patients with needle phobia may

purposely miss doses of injectable at home therapies. These potential differences are not captured within this analysis.

Lastly, switching between DMTs is not modeled. In reality, after discontinuation of one DMT patients would likely switch to an agent possessing a different mechanism of action per guideline recommendations. The impact of treatment switching on costs and health outcomes is not assessed within this study.

Conclusion

This chapter presented the methods of conducting a CEA on ocrelizumab, ofatumumab, rituximab and interferon beta-1a in patients with RRMS. A Markov model is constructed for a theoretical cohort of 1,000 patients (approximately the number of patients with MS within the US). Health states are structured by EDSS levels with each state corresponding to an EDSS level 0-5. EDSS levels 6-9 are grouped together and categorized as significant disability. Patients exit the model/discontinue treatment if they reach an EDSS $\geq$6 or experience a relapse, severe adverse event or death. Suboptimal response to treatment is defined as occurrence of a relapse or disability progression of $\geq$6 on EDSS. The analysis occurs over a 5-year period with 1-year cycles. ARR and CDP data from clinical trials are applied directly to trial participants or to natural history data. This CEA takes a societal perspective and include both direct and indirect costs. ICERs are calculated for cost per suboptimal response/disease breakthrough avoided.

CHAPTER 4: RESULTS

Introduction

The previous chapters have described the context, justification**,** and methods by which this study, a cost-effectiveness analysis of the monoclonal B-cell disease modifying therapies (DMT) has been conducted. In this chapter the results of this analysis are detailed beginning with the base case analysis and then proceeding to the results of the sensitivity analysis.

Base-Case Analysis

Clinical Outcomes

In the base case analysis, the monoclonal antibodies (mAb) ocrelizumab, ofatumumab or rituximab resulted in more patients remaining on therapy at the end of the 5-year period compared to interferon beta-1a (IFN-B1a). The results of the model indicated that ofatumumab (a once monthly self-injection) had the most patients, n=338, remaining on therapy compared to interferon beta-1a (a three-time weekly injection) with only 78 patients at the end of year 5. The mean difference in patients remaining on therapy between the B-cell mAB and IFN-1BA was 211. Figure 6 provides the trends for patients remaining on therapy throughout the model. Remaining on therapy translates the avoidance of relapses, severe adverse events, progression to severe disability (EDSS >5) or death. At initiation of the model, EDSS levels 2 and 3 had the highest percent distribution of patients at 31% and 24% respectively. By year 5, there was a shift towards higher EDSS levels, particularly for patients that received IFN-B1a. Fewer of the patient's receiving B-cell DMTs (~10.7%) progressed to severe disability levels (EDSS >5) by the end of the 5-year model compared to those treated with IFN-B1a (16.7%). Table 13 provides the distribution of patients by EDSS level from the start of the model to year 5.

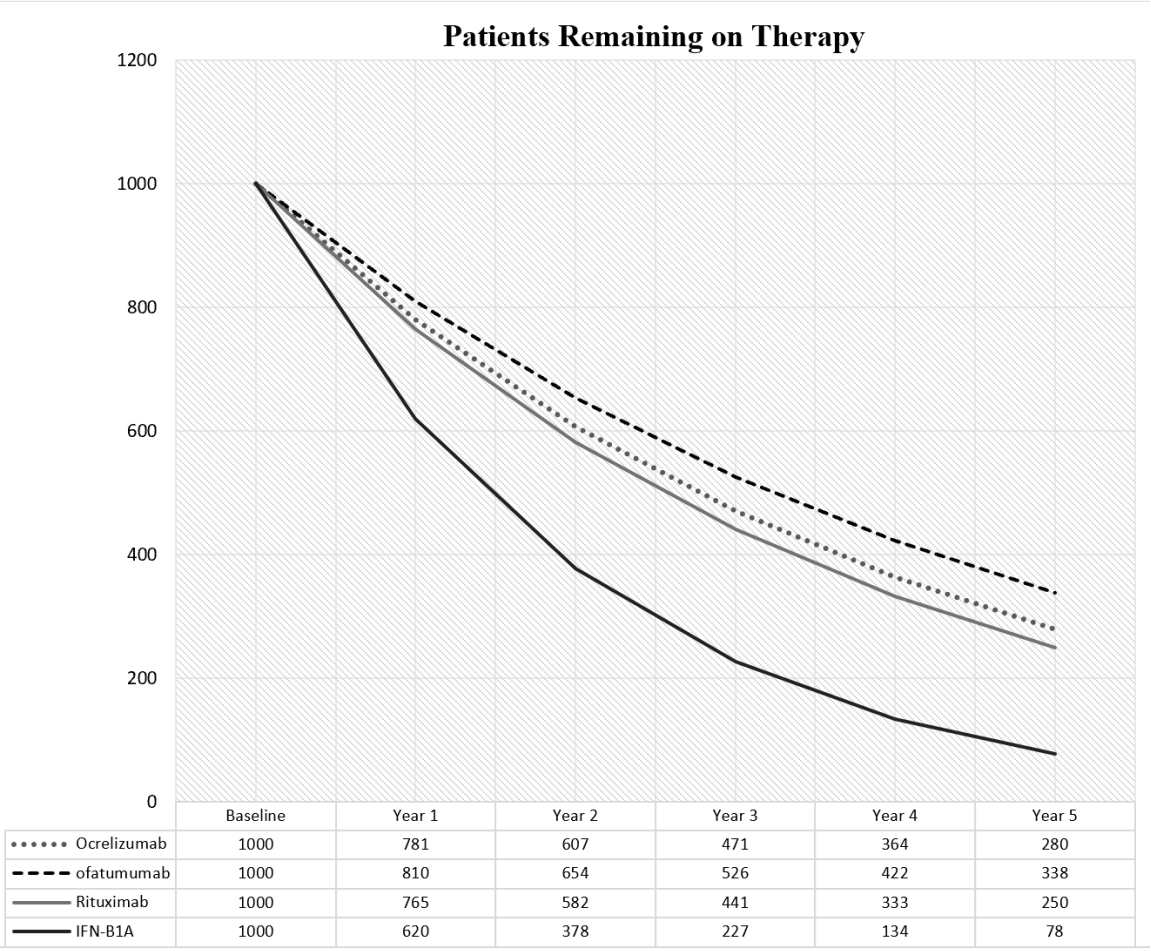


Figure 6: Patients Remaining on Therapy in Base Case Analysis

Table 13: Distribution Across Expanded Disability Status Scale (EDSS) Levels by Year 5

	Initial Distribution	**Year 5 Distribution**			
	All Treatments	**OCR**	**OFA**	**RITUX**	**IFN-B1a**
EDSS 0	3.0%	1.1%	1.13%	0.9%	0.6%
EDSS 1	18.0%	9.3%	9.5%	8.5%	6.5%
EDSS 2	31.0%	20.6%	21.0%	19.6%	16.4%
EDSS 3	24.0%	23.7%	23.1%	23.3%	21.8%
EDSS 4	17.0%	20.8%	21.1%	21.0%	21.4%
EDSS 5	7.0%	14.2%	14.3%	14.9%	16.6%
EDSS 6	0%	8.2%	8.0%	9.4%	13.1%
EDSS 7	0%	2.0%	2.0%	2.0%	3.0%
EDSS 8	0%	0.3%	0.29%	0.4%	0.5%
EDSS 9	0%	<0.1%	<0.1%	<0.1%	<0.1%

Abbreviations: IFN-B1a: Interferon-Beta 1a; OCR: ocrelizumab; OFA: ofatumumab; RITUX: rituximab

*Percents are based on the number of patients alive and remaining in model (approximately 933 by the end of year 5).

*For EDSS levels 0-5, percents shown comprise patients both on DMT & off DMT.

In total, ofatumumab had the fewest number of relapses (533) amongst the treatment groups, but also the highest number of adverse events (195) during the 5-year period. There are several potential reasons for the higher number of adverse events observed in the ofatumumab group. In clinical trials, a higher percentage of patients (5.7%) receiving ofatumumab experienced an adverse event leading to discontinuation in comparison to ocrelizumab (3.5%) and rituximab (3.0%).[40–42] Additionally, more patients remaining on therapy (due to fewer relapses and lower severe disability progression) within the ofatumumab group places them at continued risk for adverse events which likely accounts for the differences observed between ofatumumab and IFN-B1a. IFN-B1a had the highest adverse event rate leading to a 6% discontinuation rate in clinical trials with a large proportion of patients (89%) experiencing injection related reactions. This value is considerably higher than the percentage of injection/infusion related reactions seen with ofatumumab at 24%.[41,97] However, the number of patients remaining on IFN-B1a and at risk for adverse events was greatly reduced by the greater occurrence of relapses and severe disability progression. The number of deaths that occurred were consistent across treatment groups as the MS specific mortality multiplier was based on EDSS level and not the treatment itself. Table 14 presents the clinical outcomes at the end of the 5-year model period.

