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COMB157GUS37 Study Results Abstract for Public Disclosure

Title

Comparative Effectiveness of Kesimpta® (Ofatumumab) versus Ocrevus® (Ocrelizumab) in Real-world Practice: A Retrospective Study

Keywords:

Multiple sclerosis, relapsing forms of multiple sclerosis, anti-CD20 monoclonal antibody, real-world evidence, comparative effectiveness, annualized relapse rate, healthcare resource utilization, administrative claims data, ofatumumab, ocrelizumab.

Rationale and background

Multiple Sclerosis (MS) is a chronic autoimmune disease that affects the central nervous system (CNS), leading to the loss of neurological function due to inflammation, demyelination, and axonal degeneration.[1,2] This debilitating condition presents in a variety of severe symptoms, such as impaired movement, vision problems, and issues with bladder and/or bowel control, along with numbness, tingling, and pain.[3] As a leading cause of non-traumatic neurological disability in young adults, MS impacts approximately 2.3 million individuals worldwide.[2]

In most patients, the disease starts with a relapsing course, characterized by the occurrence of relapses or exacerbations (i.e., episodes of worsening symptoms or the appearance of new symptoms) that are followed by periods of partial or complete recovery (relapsing-remitting MS [RRMS]). RRMS transforms at later stages into progressive disease (secondary progressive MS [SPMS]), characterized by slow deterioration that occurs independently of acute disease relapses and does not reflect residual deficits from acute disease attacks. A minority of patients develop progressive disease from the onset (primary progressive MS [PPMS]).

Relapses in MS are caused by new or worsening inflammation in the CNS, which causes acute damage to the nerves and gives rise to symptoms.[4] In contrast, progression in MS is likely related to the accumulation of neuro-axonal loss in a lifelong inflammatory CNS environment (both adaptive and innate) and relative un-balance between damage, repair, and brain functional reserve.[5]

Ofatumumab ([OMB] 20 mg/0.4 mL solution in a single-dose prefilled pen/syringe; Novartis) and ocrelizumab ([OCR] 300 mg/10 mL intravenous [IV] infusion; Genentech) are two CD20-directed cytolytic monoclonal antibodies approved by the Food and Drug Administration (FDA) for the treatment of relapsing forms of MS (RMS), including RRMS and active SPMS. The efficacy of OMB versus teriflunomide in reducing MS relapse has been demonstrated in two pivotal clinical trials (ASCLEPIOS I & II).[6] Likewise, the efficacy of OCR versus interferon beta-1a in MS has been demonstrated in the OPERA I & II trials.[7] A network meta-analysis comparing OMB to other MS disease-modifying therapies (DMTs) found no significant differences in the effect of OMB versus OCR on annualized relapse rate (ARR).[8] Similarly, a

recent real-world United States (US) study of patients with MS treated with OMB reported an ARR of 0.10 after OMB initiation, which aligns with published ARR estimates for OCR in comparable populations (0.09 – 0.15).[9]

Despite indirect evidence suggesting comparable effectiveness in OMB versus OCR, direct comparisons in balanced populations are still needed. In the absence of head-to-head clinical trial evidence, real-world data can help assess the relative effectiveness of OMB versus OCR in a broad MS population. To this end, the following study will compare real-world clinical outcomes, including ARR, as well as healthcare resource utilization (HCRU) and healthcare costs (HCC) in treatment-naïve patients with MS initiated on OMB versus OCR using administrative claims data in the US.

Research question and objectives

The study aimed to generate real-world evidence on the clinical effectiveness and economic burden of OMB versus OCR in patients diagnosed with MS in the US. Clinical effectiveness was assessed using ARR, while economic burden was assessed using HCRU and HCC. While the primary interest was in treatment-naïve patients diagnosed with MS, the study also compared clinical effectiveness and economic burden in all patients treated with OMB versus OCR, regardless of prior treatment (i.e., both treatment-naive and -experienced patients).

Study design and Setting

This was a retrospective cohort study using claims data during the period from August 2019 through July 2024, to compare ARR and HCRU in patients with MS initiating subcutaneous (SC) OMB or intravenous (IV) OCR. The study included claims from adults aged ≥18 years who had a first claim (the index date) for either OMB (ie, pooled OMB cohort) or OCR (ie, pooled OCR cohort) from August 20, 2020, with no claim for either drug during the preceding 12 months.

