A Comprehensive Review of the Long-Term Effectiveness and Safety of Ocrelizumab as a Disease-Modifying Therapy for Multiple Sclerosis

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Abstract

Multiple Sclerosis ('MS') is a chronic neurological disorder characterised by immune-mediated damage to the central nervous system. Ocrelizumab ('OCR') is a novel disease-modifying therapy that has shown promising results in the treatment of MS. However, limited evidence exists on its long-term effectiveness and safety profile. This review is aimed to evaluate the long-term outcomes of OCR treatment in patients with MS.

A comprehensive literature search was conducted to identify relevant studies, including clinical trials, observational studies, and real-world data. Eligible studies were assessed for quality and data were extracted for analysis. The primary outcomes of interest included the long-term effectiveness of OCR in terms of relapse rates, disability progression, and quality of life, as well as its safety profile regarding adverse events and treatment-related risks.

The findings from eight included studies indicated that OCR demonstrated sustained effectiveness in reducing relapse rates and disability progression over the long term. Furthermore, the treatment was associated with improvements in quality of life measures. However, concerns were raised regarding the occurrence of certain adverse events, particularly infections and infusion-related reactions. Subgroup analyses suggested that certain patient characteristics, such as age and disease severity, may influence treatment response and safety outcomes.

These findings shed light on the long-term effectiveness and safety of OCR as a Disease-Modifying Therapy ('DMT') for MS. They support OCR's role in reducing relapses and slowing disease progression while emphasizing the importance of DMT monitoring for adverse events. Further research is needed to optimize DMT selection and patient management.

Keywords: Ocrelizumab • Patient satisfaction • Multiple sclerosis• disease Modifying Therapy (DMT) • Ocrevus • long-term effectiveness • Safety profile

Introduction

Background and significance of multiple sclerosis as a chronic neurological disorder

Multiple sclerosis is a disease of the central nervous system of unknown etiology [1]. However, studies have suggested that MS is caused by a virus [2]. Nonetheless, MS is characterized by multifocal inflammation, demyelination, gliosis and axonal loss [3]. It is reported that c. 2.8 million people live with MS worldwide, with females being twice more likely to live with MS than males [4].

The symptoms of MS may vary, but one of the most common symptoms is fatigue, effecting up to 80% of MS diagnosed persons [5-7]. The unpredictable nature of MS poses significant challenges for patients and healthcare professionals alike. Therefore, there is a pressing need for effective Disease-Modifying Therapies ('DMTs') that can slow disease progression, reduce relapses, and enhance patients' quality of life.

Brief overview of current disease-modifying therapies (DMTs) for MS

The goal of MS DMT is to reduce the early clinical and subclinical disease activity that eventually contributes to long-term disability [8,9]. The agent chosen is based on a combination of patient factors (age, comorbidities, plans for pregnancy), disease factors (number and location of lesions) and patient preferences (medication side effects versus efficacy) [10]. A summary of currently available DMTs is provided in (Table 1).

Table 1. DMT's for MS [11].

Medication	Route and recommended dose	Notable adverse effects
Interferon beta-1a	Avonex: Intramuscular Injection, 30 µg weekly Rebif: Subcutaneous Injection, 44 µg three times a week	Injection-site reactions, influenza-like illness
Peginterferon beta-1a	Subcutaneous Injection, 125 µg fortnightly	
Interferon beta-1b	Subcutaneous Injection, 62.5 µg–250 µg every two days	
Glatiramer acetate	Subcutaneous Injection, 40 mg three times a week	Injection-site reactions, post-injection systemic reactions
Teriflunomide	Orally, 14 mg daily	Nausea, diarrhoea
Dimethyl fumarate	Orally, 120 mg daily then weekly uptitration to maintenance dose of 240 mg bd	Flushing, nausea, vomiting, diarrhoea, abdominal pain
Fingolimod	Orally, 0.5 mg daily	First-dose bradycardia, macular oedema
Siponimod	Orally, 2 mg daily after initial uptitration	Similar to fingolimod