Table 14: 5-Year Clinical Outcomes from Markov Model (Base case analysis)

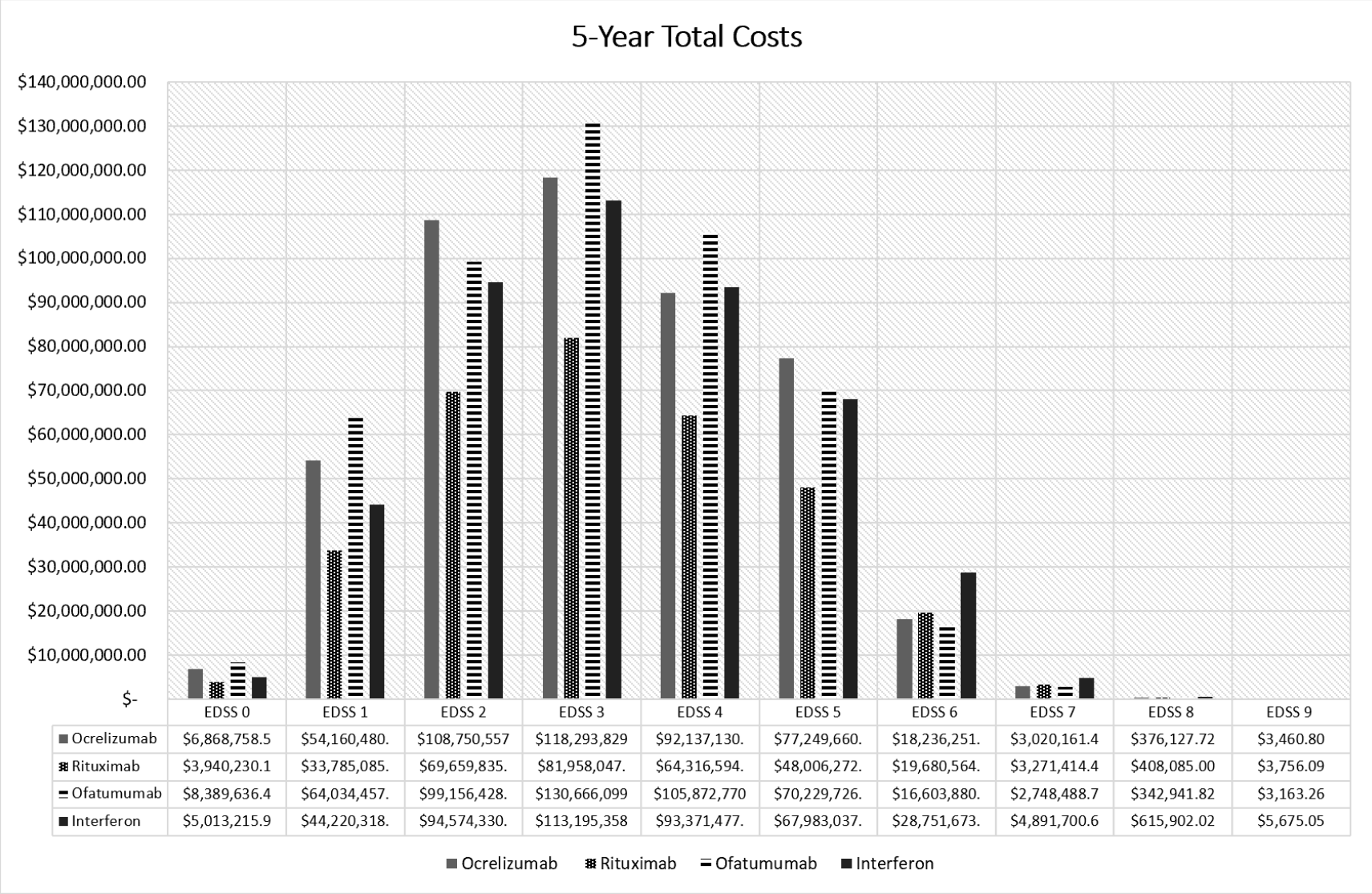
	Ocrelizumab	**Ofatumumab**	**Rituximab**	**IFN-B1a**
Remaining on Therapy	280	338	250	78
Total progressing to severe disability	103	93	110	156
Total Deaths	67	67	67	68
Total Relapses	575	533	752	972
Total Adverse Events	113	195	94	140
Abbreviations: IFN-B1a: Interferon Beta-1a				

* Total relapses and deaths are comprised of results from both on-DMT and off-DMT groups.

Costs

The 5-year total costs (direct and indirect) ranged from $3.2 million (rituximab) to $4.97 million (ofatumumab). Indirect costs comprised a range of 41% to 77% of the total costs across EDSS levels and treatment groups. In general, lower EDSS levels were associated with lower indirect costs. Figure 7 shows the distribution of total costs amongst the EDSS levels by the end of year 5. EDSS 3 was associated with the highest costs due to the number of patients within this disability level at the model's end. Table 15 shows the 5-year cost and incremental cost-effectiveness ratio (ICER) results for the base case analysis. Rituximab was first-order dominant over IFN-B1a and resulted in cost savings of $740,555 in the base case analysis as it was less costly and more effective at retaining patients on therapy than IFN-B1a. Ocrelizumab was both more expensive and more effective than IFN-B1a and generated an ICER of $133,373 in the base case analysis which is below the cost effectiveness threshold.

Despite ofatumumab's superior efficacy in retaining patients over IFN-B1a, its current cost generated an ICER for ofatumumab compared to IFN-B1a of $175,591 which is $37,000 greater than the cost-effectiveness threshold of $138,576. Average annual per person total & direct costs were highest for ofatumumab and lowest for rituximab. Per person costs were calculated by dividing total costs by the number of patients alive by the end of the model. Figure 8 shows the relationship between total costs and patients remaining on the respective disease modifying therapy (DMT) compared in the study.



	EDSS 0	EDSS 1	EDSS 2	EDSS 3	EDSS 4	EDSS 5	EDSS 6	EDSS 7	EDSS 8	EDSS 9
Ocrelizumab	$6,868,758.5	$54,160,480.	$108,750,557	$118,293,829	$92,137,130.	$77,249,660.	$18,236,251.	$3,020,161.4	$376,127.72	$3,460.80
Rituximab	$3,940,230.1	$33,785,085.	$69,659,835.	$81,958,047.	$64,316,594.	$48,006,272.	$19,680,564.	$3,271,414.4	$408,085.00	$3,756.09
Ofatumumab	$8,389,636.4	$64,034,457.	$99,156,428.	$130,666,099	$105,872,770	$70,229,726.	$16,603,880.	$2,748,488.7	$342,941.82	$3,163.26
Interferon	$5,013,215.9	$44,220,318.	$94,574,330.	$113,195,358	$93,371,477.	$67,983,037.	$28,751,673.	$4,891,700.6	$615,902.02	$5,675.05

Figure 7: Five Year Total Costs by EDSS Level in Base Case Analysis

Table 15: 5-Year Cost Outcomes and ICERS from Markov Model (Base Case Analysis)

Base-Case Analysis	**Ocrelizumab**	**Ofatumumab**	**Rituximab**	**IFN-B1a**
5yr Total Cost	$479,096,418	$497,827,017	$324,737,062	$452,213,573
Average Annual Per Person Total Cost	$97,120	$100,918	$65,830	$91,671
5yr Direct Cost	$252,359,363	$273,714,138	$98,158,872	$218,463,165
Average Annual Per Person Direct Cost	$51,157	$55,486	$19,898	$44,286
Remaining on Therapy	280	338	250	78
ICER*	$133,373	$175,591	DOMINATES	
Abbreviations: ICER: incremental cost effectiveness ratio; IFN-B1a: interferon beta-1a; YR: year				

