Cost-effectiveness of ocrelizumab for treatment of Iranian patients with relapsing multiple sclerosis

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Abstract
Background: The current study desired to conduct an economic analysis on ocrelizumab (OCR), a new relapsing multiple sclerosis (RMS) treatment strategy, in comparison to natalizumab (NTL), as one of the mostly-used disease-modifying therapies (DMTs) in Iran.

Methods: A 31-health-state Markov model, based on Expanded Disability Status Scale (EDSS), containing patients on- and off-treatment with annual cycles was developed. Baseline demographics and utility scores were extracted from OPERA 1 and 2 trials. Confirmed disability progression (CDP) and annualized relapse rates (ARR) were extracted from the literature. Mortality was calculated based on age, sex, and disease state. Quality-adjusted life years (QALYs) and life years gained (LYG) were measurements of efficacy. Direct and indirect costs were identified and calculated based on the national book of tariffs in Iranian Rial (IRR) rates, then converted to the 2020 United States Dollar (USD). Final results were reported in terms of incremental cost-effectiveness ratio (ICER), which showed extra costs required for one additional QALY. Robustness of the model was analyzed through deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA).

Results: OCR dominated NTL and was associated with cost-savings of 6971 USD, longer LYG (0.004), and higher QALYs (0.27). Although OCR had higher acquisition costs, which was the main component in both comparator arms, it was associated with lower total costs, due to lower disability progression and productivity loss. Results remained robust in DSA and PSA (93.5% cost-effectiveness in Iran’s pharmacoeconomic threshold, 2709 USD).

Conclusion: Results suggested that OCR was a more cost-effective option than NTL for the treatment of patients with RMS in Iran.

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Introduction
Multiple sclerosis (MS) is the most common neurodegenerative central nervous system (CNS) immune-related disorder, and negatively impacts both functional ability and quality of life (QoL) of patients. Due to the 2019 global burden of disease (GBD) report, prevalence of MS in 2016 was estimated to be 2.22 million, which represented an increasing trend of 10.4% since 1990.

MS usually starts in most productive years of adult life (15-45 years) and mostly in women. This disorder is categorized into four types: relapsing-remitting MS (RRMS), primary progressive MS (PPMS), secondary progressive MS (SPMS), and progressive-relapsing MS (PRMS). The most common type is RRMS (85%), in which the patient experiences an episode of exacerbation in neurological symptoms, followed by remission.

MS has a considerable economic and socioeconomic burden on the society, healthcare systems, patients, and associated families, especially in the low- and middle-income countries, due to scarcity of data, resources, and surveillance. This burden tends to increase with chronic disability progression and occurrence of relapses and is mainly due to direct medical costs in first stages; however, with disease progression, direct non-medical costs and indirect costs tend to significantly increase. Iran is a middle-income country with relatively high incidence (5.87/100000) and prevalence (54.51/100000) of MS, based on the Kurtzke categorization. Mean one-year cost per Iranian patient with MS in 2012 was calculated to be between $27000 and $31661 in first three stages of disease and was presumed to become more with disease progression. The majority of costs were due to pharmacological treatments.

MS disease-modifying therapies (DMTs) aim to slow the confirmed disability progression (CDP) and decrease the number of annual relapses. Second-line DMTs which are available in Iran are fingolimod and natalizumab (NTL) and recently, ocrelizumab (OCR). These were mostly used in patients who had inadequate response to first-line DMTs or had high disease activity RRMS (HAD-RRMS). OCR, a humanized anti-CD20 monoclonal antibody (MAB), was approved by Food and Drug Administration (FDA) (2017) and European Medicines Agency (EMA) (2018) to be prescribed in patients with RRMS and also patients with PPMS, based on the results of two main active-controlled phase-three randomized controlled trials (RCTs), OPERA I and II in RRMS and one placebo-controlled phase-three RCT, ORATORIO, in PPMS.