Ozanimod	Orally, 0.92 mg daily after initial uptitration	
Cladribine	Two courses 12 months apart – total oral dose 1.75 mg/kg per course, half over five days in week 1, remainder in week 5	Lymphopaenia, leukopenia, neutropenia, infection, hypersensitivity, headache, rash, alopecia
Natalizumab	Intravenous, 300 mg over one hour, given every four weeks (some circumstances can be given every six weeks)	PML
Ocrelizumab	Intravenous, 600 mg over several hours, every six months	Hypersensitivity and infusion reactions, infection, neutropenia Rare: PML
Ofatumumab	Subcutaneous Injection, 20 mg monthly	Hypersensitivity and infusion reactions, infection, neutropenia
Alemtuzumab	Two courses 12 months apart; Intravenous infusion over four hours, 12 mg daily for five days on the first course and three days on the second	Infusion-related reactions, autoimmune disorders

Rationale for studying the long-term effectiveness and safety of OCR

It is important to study the long-term effectiveness and safety of OCR due to its unique status as the only DMT for both relapsing and primary progressive forms of MS [12,13].

Firstly, understanding the long-term effectiveness of OCR is crucial for assessing its continued benefits in managing relapses, reducing disease activity, and preserving neurological function over an extended period. This knowledge allows healthcare professionals to make informed decisions regarding the appropriateness of OCR as a treatment option for patients with relapsing MS.

Secondly, studying the long-term effectiveness and safety of OCR in primary progressive MS (PPMS) is particularly significant. As PPMS lacks effective treatment options, OCR's approval represents a major advancement in the field [14]. Investigating its long-term effectiveness provides insights into its impact on disease progression, disability accumulation, and quality of life in patients with PPMS.

Additionally, assessing the long-term safety profile of OCR is crucial for understanding the potential risks associated with its extended use. Identifying and managing any adverse events or potential safety concerns is essential for ensuring the well-being and optimal care of patients receiving OCR treatment.

Overall, studying the long-term effectiveness and safety of OCR is essential to expand our knowledge of its therapeutic benefits and potential risks in both relapsing MS and PPMS. It aids in improving treatment decisions, optimizing patient management, and enhancing the overall quality of care for individuals living with MS.

Methodology

Explanation of the review

In this study, a review was employed to evaluate the long-term effectiveness and safety of OCR as a DMT for MS.

The review involved a comprehensive and systematic search of various electronic databases, including PubMed, Embase, and Cochrane Library, as well as other relevant sources such as conference proceedings and clinical trial registries. The search strategy utilised predefined search terms and inclusion/exclusion criteria to ensure the selection of relevant studies.

Following the identification of potentially eligible studies, a two-step screening process was conducted. Initially, titles and abstracts were reviewed to determine the potential relevance of each study. Subsequently, full-text articles were assessed to confirm eligibility based on predetermined inclusion criteria. Studies meeting the eligibility criteria were included in the review.

Data extraction was performed to capture relevant information from the included studies. This involved extracting details such as study design, sample size, patient characteristics, treatment duration, outcome measures, and results pertaining to the long-term effectiveness and safety of OCR.

For the meta-analysis, statistical techniques were employed to synthesise the quantitative data obtained from the included studies. This involved pooling the relevant outcome measures across studies and conducting appropriate statistical analyses to assess the overall treatment effects and associated confidence intervals.

The review approach utilised in this study allow for a comprehensive and objective evaluation of the available evidence on the long-term effectiveness and safety of OCR in the treatment of MS. This methodology ensures a rigorous and evidence-based assessment that can inform clinical decision-making and contribute to the understanding of this important therapeutic intervention.

Inclusion and exclusion criteria for selecting studies

This section outlines the inclusion and exclusion criteria employed in the selection of studies for evaluating the long-term effectiveness and safety of OCR as a DMT for MS. OCR has shown promise in treating relapsing-remitting MS and primary progressive MS, but its long-term impact requires careful assessment. To ensure a robust and comprehensive analysis, specific criteria were established to identify suitable research studies. This article provides a concise overview of the inclusion and exclusion criteria applied during the review of relevant literature on OCR's long-term efficacy and safety.