*ICER is calculated between drug listed and interferon beta-1a

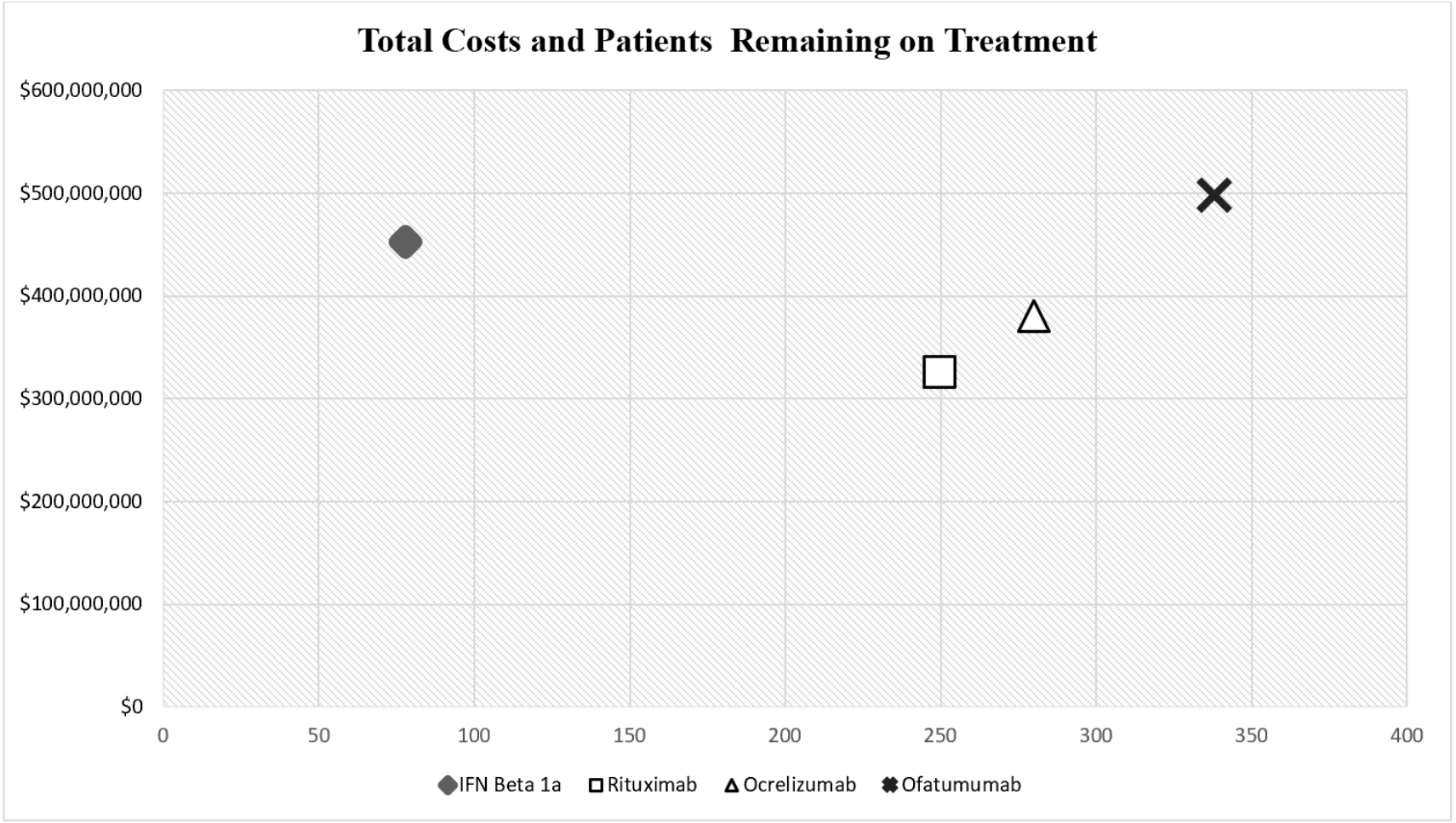


Figure 8: Total Costs in Comparison to Patients Remaining on Treatment

Sensitivity Analyses

One-way sensitivity analyses were performed on the annualized relapse rates (ARR), confirmed disability progression (CDP) effects, and on the treatment costs. ARR and CDP at lower rates resulted in more patients remaining on treatment by the end of the model. ARR reduction had a more profound impact on patient retainment with a mean increase of 79 patients versus CDP reduction with a mean increase of 11 patients beyond the base case analysis. Figure 9 presents the number of patients remaining on therapy at model end by the sensitivity analysis and DMT.

Table 16 and 17 show the results of the sensitivity analyses in comparison to the base case analysis. IFN-B1a is presented separately in table 14 to more clearly present the impact of varying IFN-B1a parameters on the ICER against the DMTs of interest (while leaving the other DMT values unaltered).

Reduction of drug costs had the largest impact on the ICERs across all treatment groups. Focusing specifically on ofatumumab, the only B-cell DMT that did not meet the cost effectiveness threshold in comparison to IFN-B1a in the base case analysis, a 5% reduction in annual drug acquisition costs would reduce the ICER to $136,200—a value that is below the cost-effectiveness threshold. At a 25% reduction, ofatumumab would be a dominant therapy with a cost savings compared to IFN B1a of $218,323. Similarly, a 25% cost reduction of ocrelizumab would generate a cost savings of $113,039. Increased cost savings was observed across all DMTs analyzed in response to drug cost reductions.

The current drug acquisition cost of the DMTs influenced the results observed for the other sensitivity analyses. ARR and CDPs varied to higher rates (more relapses/disability progression) resulted in lower ICERs than base case analysis. Since relapses and progression to severe disability resulted in treatment discontinuation, it was more cost effective when these events/treatment discontinuations occurred at higher rates than to continue receiving the treatment for longer periods of time. Figures 10-12visually present the ICERs generated by the sensitivity analyses in comparison to the base case.