To be included, patients needed to have either: a) two or more outpatient claims associated with an MS diagnosis (per the International Classification of Diseases, 10th Revision: G35.xx) in any position (ie, regardless of whether MS was listed as the primary diagnosis on the claim). Claims needed to occur at least 30 days apart, with the first claim placed during the pre-index period (ie, in the 12 months up to and including the index date) and the second could occur in the pre-index period or up to 6 months after the index date; or b) at least one inpatient claim with a primary MS diagnosis during the pre-index period. Additional inclusion criteria were continuous patient enrollment (ie, uninterrupted health plan coverage) throughout the pre-index period and at least 6 months after the index date and persistent use of OMB or OCR for at least 6 months after the index date, with no gaps exceeding 60 days and no treatment switches.

Variables

ARR was measured in a period of at least 6 months starting from the index date until the end of persistence, continuous enrollment, or the study period, whichever came first. Relapse was defined as an inpatient stay with a primary MS diagnosis or an outpatient or emergency department (ED) visit with an MS diagnosis (in any position) plus a claim for high-dose oral corticosteroid, intravenous methylprednisolone (excluding ± 5 days around OCR infusion),

corticotropin, or plasma exchange within 7 days.[10, 11] Relapses within 30 days were combined into a single episode. Inpatient, outpatient, or ED claims with a code for an index DMT were excluded.

Assessment of HCRU and HCC included MS-related inpatient stays, inpatient days, outpatient visits, and ED visits. To be designated as MS-related, inpatient stays were required to have an MS diagnosis in the primary position, while outpatient and ED visits could have an MS diagnosis in any position. HCRU and HCC were restricted to non-DMT claims. Claims with a National Drug Code or Healthcare Common Procedure Coding System for administration of index DMT, or other DMT indicated for MS, were excluded.

Statistical methods

ARR was assessed using Poisson regression or negative binomial regression, depending on dispersion, and compared between cohorts using incidence rate ratios (IRR) with 95% confidence interval (CI). Covariates that remained imbalanced after matching (standardized mean difference >0.2) were adjusted for in the models.

For the HCRU analysis, annualized rates of inpatient stays, outpatient visits, and ED visits were modeled using Poisson or negative binomial regression, depending on dispersion. For the HCC analysis, generalized linear models with a Tweedie distribution and log-link function was used to compare mean of each cost component between cohorts.

Results

Demographic and Baseline Clinical Characteristics

A total of 2604 patients were included in the analysis, with 751 in the pooled OMB cohort and 1853 in the pooled OCR cohort. The treatment-naïve sub-cohorts included 315 patients receiving OMB and 1104 patients receiving OCR. Before matching, the pooled OMB cohort was younger, had more female patients, more recent index dates, and greater prior DMT use. After matching, there were 751 patients in each overall cohort and 315 patients in each treatment-naïve sub-cohort with baseline characteristics balanced between cohorts except for year of index date. In the matched cohorts, patients had low comorbidity burden, with mean Deyo-Charlson Comorbidity Index (DCCI) ranging from 0.8 to 1.0, a mean age ranging from 45 to 48 years, and were predominantly female (72-75%), White (51-53%), and commercially insured (67-76%).

MS Treatment History

Approximately 58% of patients in the matched pooled cohorts used at least 1 DMT during the pre-index period. In the pre-index period, the most commonly used low- or moderate-efficacy DMTs in the OMB cohort were teriflunomide (12.5%), dimethyl fumarate (12.1%), and glatiramer acetate (10.8%), while natalizumab was the most commonly used high-efficacy DMT (8.9%). In the OCR cohort, the same four DMTs were most commonly used, but in slightly different proportions: dimethyl fumarate (13.5%), glatiramer acetate (9.9%), teriflunomide (10%), and natalizumab (9.5%).

ARR Outcomes

A comparison of relapses between the matched cohorts during the follow-up period revealed a significantly lower ARR [95% CI] in the pooled OMB cohort (0.10 [0.08, 0.13]) compared with the pooled OCR cohort (0.14 [0.12, 0.17]), equating to a 31% lower incidence of relapse with OMB (IRR [95% CI]: 0.69 [0.51, 0.94]; p=0.019). This difference remained statistically significant after adjusting for index year (adjusted IRR [95% CI]: 0.69 [0.51, 0.95]; p=0.021). Similarly, there was a significantly lower ARR [95% CI] in the treatment-naïve OMB cohort (0.10 [95% CI: 0.07, 0.15]) versus the treatment-naïve OCR cohort (0.18 [0.13, 0.25]), equating to a 41% lower incidence of relapse with OMB (IRR [95% CI]: 0.59 [0.35, 0.99]; p<0.05). After adjusting for index year, the ARR remained numerically lower in the treatment-naïve OCR cohort, although the difference was no longer statistically significant (adjusted IRR [95% CI]: 0.61 [0.36, 1.02]; p=0.06).