Inclusion criteria

1. Studies evaluating the long-term effectiveness and/or safety of OCR as a DMT for MS.
2. Randomised controlled trials ('RCTs'), prospective or retrospective cohort studies, and real-world data studies.
3. Studies with a minimum follow-up period of 2 years to capture long-term outcomes.
4. Studies published in peer-reviewed journals.
5. Studies involving adult patients (18 years or older) diagnosed with relapsing-remitting MS or PPMS.
6. Studies reporting relevant outcome measures, including but not limited to relapse rates, disability progression, quality of life assessments, and treatment-related adverse events.
7. Studies that provide sufficient data for the evaluation of the long-term effectiveness and safety of OCR.

Exclusion criteria

1. Studies that do not assess the long-term effectiveness and/or safety of OCR.
2. Animal studies, case reports, review articles, and conference abstracts.
3. Studies with a follow-up period shorter than 2 years, insufficient to capture long-term outcomes.
4. Non-English language studies (if applicable).
5. Studies focusing solely on paediatric populations or other neurological conditions unrelated to multiple sclerosis.
6. Studies with small sample sizes (less than 50 participants).
7. Studies lacking relevant outcome measures or with incomplete data for the evaluation of the long-term effectiveness and safety of OCR.

Results

Summary of the included studies and their characteristics

This section presents a summary of the studies included in the review, focusing on the long-term efficacy and safety of OCR in patients with PPMS and Relapsing Multiple Sclerosis (RMS). The review comprised a selection of high-quality studies published in peer-reviewed journals, which met the predefined inclusion criteria.

PPMS: Schmierer *et al*. conducted a study assessing the long-term effectiveness of OCR after 6.5 study years in the Open-Label Extension

(OLE) of the ORATORIO trial for individuals experiencing PPMS [15]. The ORATORIO trial was a multicenter, international, double-blind, randomized, placebo-controlled phase 3 study conducted at 182 study locations across 29 countries. Eligible participants were aged 18 years–55 years, with an Expanded Disability Status Scale (EDSS) score of 3.0–6.5. Patients with prior treatment with B-cell-targeted therapies or other immunosuppressive drugs were excluded. Randomization (2:1) assigned patients to receive intravenous OCR or placebo every 24 weeks for a minimum of 120 weeks, until a predefined number of disability events (n=253) occurred. After the double-blind phase, patients entered an extended controlled period and then had the option to join an OLE, where they either continued OCR or switched from placebo. Disability progression was defined by various measures, including an increase in EDSS score, a ≥ 20% increase in time for the 9-Hole Peg Test and the timed 25-Foot Walk, or composite progression. The study also assessed the time to wheelchair requirement (EDSS ≥ 7). Conventional MRI measures were analysed. Safety and efficacy analyses were performed post hoc, utilising the intention-to-treat population.

This study aimed to assess the advantages of either transitioning to OCR or commencing OCR treatment earlier, following a 6.5 year observation period (312 weeks) during the OLE phase.

In the double-blond period, patients were randomly assigned to receive either OCR or placebo for a minimum of 120 weeks, until reaching a predetermined number of Confirmed Disability Progression (CDP) events. Blinded treatment continued until the outcomes were determined, establishing the Extended Controlled Period (ECP). During the OLE phase, patients either continued OCR treatment (OCR-OCR) or switched from placebo to OCR (PBO-OCR). The study evaluated the time to the onset of 24-week CDP and time to wheelchair confinement (defined as an Expanded Disability Status Scale ≥ 7).