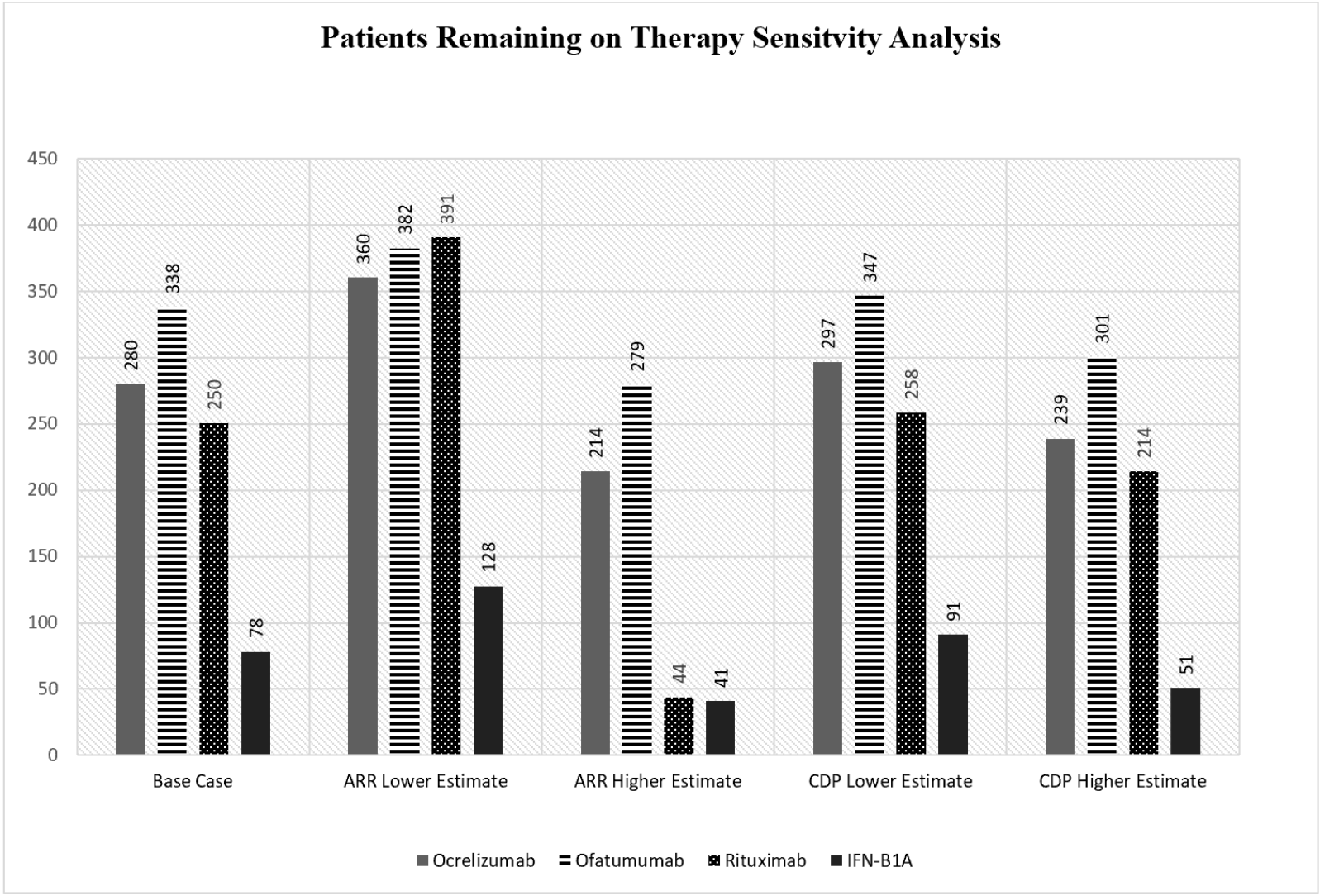


Figure 9: Patients Remaining Therapy in Sensitivity Analyses

Table 17: ICER Results of Sensitivity Analyses

	Ocrelizumab			Ofatumumab			Rituximab		
	5yr Total Cost	ROT	ICER*	5yr Total Cost	ROT	ICER*	5yr Total Cost	ROT	ICER*
Base Case	$ 380,185,325	280	$133,373	$ 497,827,017	338	$ 175,591	$ 324,737,062	250	DOMINATES
ARR Lower Estimate	$ 391,596,495	360	$184,580	$ 510,388,384	382	$ 191,262	$ 330,889,874	391	DOMINATES
ARR Higher Estimate	$ 370,048,492	214	$32,916	$ 480,251,766	279	$ 139,506	$ 311,910,302	44	$ 4,096,780
CDP Lower Estimate	$ 377,478,520	297	$124,071	$ 497,456,668	347	$ 168,636	$ 322,523,474	258	DOMINATES
CDP Higher Estimate	$ 385,080,102	239	$157,162	$ 499,985,699	301	$ 214,957	$ 333,538,970	214	DOMINATES
Drug Cost 25% Reduced	$ 355,141,428	280	DOMINATES	$ 446,663,291	338	DOMINATES	$ 313,407,523	250	DOMINATES
Drug Cost 50% Reduced	$ 330,097,531	280	DOMINATES	$ 395,499,565	338	DOMINATES	$ 302,077,985	250	DOMINATES
Drug Cost 75% Reduced	$ 305,053,633	280	DOMINATES	$ 344,335,839	338	DOMINATES	$ 290,748,447	250	DOMINATES

Acronyms: ARR: annualized relapse rate; CDP: confirmed disability progression; ICER: incremental cost effectiveness ratio; ROT: remaining on treatment
*ICER is calculated between drug listed and interferon beta-1a

Table 16: IFN-B1a Impact on ICER Results in Sensitivity Analyses

	IFN-B1a		OCR vs IFN-B1a			OFA vs. IFN-B1a			Rituximab vs. IFN-B1a		
	5yr Total Cost	**ROT**	**5yr Total Cost**	**ROT**	**ICER Impact**	**5yr Total Cost**	**ROT**	**ICER Impact**	**5yr Total Cost**	**ROT**	**ICER Impact**
Base Case	$ 452,213,573	78	$380,185,325	280	$ 133,373	$497,827,017	338	$ 175,591	$ 324,737,062	250	DOMINATES
ARR Lower Estimate	$ 485,665,133	128	$380,185,325	280	DOMINATES	$497,827,017	338	$ 57,785	$ 324,737,062	250	DOMINATES
ARR Higher Estimate	$ 420,021,742	41	$380,185,325	280	$ 247,529	$497,827,017	338	$ 262,088	$ 324,737,062	250	DOMINATES
CDP Lower Estimate	$ 451,812,325	91	$380,185,325	280	$ 144,374	$497,827,017	338	$ 186,150	$ 324,737,062	250	DOMINATES
CDP Higher Estimate	$ 451,251,187	51	$380,185,325	280	$ 121,518	$497,827,017	338	$ 162,085	$ 324,737,062	250	DOMINATES
Drug Cost 25% Red.	$ 412,437,273	78	$380,185,325	280	$ 330,714	$497,827,017	338	$ 328,712	$ 324,737,062	250	DOMINATES
Drug Cost 50% Red.	$ 372,660,974	78	$380,185,325	280	$ 528,055	$497,827,017	338	$ 481,832	$ 324,737,062	250	DOMINATES
Drug Cost 75% Red.	$ 332,884,674	78	$380,185,325	280	$ 725,396	$497,827,017	338	$ 634,953	$ 324,737,062	250	DOMINATES

Acronyms: ARR: annualized relapse rate; CDP: confirmed disability progression; ICER: incremental cost effectiveness ratio; IFN-B1a: interferon-beta 1a; ROT: remaining on treatment; RED: reduced

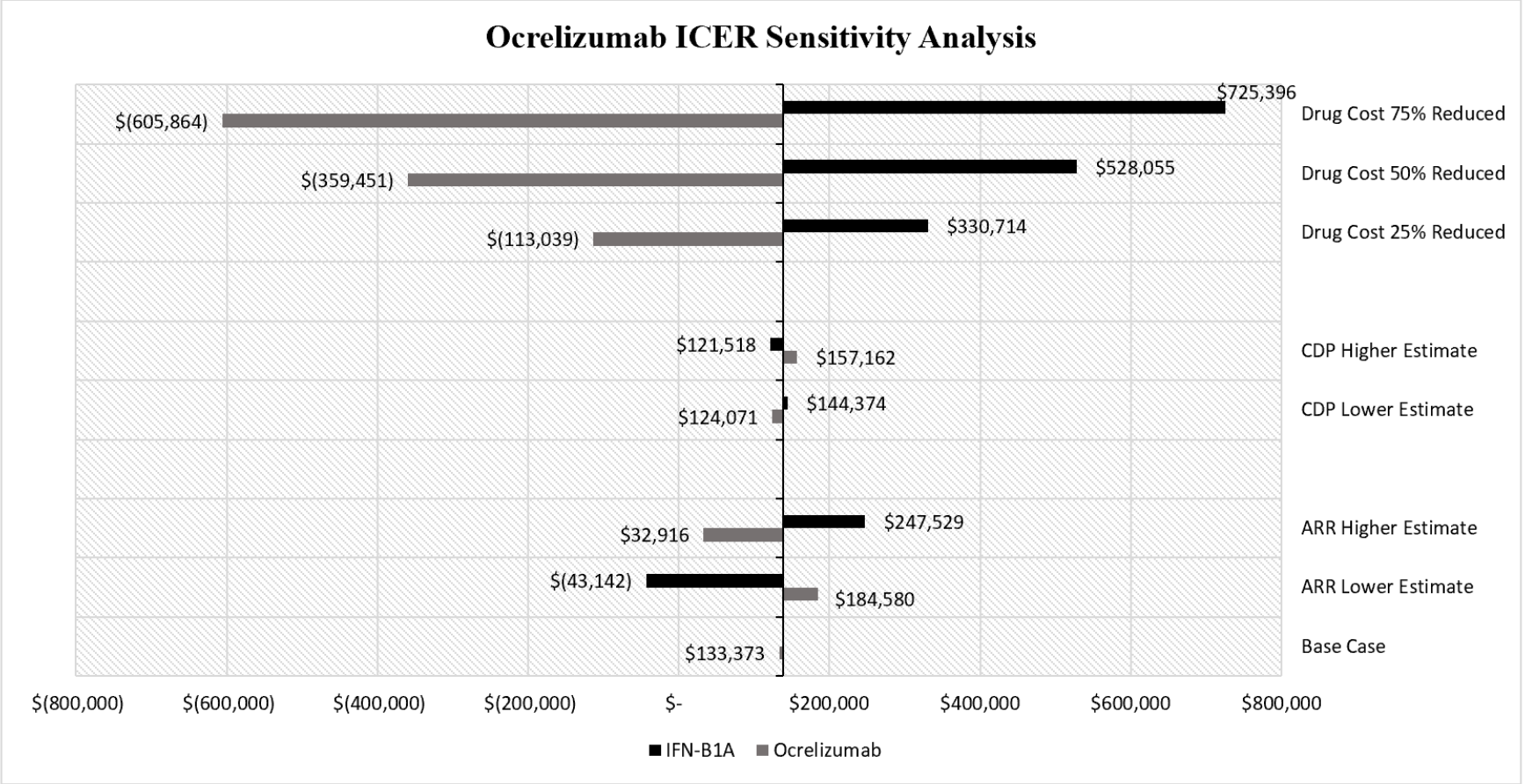


Figure 10: Ocrelizumab ICER Sensitivity Analysis Results

*Center vertical line corresponds to a value close to the base-case ICER, but not exact to allow base case ICER to appear on graph.