Regarding that the DMTs costs are the main component of MS economic burden, a comparison of their costs in parallel to their ability to reduce disability progression and number of relapses can be helpful to the healthcare providers and other stockholders. The purpose of this study was to conduct a cost-utility analysis (CUA) of OCR in comparison to NTL, the commonly-used DMT in the same pharmacological class, from societal perspective and in the context of Iran.

Materials and Methods
Overview and model structure: A hypothetical cohort Markov model with a 10-year time horizon was developed to compare OCR versus NTL in Iranian patients with RRMS who failed to respond to at least one first-line DMT. Quality-adjusted life years (QALYs) and life years gained (LYG) were measurement units of effectiveness. Due to the disabling nature of MS and high costs of productivity loss, a societal perspective was chosen and both direct and indirect costs were taken into account. Costs and QALYs were discounted by 7.2% and 3.5%, respectively. Results were presented in terms of incremental cost-effectiveness ratio (ICER), which showed cost needed per one extra QALY, and was compared to the national threshold, that was 1 times the national gross domestic product (GDP) per capita in the conducting year [2709 United States Dollar (USD) in 2020].

One of the most popular progression scoring tools used in RCTs, Expanded Disability Status Scale (EDSS), which has an ordinal rating system from 0 (normal neurological health) to 10 (death), was used for developing a 31-health state model, 10 health states for RRMS on-treatment, 10 for RRMS off-treatment, 10 for SPMS, and also 1 absorbing state of death, in Microsoft Excel (2013 Plus). The model is shown in figure 1. In each 1-year cycle, patients could have stayed in the same state, progressed or regressed to other EDSS states, or died. Patients used medication until entering EDSS 7 or discontinued treatment, due to accordance of adverse drug reactions (ADRs) or lack of response.

In this analysis, baseline demographic characteristics of patients, such as age (mean = 37), female to male ratio (3.34), and starting patient distribution, were extracted from OPERA 1 and 2 trials.
Model inputs

**Transition probabilities and relapse rates**: State transition probabilities and relapse rates in the absence of active drug, which presented natural history of disease, were taken from Palace et al.\textsuperscript{18} for disability progression and Orme et al.\textsuperscript{19} and Patzold and Pocklington\textsuperscript{20} for relapse rates. London (Ontario) dataset transition probabilities were used for patients with RRMS progressing to SPMS.\textsuperscript{21} SPMS natural history transition probabilities were derived from Palace et al. Conversion to SPMS for patients on DMTs was assumed to be only dependent on EDSS score (natural history transition probabilities).

In the absence of a head-to-head clinical trial comparing OCR versus NTL, an indirect treatment comparison, in terms of systematic review and network meta-analysis (NMA), was acquired.\textsuperscript{22} This NMA compared OCR with all approved DMTs, in terms of seven efficacy and safety measurements, using all available clinical trials with more than 75% of relapsing MS (RMS) patient population. Efficacy and safety variables which were reported were: annualized relapse rate (ARR), CDP at 12 weeks, CDP at 24 weeks, proportion of relapse free, serious adverse events, all-cause discontinuation of treatment, and discontinuation due to adverse events. The results of NMA are shown in table 1. To calculate 12- and 24-week CDP and also ARR probabilities per one year, NMA results, natural history transition probabilities, and also waning effect were taken into consideration for both comparators. In this analysis, it was assumed that treatment efficacy would wane over time by 0% in years 0 to 5, 25% in years 6 to 9, and 50% in year 10, for both comparator arms.\textsuperscript{22}

**Safety**: Adverse events’ types and rates were included from daclizumab submission to National Institute for Health and Care Excellence (NICE)\textsuperscript{23} for both arms and ADR-management components in Iran were derived from expert opinion.