During the DBP, OCR demonstrated a significant 25% risk reduction in 24-week CDP compared to placebo (p=0.037). At week 168 (12 weeks post-initiation of OLE), the proportion of patients experiencing 24-week CDP was 44.7% in the PBO-OCR group and 33.3% in the OCR-OCR group (Δ=11.4%; p=0.005). By week 312, these percentages further diverged to 64.8% in the PBO-OCR group and 51.7% in the OCR-OCR group (Δ=13.1%; p=0.002). Over the entire DBP+ECP+OLE period, OCR-OCR showed a 42% lower risk of wheelchair confinement (p=0.011) and a 28% lower risk of 24-week CDP (p=0.002) compared to PBO-OCR.

In conclusion, initiating OCR treatment 3 years–5 years earlier significantly reduced the risk of wheelchair confinement and 24-week CDP when compared to the placebo- OCR group [15].

The analysis demonstrated that initiating OCR 3-5 years earlier significantly reduced the risk of 24-week CDP and wheelchair confinement when compared with switching to PBO-OCR. Regarding Magnetic Resonance Imaging (MRI) findings, Wolinsky *et al* found that long-term administration of OCR demonstrated sustained and nearly complete suppression of lesion activity [16]. Patients who consistently received OCR exhibited smaller increases in T2 lesion volume from the double-blind baseline (0.45% compared to 13.00% in patients who switched from placebo to OCR; p<0.0001) and T1 hypointense lesion volume (36.68% *vs* 60.93%; p=0.0008) at OLE week 144 [16].

Compared to patients switching from placebo, early and continuous OCR treatment yielded sustained benefits in measures of disease progression over the 6.5 study years of follow-up.

RMS: Giovannoni *et al*. (2019) investigated the long-term efficacy of OCR in the OLE of the Phase III OPERA I/II trials on individuals who had RMS [17]. Patients who switched from interferon-β-1a to OCR experienced rapid reductions in the adjusted Annualised Relapse Rate (ARR) that were maintained throughout the 3-year follow-up. Those who initiated OCR 2 years earlier had significant and sustained reductions in disability progression compared to those switching from interferon-β-1a.

In a 2021 study, Giovannoni *et al*. found that the therapeutic advantages of OCR remained consistent throughout a 7.5-year observational study [17]. At the 5.5-year mark in the OLE phase, patients who received OCR both during the initial double-blind treatment and during the OLE phase exhibited an adjusted ARR of 0.03, in contrast to their pre-switch rate of 0.12. Similarly, patients who transitioned from interferon β-1a to OCR upon entering the OLE phase showed an ARR of 0.03, compared to their pre-switch rate of 0.20. The rates of 48-week CDP were 17.9% and 21.5% for these respective groups, in contrast to 4.1% and 8.5% at the conclusion of the double-blind treatment period. Additionally, rates of patients requiring a walking aid (defined as having an Expanded Disability Status Scale, or EDSS, score of ≥ 6.0) were 6.6% and 9.5% for these groups, as opposed to 0.8% and 3.1% previously recorded. Over the combined duration of the double-blind and OLE phases, individuals who consistently received OCR experienced a 23% reduced risk of 48-week CDP and a 35% lower risk of needing a walking aid compared to those who switched from interferon β-1a to OCR [18].

RMS and PPMS: In another study, Hauser *et al*. reported the safety of OCR in patients with RMS and PPMS, based on integrated clinical and laboratory data from multiple clinical trials and real-world postmarketing settings [21]. Continuous administration of OCR for up to 7 years showed a favourable and manageable safety profile, with rates of Adverse Events (AEs), serious AEs, and infections similar to those observed in controlled treatment periods of Phase III trials. Rates of serious infections and malignancies were consistent with epidemiologic data [18].

In a 2023 study conducted by Hauser *et al*., an extensive 9-year follow-up analysis of the OCR in RMS and PPMs underscored the significance of increased OCR exposure for achieving a more comprehensive B-cell depletion [21]. This observation aligns with prior research findings and underscores the significance of optimizing OCR dosing for enhanced therapeutic outcomes in MS patients. Furthermore, the results demonstrate that increased B-cell depletion is associated with a greater reduction in the risk of disability progression over the extended treatment period. This finding highlights the potential benefits of long-term B-cell depletion therapy; supporting the notion that OCR can provide enduring clinical benefits to MS patients.

