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Cladribine Tablet, is a dominant comparator to Natalizumab in High-Disease Activity Relapsing Multiple Sclerosis patients, in the context of a developing country

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INTRODUCTION

- Multiple sclerosis (MS), is a central nervous system (CNS) chronic autoimmune disorder, characterized by progressive neurodegenerative mechanisms and highly impacts on patients' quality and quantity of life(1).
- Due to early onset of disease (15-45), MS leads to considerable productivity loss and economic burden on patients, health care systems and society; This productivity loss increases with disability progression and relapse incidences(2).
- Global estimates showed that approximately 2.5 million people are affected by MS worldwide(3) and there is an increase in incidence and prevalence of MS in the Middle Eastern countries(4).
- In Iran, incidence and prevalence of MS was estimated 5.87 and 54.51 in 100,000 people, respectively at year 2014(5).
- MS consists of reversible neurological deficits, followed by progressive neurological deterioration. Common symptoms are sensory loss, weakness in the muscles, cognitive disorder, optic neuritis and gait ataxia(6).
- MS is categorized as follow: relapsing-remitting MS (RRMS), progressive- relapsing MS (PRMS), primary progressive MS (PPMS) and secondary progressive MS (SPMS). Relapsing MS (RMS) accounts for about %85 of the cases and is categorized by 45 to 90 days period of neurological symptom worsening, followed by remission of symptoms(7).
- RMS patients who are experiencing at least one relapse in previous year and magnetic resonance imaging (MRI) evidences of disease activity, despite treatment with at least one drug modifying therapy (DMT) or patients with two or more relapses in the previous year, whether on DMT treatment or not, are considered as high disease activity relapsing multiple sclerosis (HDA-RMS)(8).
- Management of HDA-RMS in Iran is primarily achieved by the use of available potent DMTs; fingolimod and natalizumab(9).
- Cladribine tablets are the first oral treatment hypothesized to act as an immune reconstitution therapy for HDA-RMS(10). The recommended dose of cladribine tablets is 3.5 mg/kg (consisting of 2 annual courses that are each comprised of 2 treatment weeks); as indicated by two pivotal trials (CLARITY and CLARITY Extension). Over 75% of patients treated with cladribine tablets in Years 1 and 2 remained relapse-free without active treatment in Years 3 and 4 during pivotal trial (CLARITY Extension)(11).

OBJECTIVES

- **The objective is to conduct an economic analysis by developing a decision analytic model to assess cost-utility of cladribine tablets in comparison to natalizumab in HDA-RMS patients, from a societal perspective, in Iranian setting.**

METHODS

Overview and Model Structure:

- Microsoft® Excel based multi-state Markov model for cost-utility analysis (CUA) was adopted(12) to understand economic implications of introducing cladribine tablets, as an alternative to natalizumab, for the treatment of HDA-RMS patients in Iranian setting.
- The model was based on Kurtzke's Expanded Disability Status Scale (EDSS) system and was presented using a 11-health state structure comprising 10 EDSS-based on and off-treatment states and state of death.

Model Inputs:

- The model consisted of below-written variables and settings (Table 1):
  - **Clinical Data**: Due to lack of head-to-head trials, Siddiqui et al.'s network meta-analysis (NMA) and also Boradi et al.'s Meta-regression study results, were adopted; in terms of indirect treatment efficacy comparison (ITC)(13, 14).
  - **Direct Medical Costs**: Drug acquisition, administration, monitoring and adverse drug reaction (ADR)'s management costs and also disease-related costs (psychotherapy, rehabilitation, side prescription medicine and supportive care) were adopted from Iran food and drug administration website, Iranian book of tariffs, 2019 national tariffs for health services(15) and expert interview.
  - **Direct Non-Medical Costs**: Nursing and one time per treatment costs (e.g. axillary instruments) were included, based on expert.
  - **Indirect Costs**: Human capita method was used to calculate loss of productivity due to work absence based on EDSS-based frequency(16) and lowest governmental wage of a simple worker per day (8.819 US$, according to Iran work law).
  - **Health Utility:** EDSS-based health utility data was sourced from secondary literature(17). Disutility associated with relapses, injection and occurrence of ADR and also, the Impact of MS on patient's caregiver health utility was included (18, 19).
  - **Mortality**: Mortality was calculated as a covariate of MS presence (fixed standardized mortality ratio of 1.680 versus general population) (20) and also age and sex (based on WHO life table for Iran).
  - **Discontinuation**: This occurred in cases of EDSS>7, lack of response or intolerability (based on CLARITY and AFFAIR trials).
  - **Treatment Waning**: The drug effect is assumed to wane over time to reflect uncertainty in the longer-term benefits of therapy.