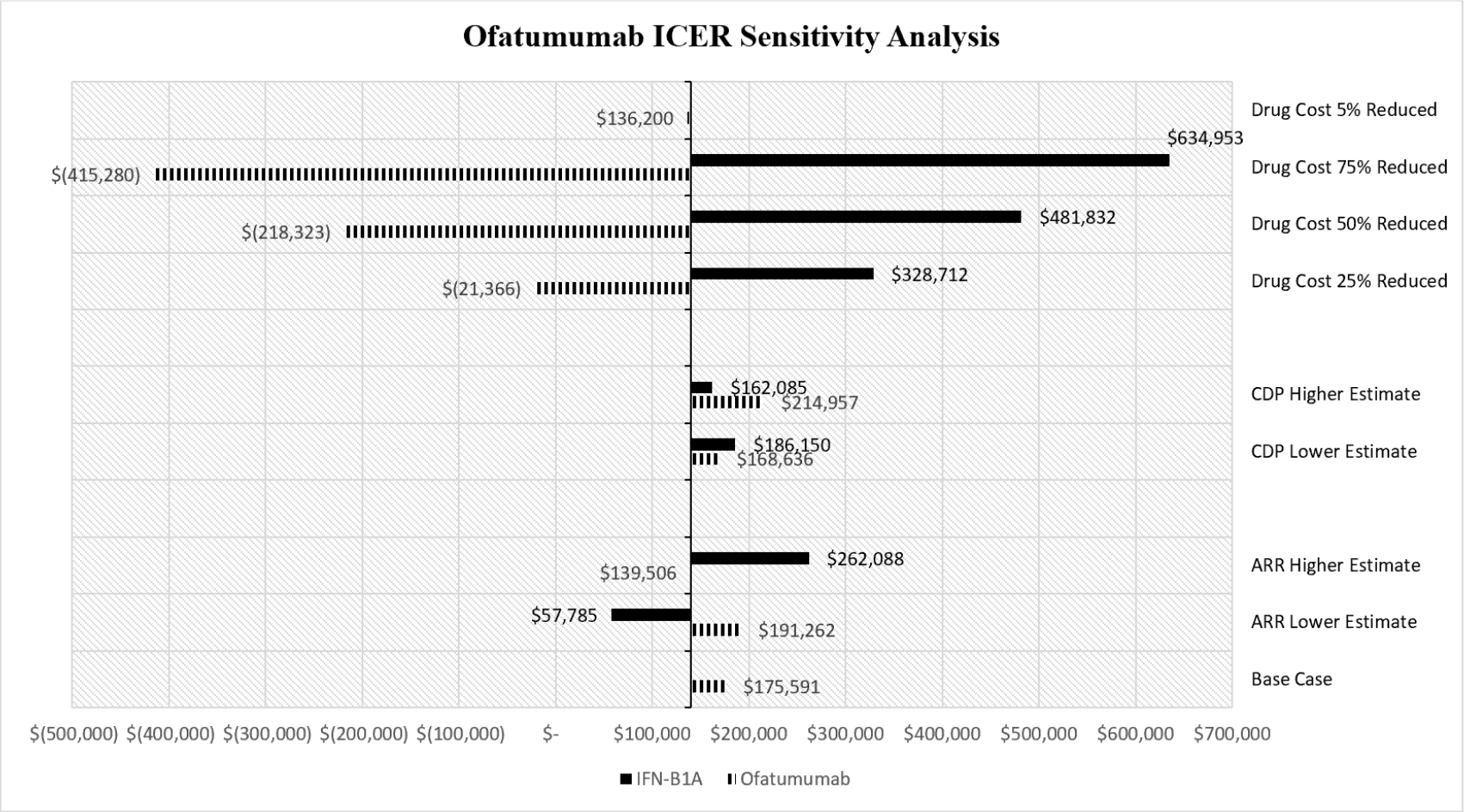


Figure 11: Ofatumumab ICER Sensitivity Analysis Results

*Center vertical line corresponds to a value close to the base-case ICER, but not exact to allow base case ICER to appear on graph.

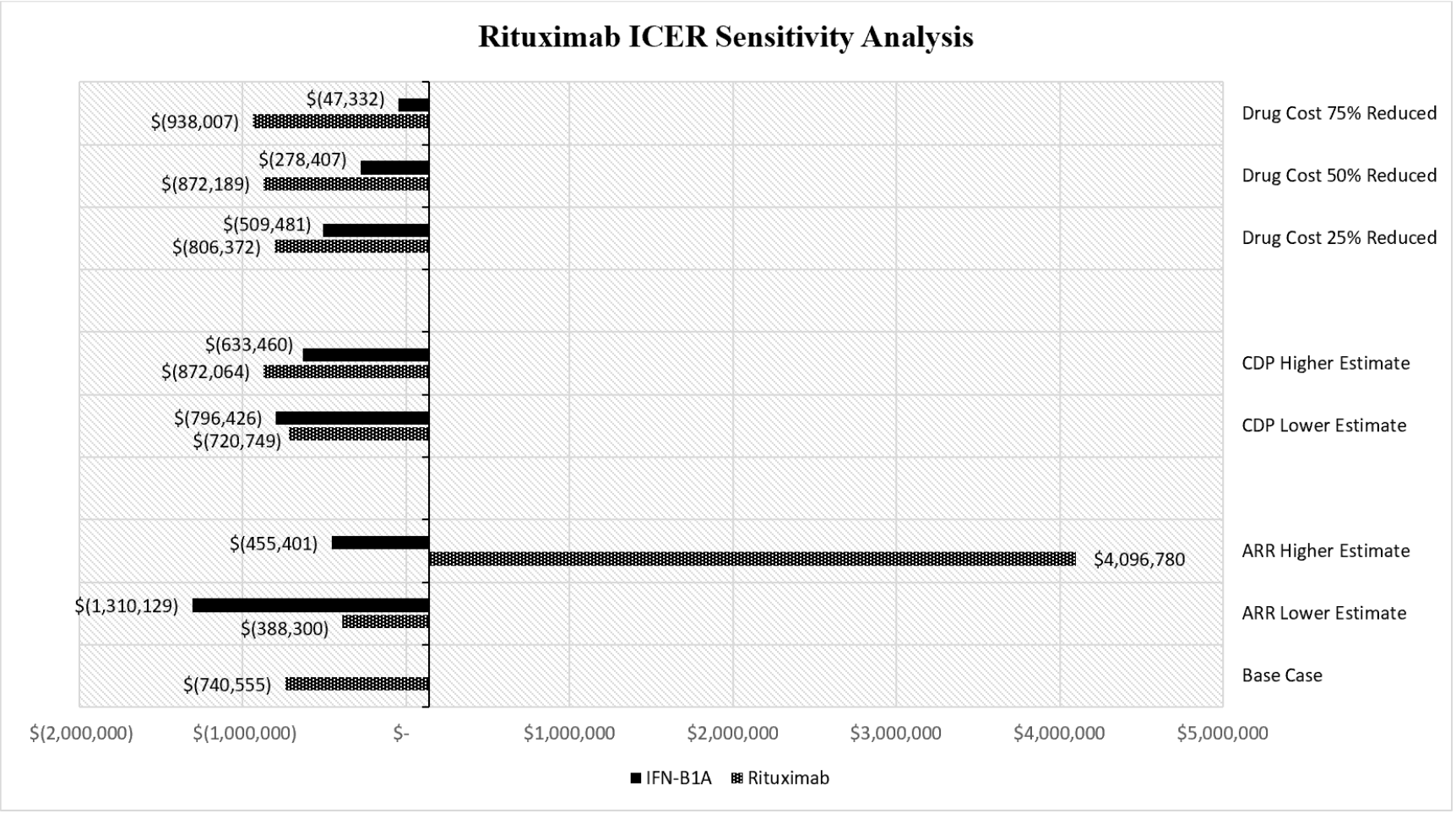


Figure 12: Rituximab ICER Sensitivity Analysis Results

*Center vertical line corresponds to a value close to the base-case ICER, but not exact to allow base case ICER to appear on graph.

Conclusion

All B-cell DMTs (ocrelizumab, ofatumumab, and rituximab) resulted in more patients remaining on therapy and thus less relapses and severe disease progression than IFN-B1a. Ofatumumab was the most effective DMT at retaining patients, but also the most expensive generating $497,827,017 in total costs over 5 years. Rituximab first-order dominated IFN-B1a, while ocrelizumab generated a cost effective ICER compared to IFN-B1a. Ofatumumab was not cost-effective in the base case analysis compared to IFN-B1a with an ICER of $175,591 which is $37,000 over the cost-effectiveness threshold of $138,576. A 5% reduction in ofatumumab's drug acquisition cost/price would result in an ICER of $136,200 and below the cost-effectiveness threshold. One-way sensitivity analyses demonstrated that ICERs were more sensitive to drug acquisition cost reductions. Lowering of ARR during the sensitivity analysis resulted in more patients remaining on therapy versus lowering the CDP hazard ratios; however, more patients remaining on therapy did not impact the ICER (and corresponding cost-effectiveness) favorably due to the high costs of receiving DMTs for an extended period of time.

CHAPTER 5: DISCUSSION

Introduction

In the previous chapter, the results of the cost-effectiveness analysis (CEA) of the monoclonal B-cell disease modifying therapies (DMTs) in relapse remitting multiple sclerosis (RRMS) were presented. The background, justification, and methods for this study have been described in earlier chapters. In this final chapter, the results of the study are discussed in the context of the current RRMS treatment guidelines and relevant published literature on this subject. The strengths and limitations of this current study and their potential impact on study results are discussed. Finally, questions remaining unanswered and areas for future research are highlighted.