**Utilities**: An state-related utility score was utilized, using OPERA 1 and 2 trials’ reported data.\textsuperscript{17} For patients with SPMS, a decrement of 0.0450 was used, compared to RMS utility scores. Disutility of relapse was -0.071 and its mean duration was 46 days.\textsuperscript{19} It was assumed that 60 percent of relapses required hospitalization, based on expert opinion. Disabilities for severe relapses were taken from the Lemtrada manufacturer submission to NICE\textsuperscript{24} and was used to adjust the Orme et al.\textsuperscript{19} data (-0.071) to give a utility value of -0.2356 for relapses leading to hospitalization. These were calculated for relapses in SPMS, as well. Caregiver disutility was also included in the model, based on EDSS score of patients using the method reported in the NTL submission.\textsuperscript{25} As actual measurements were not available, it was assumed that disutility had a maximum value of -0.14, based on the value accepted by NICE in an assessment of treatments for Alzheimer’s Disease (AD).\textsuperscript{26} MS caregivers’ disutility, by patient EDSS state, was calculated as the product of the percentage of time spent caring and the maximum disutility of 0.14. This was then divided by the maximum percentage of time spent caring, which occurred at EDSS of 8.5-9.5. Accordingly, an index of disabilities from 0.00 at EDSS 0 to 0.14 at EDSS 8.5-9.5 was generated. Utility and disutility data are presented in table 2. ADR disutility data were taken from daclizumab submission to NICE,\textsuperscript{23} except for progressive multifocal leukoencephalopathy (PML) which was assumed to be -0.4, for the year patient suffering it.\textsuperscript{27}

![Figure 1. Model structure](image)

**RRMS**: Relapsing-remitting multiple sclerosis; **SPMS**: Secondary progressive multiple sclerosis

| Table 1. Network meta-analysis (NMA) results |
|------------------------------------------|
| **Outcome**                             | **OCR versus Placebo** | **OCR versus NTL** |
| ARR (RR)                                | 0.34 (0.26, 0.43)      | 1.07 (0.77, 1.46)  |
| CDP at 12 weeks (HR)                    | 0.38 (0.24, 0.61)      | 0.67 (0.38, 1.18)  |
| CDP at 24 weeks (HR)                    | 0.45 (0.23, 0.84)      | 0.97 (0.44, 2.07)  |
| Proportion relapse free (OR)            | 4.90 (3.12, 8.10)      | 1.61 (0.84, 3.25)  |
| Serious adverse events (OR)             | 0.61 (0.31, 1.19)      | 0.83 (0.37, 1.93)  |

ARR: Annualized relapse rate; CDP: Confirmed disability progression; RR: Rate ratio; HR: Hazard ratio; OR: Odds ratio; NTL: Natalizumab; OCR: Ocrelizumab
Table 2. Utility and disutility data by Expanded Disability Status Scale (EDSS) state

| EDSS state | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|------------|---|---|---|---|---|---|---|---|---|---|
| Patient utility in RRMS | 0.870 | 0.799 | 0.705 | 0.574 | 0.610 | 0.518 | 0.460 | 0.297 | -0.049 | -0.195 |
| Patient utility in SPMS | 0.825 | 0.754 | 0.660 | 0.529 | 0.565 | 0.473 | 0.415 | 0.252 | -0.094 | -0.240 |
| Caregiver disutility in RRMS and SPMS | 0.000 | -0.001 | -0.003 | -0.009 | -0.009 | -0.020 | -0.027 | -0.053 | -0.107 | -0.140 |

EDSS: Expanded Disability Status Scale; RRMS: Relapsing-remitting multiple sclerosis; SPMS: Secondary progressive multiple sclerosis

Costs: Direct (medical and non-medical) and indirect costs were accounted in present analysis, based on previous literature and expert opinion. Drug cost data were derived from Iran FDA official website and data on monitoring, hospitalization, and physicians’ visits were calculated using Iranian national book of tariffs for prices and also literature and expert opinion for resource use data. All costs were identified in Iranian Rial (IRR) rates and converted to USD, using an exchange rate of 42000 (Iran central bank announced currency rate on 1/19/2019) IRR/USD. For all costs which had different governmental and private sector costs, a weighted mean price (80% public and 20% private) was included. Costs are summarized in table 3.