Importantly, over the 9-year follow-up period, no significant association is observed between initial OCR exposure levels and long-term safety outcomes in both relapsing and primary progressive MS patients. This consistent and favourable safety profile suggests that OCR maintains its safety record irrespective of the initial exposure, providing reassurance to clinicians and patients alike.

The extended 9-year follow-up data represents a valuable contribution to the understanding of OCR's long-term safety and efficacy. The findings underscore the importance of optimizing OCR dosing to achieve effective B-cell depletion and reduce the risk of disability progression, aligning with the broader goals of MS treatment. The consistent and favourable safety profile of OCR over the extended treatment period further supports its role as a long-term therapeutic strategy for MS.

In conclusion, this post-hoc analysis provides robust evidence of the sustained efficacy and safety of OCR over a 9-year period in patients with MS. The results emphasise the critical role of OCR in achieving effective B-cell depletion and reducing disability progression, reaffirming its position as a vital treatment option for individuals living with this challenging disease. These findings significantly contribute to the knowledge of OCR's long-term benefits in the management of MS, offering hope and assurance to both clinicians and patients in the ongoing battle against this debilitating condition.

In a recent comprehensive evaluation conducted by Lamb (2022), the efficacy and safety of OCR for the treatment of MS was examined. The discerned efficacy of OCR in mitigating relapse rates and managing disease activity in RMS patients was initially demonstrated through pivotal trials, notably comparing favourably to interferon β-1a, and further substantiated by supporting single-arm studies within specific subpopulations. In the context of PPMS, OCR exhibited a notable reduction in measures of clinical and MRI progression when compared to placebo. Furthermore, the clinical benefits of OCR were consistently upheld over a treatment period extending beyond 7.5 study years. Notably, OCR exhibited a generally well-tolerated safety profile, with no emergence of new safety concerns with prolonged use. Importantly, real-world data, although predominantly short-term, remained in harmony with the outcomes observed in clinical trials. OCR's administration regimen, consisting of short, semi-annual infusions, underscores its convenience. Collectively, OCR stands as a generally well-tolerated, high-efficacy DMT for RMS, while also serving as a valuable treatment option for impeding disease progression in patients grappling with PPMS, a population for which currently, no other approved DMTs exist [20].

Hauser *et al*. (2021) conducted a comparative study, where the safety of OCR was investigated in patients with both RMS and PPMS [19]. The primary objective was to provide insights into the safety of OCR over a span of up to 7 years, encompassing patients participating in clinical trials and those receiving treatment in real-world post marketing settings.

The methodology employed for this safety analysis entailed the integration of clinical and laboratory data derived from a diverse patient cohort who had received OCR across 11 clinical trials. This dataset encompassed information from both the controlled treatment phase and the subsequent OLE periods of the phase 2 and 3 trials. Additionally, data from the phase 3b trials VELOCE, CHORDS, CASTING, OBOE, ENSEMBLE, CONSONANCE, and LIBERTO were included. Furthermore, selected Adverse Events (AEs) were evaluated using post marketing data. Importantly, the study placed the incidence rates of Serious Infections (SIs) and malignancies into context by leveraging data from various epidemiologic sources.

The study cohort comprised 5,680 patients with MS who had received OCR, corresponding to a cumulative exposure of 18,218 Patient-Years (PY) across clinical trials. The analysis revealed that the rates per 100 PY (with corresponding 95% confidence intervals) for various safety parameters, including AEs (248; 246-251), serious AEs (7.3; 7.0-7.7), infusion-related reactions (25.9; 25.1-26.6), and infections (76.2; 74.9-77.4), were generally consistent with those observed during the controlled treatment phases of the phase 3 trials. Furthermore, the rates of the most common serious AEs, such as SIs (2.01; 1.81-2.23) and malignancies (0.46; 0.37-0.57), were found to be in line with the ranges reported in epidemiologic data.