Model Outputs:

- Efficacy was measured in terms of quality adjusted life years (QALYs) and life years gained (LYG). QALY was discounted by 3.5%.
- Costs were measured and calculated in Iranian Rial rates (IRR) and converted to US dollars using the 2019 governmental conversion rate. Costs were discounted by 7.2%(21).
- Final comparison outcome was incremental cost-effectiveness ratio (ICER); which indicates additional costs per extra QALY gained.
- Deterministic sensitivity analysis (DSA) was performed to identify parameters that exhibit a significant influence on the model results, by %95 change in their confidence interval or a fixed amount of %20 change. Results were presented as tornado diagram.
- PSA was performed to assess joint variable uncertainties on final results by assigning a probabilistic distribution to each model variable. Results were presented as scatter plot.

Table 1: Base case settings for the cost-utility analysis

Setting	Input
Perspective	Societal
Willingness to pay	2,709 USD (1 Iranian GDP per capita)
Discounting rate	3.5% for outcomes and 7.2%(21) for costs.
Time horizon	Base case of 5-years
Costs	Direct medical, direct non-medical and indirect costs.
Clinical natural history – Relapse	As a function of EDSS, Based on data from UK MTA assessment group model.
Clinical natural history – Disability progression	BCMS matrix (median age of onset >=28 years)
Clinical – Mortality	Fixed Standardized Mortality Ratio for MS
Health utility	Hawton plus CLARITY data for EDSS(17), Orme for relapse(18)
Direct costs (public sector, 80%- private sector, 20%)	Iran book of tariffs & 2019 medical tariff rates, Iran FDA official website
Indirect Costs	Human capita, based on data of Orlewska E., et al study(15)

Abbreviations: BCMS: British Columbia multiple sclerosis; **EDSS:** Expanded Disability Status Scale; **GDP**: gross domestic product; **KSA:** Kingdom of Saudi Arabia; **NSSF:** National Social Security Fund; **SMR**: standardized mortality ratio