Clinical Outcomes

Relapses and Disability Progression

The results of the Markov model portion of this cost-effectiveness analysis demonstrated the superior efficacy of the monoclonal B-cell therapies ocrelizumab, ofatumumab or rituximab in retaining patients on therapy versus interferon-beta 1a (IFN-B1a) over a 5-year period. Retainment on DMT is the direct result of avoidance of relapses, severe disability progression, death, and severe adverse events. Ofatumumab retained the most patients on therapy (338), followed by ocrelizumab (280), rituximab (250) and finally IFN-B1a (78). Across the B-cell DMTs the mean percentage of patients remaining at EDSS $\leq$5 was 89.3% compared to IFN-B1a at 83.3%. For the B-cell DMTs, the results generated by the model, particularly relapses and disability progression, were anticipated given the lower annualized relapse rates (ARR) and confirmed disability progression (CDP) demonstrated in clinical trials relative to the respective comparators.[40–42] As discussed in Chapter 2, there have been several network meta-analyses (NMAs) conducted on the available DMTs.[44,45,73,74] The results of these NMAs are congruent with the findings from this model in that B-cell DMTs (ocrelizumab & ofatumumab) are predicted to have superior efficacy to IFN-B1a on the basis of relapse and disability progression. [44,45,73,74]In NMAs where both ofatumumab and ocrelizumab were included, ofatumumab was predicted to have increased efficacy over ocrelizumab—a finding reflected in the results of the present study. [44,45,73,74]

Rituximab is the exception to the previous statement as it was not included within any of the NMAs identified, likely due to its off-label use in RRMS. Sample sizes within clinical trials conducted for rituximab were considerably smaller in comparison to the other B-cell DMTs (ocrelizumab & ofatumumab), and between trials there was variance of outcomes measured and results.[42,70,72] In particular, the ARR in the rituximab Phase 1 & 3 (0.18, 0.19) trials varied greatly from the Phase 2 trial (0.40) and therefore, this was incorporated into the sensitivity analysis for rituximab. [42,70,72] As expected, the model results under the higher ARR of 0.40 resulted in only 44 patients remaining on rituximab therapy in comparison to the base case analysis of 250. Disability progression was only assessed in the Phase 3 trial for rituximab under the outcome of No Evidence of Disease Activity (NEDA) which incorporated both relapses and disability progression.[42] This does vary from how disability progression was assessed in ocrelizumab, ofatumumab and IFN-B1a clinical trials, which were solely on the basis of level changes on the expanded disability status scale (EDSS). Despite these differences in methodology, both the ARRs (from Phase 1 & 3) and the hazard ratio (HR) related to disability progression (from Phase 3) for rituximab were within range of results demonstrated by ocrelizumab and ofatumumab (see tables 2-4). Overall, although rituximab clinical trials were not as robust as ocrelizumab and ofatumumab trials, efficacy outcomes were generally within range of one another and thus produced superior efficacy within this model when compared to IFN-Ba. As a result, rituximab's results from the Markov model should be regarded more cautiously than ocrelizumab or ofatumumab due to the reasons discussed above.

Previously reported Markov models that have been constructed for ofatumumab have demonstrated similar results in that ofatumumab produces higher efficacy outcomes in comparison to other DMTs. In one study modeled for a Canadian population, ofatumumab demonstrated the highest efficacy with a mean incremental QALY of ~1.8 compared to other DMTs.[75] In another Markov model assessing Ofatumumab's use in a German population, 76% of patients that were treated with ofatumumab for 10 years remained in lower/mild disability states (EDSS 0-3) versus 62% and 56% for dimethyl fumarate and glatiramer acetate recipients respectively.[76] Additionally, 5.9% of patients receiving ofatumumab

reached a disability status of immobile (EDSS 7-9).[76] In comparison, within the present study 55% of patients within the ofatumumab group remained at levels EDSS 0-3 and 2.3% reached levels 7-9. Results from Markov models constructed for ocrelizumab were generally similar in that ocrelizumab demonstrated higher efficacy than IFN-B1a though not all studies reported clinical outcomes separate from economic outcomes. In studies that compared ocrelizumab against other mAB DMTs such as natalizumab or alemtuzumab, ocrelizumab was dominated by these other agents.[84] In a study comparing rituximab against natalizumab, rituximab was associated with a positive incremental QALY of 0.125. [82] While this finding is not directly related to the specific results of the present study it does suggest that rituximab is an effective DMT even in comparison to another mAB.[82] The present study stands apart, as there are no known reported CEA/Markov models comparing all three B-cell DMTs ocrelizumab, ofatumumab, and rituximab.

The mechanism of action may account for the differences observed between the B-cell DMT and IFN-B1a. Ocrelizumab, ofatumumab, and rituximab bind to surface protein CD20 on B-cells and through both antibody dependent cellular cytotoxicity and complement dependent cytotoxicity lead to B-cell lysis.[98] The result is a quantifiable decline in the number of B-cells available to mount an attack on the central nervous system in RRMS. In contrast, the mechanism of IFN-B1a is not well understood. It is hypothesized to alter the secretion of inflammatory cytokines and suppress T-cell activation without causing a decline in circulating lymphocyte numbers.[99] Among the B-cell DMTs, a study that compared the impact of administration routes on lymphocyte numbers in mice found that subcutaneous administration of ofatumumab lead to more lymphocyte decline than IV ocrelizumab.[100] Additionally, subcutaneous ofatumumab appeared to have improved access to lymph nodes as well as faster clearance from the blood.[100] This may explain the differences in efficacy observed between ofatumumab and ocrelizumab in their respective clinical trials and the consistent ranking of ofatumumab over ocrelizumab in NMAs—all of which have been translated into the results of the present Markov model.

Adverse Events

Despite its improved efficacy on the basis of relapses and disability progression, in the Markov model, ofatumumab was associated with the highest number of adverse events (195) compared to ocrelizumab (113), Rituximab (94) and IFN-B1a (140). As discussed in Chapter 4, this is a reflection of the higher discontinuation rate due to adverse events observed in ofatumumab clinical trials and also due to the larger number of patients remaining on therapy and thus at risk to experience an adverse event. The latter highlights an issue in this model's use of an "Off-DMT" treatment group which will be discussed further in the limitations section. The most common adverse events amongst the DMTs of interest in this study are infections and infusion/injection related reactions (IRRs). Interestingly, ofatumumab did not have higher rates of these adverse reactions than the other DMTs in the model.[40–42] The only notable difference was the rate at which patients discontinued ofatumumab (5.7%) due to adverse events in comparison to discontinuation for the other B-cell DMTs (3.0-3.5%).[40–42] Therefore, there was a difference in how patients who received ofatumumab tolerated the adverse events but not necessarily a difference in how often the adverse events occurred.

One potential explanation for this may be how IRRs were managed within clinical trials. The use of pre-medication before IV infusions of mAB DMTs is standard of care. Pretreatment with acetaminophen, an antihistamine, and a corticosteroid 30 minutes prior to administration is required for both ocrelizumab and rituximab and was incorporated into the protocol of agents respective clinical trials.[40,42] Additionally, IFN-B1a is well known for its flu-like symptoms (49-59%) and injection site reactions on dosing days (89-92%).[97] Use of analgesics/antipyretics is recommended on treatment days.[101] In the OPERA clinical trial, patients within the IFN-B1a arm received either ibuprofen or acetaminophen on treatment days.[40] In ofatumumab clinical trials, use of a methylprednisolone 1000mg 30-60 minutes prior to first injection was allowed at the discretion of investigator, but not mandatory as seen in the other DMT trials.[41] For the first dose, 69% of participants received premedication and by the 4th dose, use of premedication declined to 20%.[41] Results showed that use of premedication did little to influence the occurrence of IRRs and therefore, is not recommended.[41]

Costs

The 5-year total costs modeled for all DMTs was substantial, ranging from $3.2 million (rituximab) to $4.97 million (ofatumumab). Direct medical costs comprised on average 47% percent of the total 5-year costs across the treatment groups. However, this high cost is not uncharacteristic of biologic/specialty medications. A report from US Department of Health and Human Services estimated $301 billion in spending on specialty medications in 2021, which was a 42.5% increase from 2016.[102]

Despite the substantial costs, incremental cost-effectiveness ratios (ICERs) for both ocrelizumab and rituximab were both cost-effective versus IFN-B1a, with rituximab being first order dominant. A dominant ICER suggests that the treatment in question is both more effective on prespecified outcomes (patients remaining on therapy) and less costly, as was the case when rituximab was compared to IFN-B1a. Costs savings of $740,555 for rituximab compared to IFN-B1a were predicted by the model. These cost savings are not only reflective of the drug cost differential between agents but also the result of fewer relapses and progression to severe adverse events. In general, lower EDSS levels were associated with lower indirect costs. As discussed above, all B-cell DMTs were superior at retaining patients at lower EDSS levels compared to IFN-B1a which translates potential to economic benefit.