Table 3. Cost input components

| Type | Parameter | Intervention | Frequency (annual) | Unit cost ($) | Total cost (annual-\$) |
|------|-----------|--------------|--------------------|---------------|------------------------|
| Direct medical costs | Drug acquisition cost | NTL | 13 | 1509.95 | 19629.38 |
| | | OCR | 4 | 5238.10 | 20952.38 |
| | MAB injection | NTL | 13 | 27.09 | 352.17 |
| | | OCR | 2 | 27.09 | 54.18 |
| | Hospitalization during injection | NTL | 13 | 23.81 | 309.52 |
| | | OCR | 2 | 23.81 | 47.62 |
| | Physician visit | NTL | 2 | 5.67 | 11.34 |
| | | OCR | 2 | 5.67 | 11.34 |
| | Psychotherapy | OCR | 2 | 5.67 | 11.34 |
| Supportive care (in EDSS > 6) | Both | - | - | 119.05 |
| Side prescription drugs | Both | - | - | 28.57 |
| Rehabilitation (in EDSS > 6) | Both | - | - | 817.34 |
| Diagnostics | NTL | Based on guideline | | 113.93 |
| | OCR | Based on guideline | | 58.59 |
| Relapse | Both | 166.00*** | | |
| Infusion-related ADR | Both | 0.21** | 3.57 |
| UTI (ADR) | Both | 0.06** | 0.31 |
| Headache (ADR) | Both | 0.06** | 0.01 |
| URTI (ADR) | Both | 0.08*** | 1.00 |
| Nasopharyngitis (ADR) | Both | 0.08** | 0.43 |
| PML (ADR) | Both | 0.01** | 149.52 |
| Depression (ADR) | Both | 0.11** | 11.30 |
| UTI (ADR) | Both | 0.11** | 0.31 |
| Headache (ADR) | Both | 0.24** | 0.01 |
| Fatigue (ADR) | Both | 0.16** | 0.19 |
| Nursing (EDSS 6, 7) | Both | 3428.57 |
| Nursing (EDSS > 8) | Both | 4285.71 |
| House reconstruction | Both | 2380.95* |
| Car rebuilding | Both | 1190.48* |
| Auxiliary instruments | Both | 476.19* |
| Indirect costs | Work absence (EDSS 1-3.5) | Both | 1.9 days/month | 8.81 |
| | Work absence (EDSS 3-5.5) | Both | 14.4 days/month | 8.81 |
| | Work absence (EDSS ≥ 6) | Both | 365 days | 8.81 |

*First year included three Mab injections and consequently 3 hospitalizations during injections; **Probability of event; ***Per relapse; #One time per treatment cost
ADR: Adverse drug reaction; MAB: Monoclonal antibody; EDSS: Expanded Disability Status Scale; NTL: Natalizumab; OCR: Ocrelizumab; PML: Progressive multifocal leukoencephalopathy; UTI: Urinary tract infection; URTI: Upper respiratory tract infection

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**NTL-related costs:** NTL is administered as 300 mg every 28 days. For this arm, drug acquisition cost (public price without discounts), MAB injection, and monitoring (due to FDA label) were considered. In addition, PML management cost was calculated and inserted in the model.

**OCR-related costs:** OCR is administered as 300 mg (1 vial) every 2 weeks in first month and then 600 mg (2 vials) every 6 months, via intravenous (IV) infusion. To calculate OCR-related costs, drug acquisition cost, administration, and monitoring (same as NTL arm) were considered. Public drug acquisition cost of OCR was calculated based on carriage paid to (CPT) price for Iran, using 2020 governmental conversion rates and pricing regulation mark-ups.

**Relapse-related costs:** This part of costs were derived from alemtuzumab (ALM) cost-effectiveness analysis (CEA) study in Iran, which used hospital records on patients with RRMS and also a local cost-of-care study.