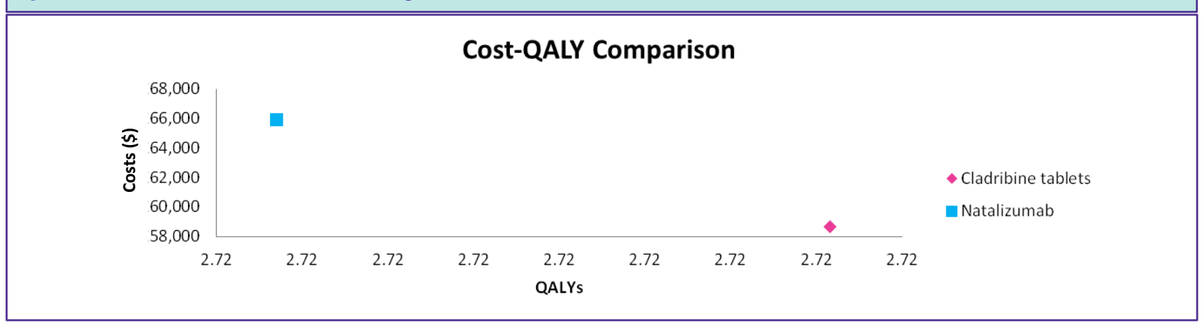
RESULTS

Cost – utility analysis

- The results of CUA showed that cladribine tablets were associated with the **least cost** while yielding the **highest QALYs** compared with natalizumab for treating HDA-RMS patients at a willingness to pay **threshold of 2,709 USD** (1 Iranian GDP per capita).
- Total cost associated with cladribine tablets was **$58,643** compared to **$65,924** for natalizumab. **The incremental cost for cladribine tablets was -$7,281 (vs. natalizumab), in a 5 year time horizon** (Figure 1).
- Total QALYs associated with cladribine tablets was **2.720 QALYs** compared to **2.716 QALYs** for natalizumab. **The incremental QALYs for cladribine tablets were +0.003 (vs. natalizumab), in a 5 year time horizon** (Figure 1).
- **Life years gained** was comparable between comparators (**both 4.655 years**).

RESULTS (continued)

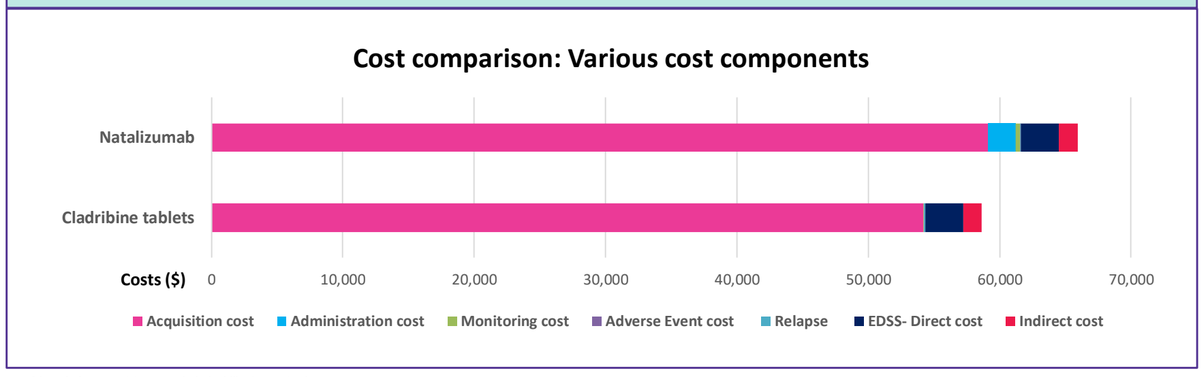
Figure 1. Cladribine tablets are associated with "higher QALY" and "lower costs"



Abbreviations: CUA: cost utility analysis**; QALYs:** Quality-Adjusted Life Year

- Among the different cost components, drug acquisition costs (contributing 92.4% in cladribine tablets and 89.6% in natalizumab arm) followed by EDSS-related costs (approximately 5% in both arms) were the major components to the total costs (Figure 2).

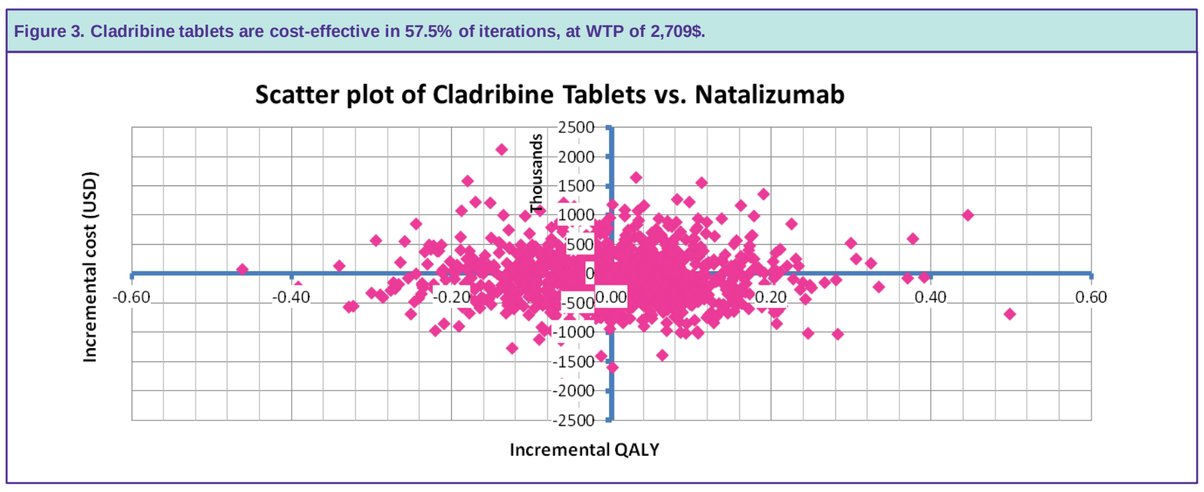
Figure 2. Cladribine tablets are associated with "lower direct & indirect" costs