HCRU Outcomes

The rate of MS-related outpatient visits per patient-year (PPY) was lower in the pooled OMB cohort compared with the pooled OCR cohort after matching (8.64 vs 9.51). The adjusted IRR [95% CI] for MS-related outpatient visits was 0.91 [0.84-0.98], indicating a 9% lower incidence in the OMB versus OCR cohorts that was statistically significant (p=0.014). The lower rate of MS-related outpatient visits PPY in the treatment-naïve OMB cohort relative to the treatment-naive OCR cohort (8.24 vs 10.42) was more pronounced than for the pooled cohorts. The adjusted IRR [95% CI] indicated a statistically significant 20% lower incidence of MS-related outpatient visits in the OMB versus OCR treatment naïve sub-cohorts after matching (adjusted IRR [95% CI]:0.80 [0.71-0.90]; p<0.001). All other HCRU measures (MS-related inpatient stays, inpatient days, and ED visits) were numerically lower in the matched OMB cohorts, both pooled and treatment-naïve, compared with the OCR cohorts, but these differences did not reach statistical significance. It should be noted that MS-related outpatient visits reported here excluded those associated with administration of DMT.

HCC Outcomes

For the pooled cohort, overall non-DMT MS-related medical costs (inpatient, outpatient, ED) were 19% lower in the OMB cohort compared with the OCR cohort (adjusted cost ratio: 0.81 [0.68-0.97]; P=0.025). MS-related outpatient costs were 18% lower for OMB (adjusted cost ratio: 0.82 [0.68-0.98]; P=0.028), and ED costs were 45% lower for OMB (adjusted cost ratio: 0.55 [0.31-0.98]; P=0.042). For the treatment-naïve cohort, overall non-DMT MS-related medical costs (inpatient, outpatient, ED) were 23% lower in the OMB cohort compared with the OCR cohort (adjusted cost ratio: 0.77 [0.61-0.98]; P=0.032). MS-related outpatient costs were 23% lower for OMB (adjusted cost ratio: 0.77 [0.61-0.98]; P=0.036). No significant differences were observed in inpatient or ED costs.

Discussion

This real-world US claims-based study compared the relative effectiveness of OMB and OCR, as determined by ARR, and measured MS-related HCRU for both treatments, including inpatient stays, inpatient days, outpatient visits, and ED visits. ARR was significantly lower in OMB- versus OCR-treated patients, with the between-treatment difference appearing more pronounced in those who were treatment naïve. Similarly, in terms of HCRU, OMB-treated

patients were significantly less likely to require MS-related outpatient visits than OCR-treated patients, even when excluding visits for DMT administration. The between-treatment difference was again more pronounced in the treatment naïve sub-cohorts than in the overall cohorts. Differences in other MS-related HCRU measures were not significant between patients treated with OMB and OCR. These findings are consistent with previous indirect comparisons of OCR and OMB, which suggest that OMB is at least as effective (and possibly more effective) than OCR in preventing relapses.[8, 9]

Pharmacokinetic and pharmacodynamic differences between OMB and OCR could potentially explain the differences observed in their effectiveness profiles. OCR, administered intravenously, rapidly depletes circulating and bone marrow B-cells in humans. However, studies in animal models of MS have shown that some B-cells persist in lymph nodes after IV OCR administration, potentially allowing residual inflammatory activity that could contribute to relapses. On the other hand, SC OMB administration achieved greater lymph node penetration in those mice models compared with IV OCR, effectively depleting B-cells in lymph nodes.[12, 13]

Given that both OMB and OCR are highly effective treatments for RMS, it is important to consider other factors, such as HCRU and cost-effectiveness, to inform treatment decisions. Consistent with the HCRU findings in the present study, economic and cost-effectiveness analyses from Canada and the United Arab Emirates showed that outpatient HCRU is lower with OMB than with OCR, a finding that was predominantly attributed to the lower resource utilization needed for self-administration of SC OMB at home, which eliminates the need for regular outpatient or infusion clinic visits for the IV administration of OCR.[14, 15] Moreover, OMB was more effective and had lower costs than OCR, meaning that OMB was both more effective and less costly, with the reduced outpatient visit burden being a key driver of this advantage.[14, 15] In the present study, however, HCRU related to the administration of OMB or OCR was excluded, suggesting that other factors may also play a substantial role.

Conclusion

In conclusion, in this real-world, propensity score matched study of claims data, OMB treatment was associated with lower AAR and lower HCRU compared with OCR treatment in patients with RMS.

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