Ofatumumab did not follow this trend with an ICER of $175,591 in the base case analysis (resulting in $37,000 greater than the cost effectiveness threshold). Despite ofatumumab's efficacy in preventing relapses and disability progression, its current cost prevented it's ICER from reaching the cost effectiveness threshold. The annual drug cost for ofatumumab ($91,548) is less costly than IFN-B1a ($110,748), but the difference in the number of patients remaining on therapy between the treatment groups lead to the results observed. Again, this is likely a flaw of using the "Off-DMT" treatment group as the switch option. Sensitivity analyses demonstrated increasing ofatumumab's efficacy further would not improve its cost-effectiveness. Only a reduction in drug cost would lead to ICERs below the cost effectiveness threshold or to first order dominance over IFN-B1a. A 5% annual price reduction (from $91,548 to $86,970) would generate a cost-effective ICER of $136,200. At a 25% reduction (from $91,548 to $68,661), ofatumumab would be a dominant therapy with a

cost savings compared to IFN-B1a of $218,323. Therefore, even a relatively small price reduction would assist in making ofatumumab a highly efficacious and cost-effective DMT while still being more costly than the other B-cell therapies.

It is interesting to review the impact of IFN-B1a cost reductions on the ICERs against the B-cell therapies as IFN-B1a retains a high cost above all the B-cell DMTs despite being available since 2002. An IFN-B1a price reduction of 25-75% would remove the cost effectiveness demonstrated by ocrelizumab; however, rituximab would retain its dominance regardless. Ofatumumab would become increasingly less cost effective as the cost of IFN-B1a was reduced further. Generic formulations of glatiramer acetate and dimethyl fumarate are now available at a 73-95% reduction, respectively, from their previous brand name pricing.[23] If Rebif (IFN-B1a) is released as a generic formulation and offered at a substantial price reduction, it would have impacts on the cost -effectiveness of other DMTs when comparisons are made.

The results of the cost-effectiveness analyses of the present study differ from the previously reported economic studies of ofatumumab. In one study, ofatumumab was found to be dominant to both IFN-B1a and ocrelizumab and generated an ICER of $28,014 over best supportive care.[75] In another, the total 10-year cost per person treated with ofatumumab was calculated to be 299,498 euros which translates to 321,000 US dollars.[76] In the present study, the per person annual cost for ofatumumab was $55,486 which in 10 years would correspond to $554,860. The difference in results between the present study and the one performed in a German population may be attributed to the pricing of DMTs in European countries vs the US as well as the general cost of direct medical care between countries.

Place in Therapy

The results of this model demonstrate that B-cell DMTs are effective at reducing relapses and preventing disability progression over IFN-B1a. Patients receiving treatment with a B-cell DMT are more likely to remain on therapy for longer periods of time than with IFN-B1a. These findings are congruent with the results of NMAs that ranked B-cell therapies and

monoclonal antibodies in general as the most effective DMTs over older agents such as IFN-B1a.

Clinical guidelines from the American Academy of Neurology (AAN) and the Consortium of Multiple Sclerosis Center (CMSC) recognize monoclonal antibodies and thus B-cell therapies as highly effective treatment options.[28,29] However, ofatumumab has not yet been included into guidelines given its recent approval. Additionally, it is doubtful rituximab will be included into guidelines, due to its off-label status, although guidelines still may discuss benefits and risks associated with use of rituximab as a management therapy. Both guidelines are clear in stating that step-wise/escalation therapy is not mandatory, meaning lower efficacy agents do not necessarily need to be trialed prior to higher efficacy agents—yet, there is not a recommendation to start treatment naïve patients on highly effective therapy like B-cell DMTs. In fact, monoclonal antibody DMTs are only explicitly recommended for patients with highly active disease. In all other scenarios, recommendations provided for this disease that has potentially debilitating consequences if not managed properly on treatment, are that treatment should be tailored to patient preferences. However, results from this study and others involving B-cell DMTs confirm that these highly active agents delay progression to severe disability over older less efficacious options.

Whether employment of highly efficacious agents as first line therapies should become standard of care to prevent relapses and disability accumulation has been addressed by subject matter experts in the literature.[103] Traditionally, an escalation approach has been utilized for patients and higher efficacy agents were only initiated when a patient had breakthrough disease activity. Recent research has identified an “early window of opportunity” in RRMS, particularly in younger patients, where there is a substantial amount of brain and CNS inflammation.[103] Should DMT be initiated during this window, inflammation can be reduced and future damage prevented. This is the underlying concept of early high efficacy treatment (HET). Different approaches exist for HET including induction therapy with a high efficacy DMT and then maintenance on a lower efficacy DMT or continuous therapy on high efficacy DMT.[103] Overall, it appears that this treatment strategy

has begun to gain traction and perhaps will be reflected in future updates of clinical guidelines.

The differences in administration route and timing of these DMTs may also serve as a deciding factor for their utilization. Adherence to DMT is crucial for its success and poor adherence is often a common cause for disease breakthrough/treatment failure. Assessing a patient's adherence to DMT is recommended in guidelines prior to switching for treatment failure. Infusion DMTs such as ocrelizumab or rituximab have benefit in that infusions are infrequent and therefore, limit the number of potential missed doses. However, patients who live in rural areas, have lack of reliable transportation, or are at high disability levels may have issues accessing infusion centers. Wait times for clinical services are high across the US, and a missed infusion appointment due to any of the above reasons may mean prolonged periods of time between infusions.

Alternatively, DMTs like ofatumumab and IFN-B1a have the benefit of self-injection thus limiting required travel. However, the responsibility of adherence is placed solely onto the patient. Self-injectable options would be a poor choice for any patient that exhibits needle/injection phobia or memory impairment due to a cognitive disorder. Additionally, patients with severe disability and those with limited fine motor/hand dexterity may find self-injection difficult and have to rely on administration from a caretaker.

Overall, the consensus from the results of this study, NMAs, treatment guidelines, and expert opinion is that monoclonal Abs should be regarded as highly efficacious therapies. That said, the coverage of these DMTs and inclusion into formularies of managed care organizations will ultimately determine utilization and patient access to such medication. At current pricing, the cost may be most prohibitive for ofatumumab.

Implications for Stakeholders:

Patients

The burden of living with RRMS paired with the number of available treatments may be overwhelming for patients, but studies such as the present one (where patient centered outcomes were selected) may help to clarify the outcomes a patient may expect from a

particular DMT. The B-cell therapies modeled in this study all had fewer relapses and severe disability progression and thus more patients remaining on therapy after 5 years in comparison to IFN-B1a. B-cell therapies are recognized as high efficacy DMTs in guidelines and literature, and therefore, patients should be aware that there is extensive evidence supporting their usage. That said, there was a substantial number of patients not remaining on therapy across all treatment groups from baseline to year 5. From a patient perspective, this translates to treatment failures and switches which can add to the stress of managing this disease. Additionally, it is important for patients to recognize that the outcomes represented in this study are only an average of effects across a population and that an individual may have greater or less success than average on a particular therapy.

B-cell DMT's most common adverse reactions include infections and injection/infusion related reactions; whereas, IFN-B1a has the above listed reactions and also flu-like symptoms on administration days (which for Rebif is three times weekly). These adverse effects have the potential to considerably impact a patient's quality of life and therefore, patients should be well informed on the risk of such events as well as the prophylaxis commonly employed (corticosteroids, antihistamines, and acetaminophen). Infusion related reactions occurring twice yearly with an infused B-cell such as ocrelizumab or rituximab may be preferable for patients than the risk of flu-like symptoms and injection related reactions three times weekly with IFN-B1a. Therefore, for many patients B-cell DMTs offer improved outcomes and a more favorable tolerability profile over IFN-B1a and should be considered as a viable treatment option.

Providers

The absence of algorithm-based treatment guidelines can make selection of the appropriate DMT for a patient complex. The results of this study highlight that patients will have fewer suboptimal events, i.e breakthrough disease activity when B-Cell DMTs are used versus IFN-B1a. This is important as IFN-B1a, due to its early approval in RRMS, continues to be highly utilized while newer B-Cell DMTs may be underutilized due to provider lack of familiarity. Additionally, reduced rates of disability progression demonstrated by B-Cell DMTs over IFN-B1a makes them desirable options for retaining patients at lower disability levels.

Though more research is needed, the concept of early high efficacy treatment in RRMS may lead to improved long-term outcomes for patients as early inflammation and CNS damage is averted. If this treatment strategy should gain traction, B-Cell DMTs will likely serve as first-line therapies given their efficacy.