**Other direct medical costs:** Neurologist’s office visit (every 6 months), psychologist visit (every 6 months), rehabilitation (two times per week, after EDSS 6), and side prescription medications (pain killers, anti-depressants, and other common prescribed drugs) were included, as other direct medical costs.

**Direct non-medical costs:** Direct non-medical costs were axillary instruments, car/house modifications, transportation, and nursing services in house. First two were only considered once for patients entering EDSS 6. Nursing costs were included after EDSS 6; however, for the patients with EDSS more than 8, the cost of nursing was higher.

**Indirect costs:** Indirect costs were indicated by calculation of work-absence days due to disease condition. It was assumed that employed patients (below the age of 65 years) were absent from work 1.9 and 14.4 days per month in EDSS < 3.0 and EDSS 3-5.5, respectively. Patients with EDSS ≥ 6 were presumed unemployed. Work absence due to drug administration was not included to avoid double counting. Indirect costs were calculated using work absence frequency and lowest rate of governmental daily wage in Iran ($8.819).

**Discontinuation of treatments:** Treatment withdrawal was due to significant side effects, development of SPMS, insufficient efficacy results, progression to EDSS 7, or pregnancy. First four were considered in model and an all-cause annual withdrawal probability was calculated for both arms, using NMA results.

**Mortality:** Mortality rates were calculated using World Health Organization (WHO) age and sex-adjusted life table for Iran and also EDSS-related mortality rates for patients with MS.

Robustness of model and its sensitivity to model variables were analyzed using one-way deterministic sensitivity analysis (DSA). Parameters included were demographic characteristics, direct medical costs, inclusion of indirect costs, relapse rates, patients’ utility and caregivers’ disutility, disutility of relapses, discount rates, dropout percentages, treatment waning, and mortality rates.

In addition, in order to indicate commutative uncertainty of all parameters together, probabilistic sensitivity analysis (PSA) was conducted by running 1000 iterations. As a result, mean cost and QALY and also acceptability percentage were calculated.

**Results**

**Base-case analysis:** The results indicated that OCR dominated NTL in terms of incremental cost per QALY gained. Discounted QALY and LYG per patient were 5.459 and 8.525 in OCR arm and 5.192 and 8.521 in NTL arm, respectively, in a 10-year time horizon. Discounted costs were calculated $106799 and $113770 for OCR and NTL, respectively. Major cost component in each of the arms was drug acquisition cost; however, regardless of lower drug acquisition cost, NTL was associated with higher total costs in selected time horizon. This was due to more progression and subsequently additional productivity loss and disease-associated costs.

**DSA:** Tornado diagram (Figure 2), which was the result of one-way sensitivity analysis of 26 variables, showed that the model was mostly sensitive to annual drug acquisition costs and also treatment waning in OCR arm. In addition, high input variation in percentages of dropouts had a considerable impact on ICER. On the other hand, the results indicated that male/female ratio, inclusion of indirect costs, mortality multiplier for both RRMS and SPMS, caregiver disutility in RRMS and SPMS, and relapse rates in RRMS and SPMS had small or no impact on ICER.

**PSA:** PSA results showed a mean discounted cost and QALY of $106178 [95% confidence interval (CI): $99037-$112480] and 5.34 (95% CI: 4.99-5.61) for OCR and $112223 (95% CI: $103405-$120308) and 5.06 (95% CI: 4.73-5.38) for NTL, respectively. In addition, results indicated that in most simulations (93.5%), OCR was dominant over NTL, with Iran’s pharmacoeconomic willingness to pay (WTP) threshold ($2709) from societal perspective.
Discussion
To the best of our knowledge, present study is one of the first pharmacoeconomic studies which compared OCR to NTL in patients with RMS in the context of a developing country, and the first in Iran. The results could offer valuable insights for policymakers and also healthcare providers and can be used to make informative decisions for patients with RMS of Iran and other developing countries.