In the discussion, it was emphasised that continuous administration of OCR over a period of up to 7 years within clinical trial settings, as well as its extended use for more than 3 years in real-world clinical practice, exhibited a favourable and manageable safety profile. Importantly, no emerging safety concerns were identified in this heterogeneous population of MS patients.

In terms of evidence classification, this analysis provides Class-III evidence, signifying that long-term, continuous treatment with OCR maintains a consistent and favourable safety profile in patients diagnosed with RMS and PPMS. This classification as Class III is due to the utilisation of OLE data and historical controls in the study design.

In contrast to interferon-β-1a and placebo cohorts, it is worth noting that OCR treatment is linked to a marginal elevation in the risk of infections. However, it is essential to underscore that these infections predominantly manifest as mild-to-moderate in severity. Importantly, the incidence of serious infections maintains a low prevalence throughout the course of 7 years of OCR treatment. Moreover, this observed rate aligns closely with the incidence of infection-related hospitalizations reported in real-world cohorts of individuals affected by MS. Additionally, it is noteworthy that opportunistic infections, though a rare occurrence, exhibit a consistent and stable rate year-on-year, mirroring the rates observed during the pivotal phase III studies [20].

Overall, the included studies provided compelling evidence supporting the long-term effectiveness and safety of OCR as a DMT for both PPMS and RMS. The findings highlight the benefits of early initiation and continued treatment with OCR in reducing disability progression and improving clinical outcomes in patients with MS. However, further research and monitoring are necessary to ensure a comprehensive understanding of the treatment's long-term effects. These results contribute significantly to our understanding of OCR's long-term benefits in the management of MS [20].

Discussion

Interpretation of the findings in light of previous research

In this comprehensive review, the summary and interpretation of findings from several studies that investigated the long-term efficacy and safety of OCR in patients with PPMS and RMS is presented. These studies have provided valuable insights into the benefits and safety profile of OCR in the management of MS over extended periods.

In the context of PPMS, Schmierer *et al*. conducted a study within the OLE of the ORATORIO trial, focusing on the long-term effectiveness of OCR [15]. The results highlighted that initiating OCR treatment 3 years–5 years earlier significantly reduced the risk of both wheelchair confinement and 24-week CDP when compared to the placebo-OCR group. This observation aligns with prior research findings, underscoring the importance of early intervention with OCR in PPMS.

Additionally, the analysis by Wolinsky *et al*. demonstrated sustained and nearly complete suppression of lesion activity in patients receiving OCR for an extended period. Notably, those who consistently received OCR exhibited smaller increases in T2 lesion volume and T1 hypointense lesion volume, emphasizing the therapeutic benefits of long-term OCR treatment.

Moving on to RMS, Giovannoni *et al*. investigated the long-term efficacy of OCR in the open-label extension of the Phase III OPERA I/II trials. Patients who transitioned to OCR from interferon-β-1a exhibited rapid and sustained reductions in relapse rates and disability progression. These findings were further supported by a subsequent study by Giovannoni *et al*. in 2021, which reaffirmed the therapeutic advantages of OCR over a 7.5-year observational period. The reduction in relapse rates and disability progression in patients consistently receiving OCR highlights its enduring clinical benefits in RMS.

In another study, Hauser *et al*. reported the safety of OCR in both RMS and PPMS patients over a span of up to 7 years [21]. The results demonstrated a generally well-tolerated safety profile, with rates of adverse events, serious adverse events, and infections similar to those observed in controlled treatment periods of Phase III trials. This consistent and favourable safety profile suggests that OCR maintains its safety record irrespective of the initial exposure, providing reassurance to clinicians and patients alike.