As recommended by the current clinical guidelines, consideration of patient specific factors remains important for selection the appropriate therapy.[28,29] The differences in administration between B-Cell DMTs and IFN-B1a have implications for patient's adherence and overall success on therapy. The availability of B-cell DMTs as both infusions (ocrelizumab, rituximab) and at home injections (ofatumumab) allows providers to select a dosage form that best fits patients' needs without sacrificing efficacy.

Payers

The results of the present study highlighted the substantial costs of B-Cell DMTs (particularly ocrelizumab and ofatumumab) as well as IFN-B1a. While the high cost of ocrelizumab and ofatumumab may be off-set by their increased efficacy, the same cannot be said for IFN-B1a which is both more costly than all the B-cell DMTs and less effective. Despite the price misalignment between cost and efficacy of IFN-B1a, it remains included on many formularies as a low tier (often preferred) therapy.[48] Ocrelizumab and rituximab both generated ICERs below the cost effectiveness threshold in the base case analysis. Rituximab is particularly appealing from an economic perspective due to its exceedingly low costs and predicted high efficacy; however, clinical trial data is not as extensive for rituximab as for the other B-Cell DMTs and therefore, cost-effectiveness conclusions are not as definitive. Though ofatumumab was not cost effective in the base case analysis, it requires only a 5% reduction in wholesale acquisition cost to reach cost-effectiveness thresholds. The B-cell DMTs should be considered for placement in lower formulary tiers due to their ability to reduce relapses and retain patients at lower disability levels which corresponds to decreased healthcare utilization. Use of B-cell DMTs earlier on in a patients RRMS course, as suggested by early high efficacy therapy, may prevent CNS damage, and retain more patients at lower levels of disability for prolonged periods of time. Aversion of CNS damage via early high efficacy treatment likely has improved long-term outcomes in comparison to step

therapy where patients must accumulate disability prior to DMT escalation. In the latter scenario, patients only reach B-cell DMTs after their RRMS has progressed to a higher level. Use of B-cell DMT earlier on in treatment may have long term benefits for payers due to lower disability related healthcare utilization, decreased relapse treatment costs, and decreased DMT switching.

Strengths & Limitations

This cost-effectiveness analysis and Markov model had several strengths. First, it attempted to compare all the available agents within the class of B-cell DMTs to a commonly utilized comparator IFN-B1a. Previous economic analyses had not included rituximab due to its off-label status. Rituximab is considerably less costly than ocrelizumab and ofatumumab, and clinical trials, though limited by their sample sizes, suggest it may have comparable efficacy to the others in its class. Second, this analysis attempted to create a Markov model reflective of how patients may utilize DMTs based on recommendations from clinical guidelines. While other economic analyses allowed for continual relapses and sometimes progression to EDSS 9 while on therapy in their Markov models, this study model necessitated that patients discontinue treatment after such events or disability progression. Finally, this study was conducted under a value-based framework in which outcomes selected for the appraisal of a therapy should hold value to patients. The outcomes selected for the present study are both clinically relevant and hold value to patients. In addition to relapses and disability progression, clinical trials often assessed lesion formation in brain and spinal tissue via MRI. While the findings of lesions are clinically significant as they are evidence of immune activity, patients are often unaware of the presence, size, or number of such lesions. Relapses, increased disability, and severe adverse events are all experienced by patients and therefore the reduction of such events holds more value to them.

Several limitations of the present study should be noted as well. First, is the “memory less” assumption used in Markov models meaning past events have no bearing on the probability of current ones. RRMS is regarded as a highly variable disease with some patients having higher levels of disease activity and thus faster progression than others. An individual patient with high disease activity may have increased probability for future events, but the model

will only capture the mean probability of an event occurring across a population. The model was created to determine costs and effectiveness on average; the treatment experience of an individual with MS may vary from model assumptions.

Secondly, this model's structure involved "On-DMT" and "Off-DMT" treatment groups. Those within the "Off-DMT" group did not receive an alternative DMT. Therefore, direct medical cost for these patients consisted solely of healthcare utilization. While it was a notable strength that patients were not kept on suboptimal therapy, in a real-world clinical scenario patients would likely be switched to another DMT. The issue that occurs from a model structure similar to that used in this study is that patients that remain on therapy, particularly a sizeable high-cost therapy like ofatumumab, will accumulate more costs than patients who discontinue treatment due to suboptimal therapy. The same can be said for adverse events – those remaining on therapy longer have potential to experience adverse events over those who discontinue treatment. To manage this model design limitation, an alternative DMT would need to be identified that patients receiving a B-cell DMT or IFN-B1a would both switch should suboptimal response/treatment failure occur. In all likelihood, this would not be a single agent. A patient failing on IFN-B1a under an escalation therapy approach would likely switch to a higher efficacy agent like a B-cell DMT. Conversely, those failing on a B-cell therapy may switch to either a moderate efficacy DMT (if the reason for discontinuation was adverse event) or a longer acting immunosuppressive therapy like alemtuzumab (if the reason for discontinuation was suboptimal response). Therefore, inclusion of such treatment switches would greatly increase the complexity of this model and the number of assumptions made.

Lastly, adherence related to the difference in dosage forms was not assessed. This should not understate the importance of adherence and how patient specific factors may influence of the suitability of certain DMTs. If more data were available on the specific adherence to the DMTs of interest within this study, sensitivity analyses could have been conducted to determine the impact on model and CEA results.

Areas for future research

The topic of multiple sclerosis is both broad and complex given the various phenotypes, the number of available DMTs, and the variability of the disease between patients. The present study only addresses a small number of questions involving DMTs in the management of RRMS. The results of this study suggest that B-cell DMT may be not only clinically effective but also cost-effective options for management of RRMS. While evidence from clinical trials of rituximab is promising, differences in methodology and sample size make it difficult to draw robust conclusions about its efficacy. Overall, more data is required to conclusively determine rituximab's role in RRMS management.

New therapies are on the horizon for RRMS. Ublituximab (Briumvi) another IV infused B-cell DMT recently was approved by the FDA in December of 2022 and became available on the market in January 2023. While ublituximab still targets CD20 on B-cells, it targets an epitope unique from the other available therapies.[104] Ublituximab is infused every 6 months and its current annual wholesale acquisition cost is ~$59,000 (not including administration fees). This is less than current annual costs of both ocrelizumab ($75,100) and ofatumumab ($91,548).[23] Other DMTs still in development include tolebrutinib and evobrutinib which are both Bruton's tyrosine kinase (BTK) inhibitors.[105] If approved, these agents will provide a novel treatment class to DMTs. Release of these agents will increase options for patients and providers but will also increase complexity of deciding on the most appropriate therapy. Further research will be required to determine the impact of these new therapies on the RRMS treatment landscape.

RRMS is a life-long disease and yet the majority of clinical data available for DMTs is acquired over relatively short time frames. The present study only assessed a 5-year time horizon in order to not over extrapolate results from clinical trials. That said, long-term trials will be required to determine the true impact of DMTs in RRMS. Additionally, future research of the different DMT dosage forms impact on adherence would be useful.

Conclusion

The B-cell DMTs ocrelizumab, ofatumumab and rituximab all demonstrated superior effectiveness over IFN-B1a in retaining patients on therapy and thus averting relapses and severe disability progression over a 5-year period. These results are congruent with NMAs that ranked B-cell DMTs as the most effective therapies. In particular, ofatumumab stands out for having demonstrated the highest retainment of patients on therapy despite also having the highest number of adverse events leading to discontinuation. Comparison of the pre-treatment management of IRRs revealed that pretreatment with corticosteroids, antihistamines, and/or antipyretics was required for ocrelizumab, rituximab and IFN-B1a but not for ofatumumab. Some uncertainty exists around the results for rituximab as the clinical trials that powered this model were not as robust as the ones conducted for ocrelizumab or ofatumumab. Future trials will be required to confirm rituximab's efficacy in RRMS management. Rituximab is currently the least costly B-cell DMT and therefore, was dominant to IFN-B1ain almost all scenarios. Ocrelizumab was cost-effective with an ICER below the cost-effectiveness threshold in the base-case analysis and when drug cost reductions were performed in sensitivity analyses. Ofatumumab did not demonstrate a cost effective ICER in the base case analysis, but only required a 5% cost reduction to reach the cost effectiveness threshold. Results of this CEA were aligned with other economic analyses in terms of efficacy outcomes but differed for ofatumumab in terms of cost-effectiveness in the base case analysis. These may be due to differences in the origin country of the studies. The release of newer DMTs will increase the availability of treatment options and advance knowledge on RRMS but will also increase complexity of selecting an appropriate therapy for patients. Debates over escalation therapy versus early HET still exist and are largely unaddressed by guidelines. Future research will need to investigate the role of new DMTs under these different treatment strategies. The goal of all future efforts placed into RRMS research should be to reduce disease burden and improve quality of life of all those affected, and given that RRMS is a life-long potentially debilitating disease, long-term studies are needed to fully understand the impact of DMTs on the disease course.

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