Study results showed that although OCR had higher drug acquisition costs, it was associated with lower total costs and higher efficacy. This resulted OCR to be dominant over NTL. Lower total costs of OCR were mainly due to decrease in disability progression and therefore, lower productivity loss and disease-associated costs. In addition, administration and monitoring costs were lower in OCR, due to durable effects and longer administration intervals. This model was mainly sensitive to OCR drug acquisition costs and percentage of treatment waning. PSA results indicated the robustness of model, which was seen in distribution of parameters, including efficacy, cost, and utility data.

The model of the current study used a 31-health state Markov model, including patients on- and off-treatment. This was due to relatively significant discontinuation rate for both OCR and NTL, which leads patients to shift to RMS-off treatment states. This is one of the differences of current model to some previous 21-state RMS models. In addition, regarding the considerable burden of SPMS occurrence, it was acknowledged in the analysis. This was in consistency with Palace et al. approach, which pooled RRMS and SPMS, as a later state of RMS. OCR is compared to interferon beta 1-alpha (IFNβ-1α) for the treatment of RMS in its main clinical trial17 and also in some pharmacoeconomic studies.31,32 However, we suppose that regarding Iran’s practice (based on expert opinion) and other available comparators, NTL could be presented as a more proper comparator, although in the study by NICE, it has been mentioned that regarding unpredictable natural history of MS in early stages, for some patients with severe relapses, OCR can be prescribed in first line, too. This occurs especially in the absence of ALM in market or in patients who are unable to tolerate ALM’s ADR.33

In Canada, OCR was compared to all available first- and second-line therapies, in the lifetime horizon. In this study’s base-case analysis, NTL, fingolimod, and daclizumab were dominated by OCR and also OCR was cost-effective versus dimethyl fumarate (DMF) and IFNβ. In addition, there was not any considerable survival differences between comparators.34 These results were in consistency with the results of current study.

The results of the study by Zimmermann et al. in 2018, which used United States (US) payer perspective to compare all available DMTs in patients with RRMS in life-time horizon, indicated that in first and second line of RRMS therapy, OCR dominated not only NTL, but also all available comparators in the first and second line of treatment. In this analysis, ICER was sensitive to DMTs’ cost and also progression relative risk;35 however, in the current study, progression relative risk did not have any considerable impact on ICER.

Conclusion
In the current analysis, NTL was dominated by OCR in management of patients with RRMS, from

![Figure 2. Deterministic sensitivity analysis (DSA) tornado diagram](http://cjn.tums.ac.ir)
societal perspective in Iran. This dominance was due to higher efficacy, in terms of QALYs and also LYG, and lower total costs. These results could be supported by future local head-to-head cost-effectiveness alongside clinical trials.

**Limitations:** The current study was subjected to some limitations. First limitation was the absence of head-to-head trials, which led to using an indirect treatment comparison. Although results were adjusted for heterogeneous variables in the NMA, there was a chance that different study characteristics had affected efficacy outcomes.

Second limitation was due to inability to generalize the results to other countries’ healthcare settings. This is not possible because of difference in costs, tariffs, and practice. In studies in the context of Iran, some costs may be underestimated due to lower wages (therefore lower indirect costs), lower hospitalization and monitoring tariffs, and also less drug acquisition costs (especially for drugs which have localized generics). Besides, as natural history data were extracted from Palace et al. study which was subjected to United Kingdom (UK) patients with MS, generalizability to Iranian patients may be a limitation. This is also true for data which were obtained from OPERA trial data, such as average age of cohort or starting patient distribution data.

The third limitation of the current study was that it analyzed OCR comparing only to NTL. This was firstly due to the clinical expert’s opinion and OCR’s place of therapy in the Middle East MS management guideline and secondly based on the pharmacological class similarity of the comparator arms.

Fourth limitation was related to the 10-year time horizon of the study. Although it is suggested to use longer time horizons in economic evaluations due to uncertainty of data in longer periods and also local economic instabilities, a 10-year time horizon was applied.

**Conflict of Interests**

The authors declare no conflict of interest in this study.

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