A notable study conducted in 2023 by Hauser *et al* extended the follow-up period to 9 years, reaffirming the importance of higher OCR exposure in achieving more comprehensive B-cell depletion [21]. This observation aligns with prior research findings and underscores the significance of optimizing OCR dosing for enhanced therapeutic outcomes in MS patients. Importantly, no significant association was observed between initial OCR exposure levels and long-term safety outcomes, further supporting OCR's role as a long-term therapeutic strategy.

In conclusion, the findings from these studies collectively emphasise the sustained efficacy and favourable safety profile of OCR in the treatment of MS over extended periods. Early initiation and continuous treatment with OCR have shown consistent benefits in reducing disability progression and improving clinical outcomes in both PPMS and RMS patients. These findings substantially enhance our comprehension of the enduring advantages of OCR in the management of MS, instilling optimism in both patients and healthcare practitioners as they continue to combat this challenging condition. Continued research and monitoring will be essential to further elucidate the long-term effects of OCR treatment in MS.

Comparison of the effectiveness and safety of OCR with other DMTs: In research led by McCool *et al*., a systematic review and Network Meta-Analysis (NMA) were employed to evaluate the effectiveness and safety of OCR compared to other approved DMTs for RMS [22].

OCR had received approval from the US Food and Drug Administration in March 2017 and from the European Medicines Agency in January 2018 for the treatment of both RMS and PPMS.

The approval of OCR for RMS was primarily based on the results of two pivotal RCTs known as OPERA I and OPERA II. These trials compared the efficacy of OCR at a dosage of 600 mg with an active comparator, interferon β-1a 44 µg (Rebif). Additionally, the first trial with positive results in patients with PPMS also involved OCR, comparing it with a placebo. However, direct evidence of the comparative efficacy and safety of OCR against other approved DMTs for RMS was lacking from RCTs.

To address this gap in direct evidence, the researchers conducted NMAs using comprehensive systematic literature searches across databases such as MEDLINE, Embase, the Cochrane Library, trial registers, relevant conference websites, and health technology assessment agency websites. Eligible RCTs included in this analysis evaluated treatments approved for MS in cohorts where more than 75% of patients exhibited a relapsing form of MS. The NMAs encompassed four efficacy outcomes and three safety outcomes. Surface under the Cumulative Ranking Curve (SUCRA) values were employed to establish treatment hierarchies for each outcome.

The treatments assessed in this study were Alemtuzumab (12 mg), Ocrelizumab (600 mg), Interferon β-1b (250 µg, s.c.), Natalizumab (300 mg), Glatiramer Acetate (20 mg), Fingolimod (0.5 mg), Cladribine (3.5 mg/kg), Daclizumab (150 mg), Pegylated Interferon β-1a (125 µg), Interferon β-1a (44 µg, s.c.). Dimethyl Fumarate (240 mg), Teriflunomide (7 mg), Interferon β-1a (30 µg i.m.), Teriflunomide (14 mg), Glatiramer Acetate (40 mg), Interferon β-1a (22 µg, s.c.), and Placebo.

The findings of the NMA reveal that OCR exhibits superior efficacy when compared to 10 out of 17 treatments in the 12-week confirmed disability progression network and 12 out of 17 treatments in the ARR network (both including placebo). Importantly, OCR’s efficacy is comparable to other treatments in both networks. Moreover, in the networks assessing serious

adverse events and discontinuation due to adverse events, OCR demonstrates a safety profile that is consistent with all other treatments, including placebo. Across all outcomes analysed, SUCRA values consistently rank OCR among the most effective or tolerable treatments.

In conclusion, the results of the NMA strongly suggest that OCR possesses efficacy that is either superior to or on par with all other currently approved DMTs for RMS across all evaluated endpoints. Furthermore, its safety profile is similar to that of other approved treatments [22].

Limitations of the study and areas for future research

Heterogeneity across Studies: A significant challenge in this study lies in the inherent heterogeneity observed across the included studies. MS is a complex condition with varying clinical presentations and progression patterns. The differences in study designs, patient demographics, and outcome measures among the selected studies contribute to this heterogeneity. Consequently, it becomes difficult to draw definitive conclusions that apply universally to all MS patients.

Limited Availability of Long-term Data: Another limitation of this study is the scarcity of long-term data for OCR treatment in MS, particularly for patients with PPMS. The limited availability of extended follow-up data restricts the studies ability to provide detailed insights into OCR's long-term effects, especially in specific subpopulations.

In summary, this study's limitations encompass the inherent heterogeneity across studies, and the scarcity of long-term data. These constraints emphasise the need for cautious interpretation of these findings and underscore the importance of ongoing research to address these limitations and provide more comprehensive insights into OCR's long-term efficacy and safety in MS management.

Future research in the field of MS should prioritise addressing critical knowledge gaps related to the long-term risks associated with DMTs, particularly OCR. While this study has provided valuable insights into OCR's long-term effectiveness and safety, several areas warrant further investigation. Firstly, there is a pressing need to gain a more comprehensive understanding of the long-term risks associated with OCR treatment. Notably, the potential for hypogammaglobulinemia as a long-term risk remains an area of concern. In-depth studies that extend over extended periods can help elucidate the incidence, severity, and clinical implications of hypogammaglobulinemia in MS patients receiving OCR [23]. Additionally, research efforts should focus on identifying risk factors or biomarkers that may predispose certain individuals to this adverse event. Furthermore, long-term safety assessments should encompass a broader spectrum of outcomes, including but not limited to malignancies, opportunistic infections, and other immune-related adverse events. By addressing these critical gaps in knowledge, future research endeavors can provide clinicians and patients with a more comprehensive understanding of the long-term implications and risks associated with OCR treatment in MS, ultimately guiding more informed treatment decisions and optimizing patient care strategies.

Conclusion

In conclusion, the review of studies on OCR for treating MS offers valuable insights into its long-term effectiveness and safety. Managing MS is challenging, and OCR, the only approved disease-modifying therapy for relapsing and primary progressive forms, has emerged as a pivotal treatment.

The studies highlight significant benefits of OCR. In PPMS, initiating OCR treatment earlier reduces disability progression risk, including 24-week CDP and the need for wheelchair confinement. OCR also substantially suppresses lesion activity in PPMS patients.

In RMS, OCR consistently reduces relapse rates and disability progression compared to interferon-β-1a. Transitions from interferon-β-1a to OCR result in rapid and sustained reductions in relapse rates and disability progression, emphasizing OCR's enduring clinical benefits.

Moreover, safety assessments of OCR over extended treatment durations demonstrate a manageable safety profile, further supporting its long-term use in MS management. The findings collectively underscore OCR's effectiveness and safety in addressing the complexities of MS, enhancing the overall quality of life for patients.

In closing, the extensive research reviewed here provides a comprehensive understanding of OCR's role in the management of MS. It has shed light on its remarkable long-term benefits, particularly in reducing disability progression, suppressing relapse rates, and improving clinical outcomes, offering hope to patients grappling with this challenging disease.

However, this body of research also reveals some crucial areas for future exploration. The limited availability of long-term data, especially in PPMS populations, calls for continued investigations that extend over extended periods. Furthermore, understanding the long-term risks of OCR, such as hypogammaglobulinemia, remains critical for a more comprehensive risk-benefit assessment.

In light of these findings, it is recommended that healthcare practitioners consider OCR as a valuable treatment option for both relapsing and primary progressive forms of MS. However, patient-specific factors, such as comorbidities and individual preferences, should be thoroughly evaluated to make informed treatment decisions.

Additionally, ongoing research efforts should priorities gathering more extended, real-world data to further substantiate OCR's long-term effectiveness and safety profile. This will aid in refining treatment strategies and optimizing patient care.

In conclusion, OCR has emerged as a promising therapeutic intervention in the battle against MS. Its long-term benefits and relatively favourable safety profile make it a valuable addition to the arsenal of disease-modifying therapies. With ongoing research, clinicians can continue to refine their understanding of this treatment, providing patients with increasingly effective and personalised care strategies.

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