Abbreviations: EDSS: Expanded Disability Status Scale

- The results of the PSA (after running 1000 Monte Carlo simulations) showed that there is 57.5% probability of cladribine tablets being cost-effective compared to natalizumab at a threshold of $2,700 (1 Iranian GDP/Capita) per QALY gained (Figure 3).
- This probability will increase to 58.6%, when considering a willingness to pay of 3 GDP/Capita.

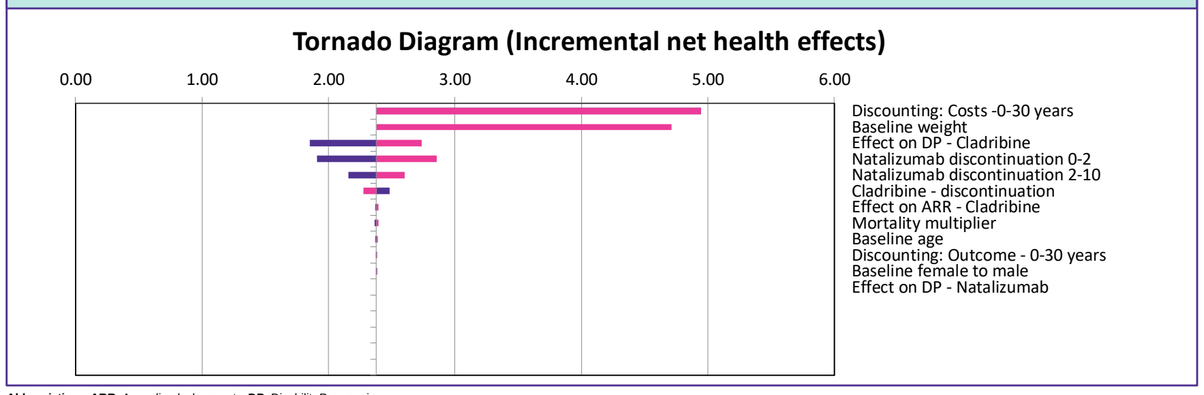
Figure 3. Cladribine tablets are cost-effective in 57.5% of iterations, at WTP of 2,709$.



Abbreviations: QALY: Quality-Adjusted Life Year; **WTP:** Willingness To Pay

- Overall, the DSA results demonstrated that the parameters that exhibited the greatest influence on results were: 1) discounting costs and 2) baseline weight of patients. The effect of cladribine tablets on disability progression and discontinuation rate of natalizumab had some influence on the results (Figure 4).

Figure 4. Tornado diagram of cladribine tablets versus natalizumab



Abbreviations: ARR: Annualised relapse rate; **DP:** Disability Progression

CONCLUSIONS

- **The CUA demonstrated that in HDA-RMS patients across Iran, treatment with cladribine tablets is not only a cost effective treatment option, but a DOMINANT comparator to natalizumab.**
- **The results may help policy makers, budget holders and also healthcare providers to build evidence-based decisions regarding registration, adoption and reimbursement of cladribine tablets.**

LIMITATIONS

- **Lack of head-to-head trials, for comparing efficacy variables across comparators: This may have lead to uncertainties resulting from different study designs, patients' baseline characteristics and assumptions.**
- **Generalizability of clinical and natural history data derived from non-local studies, to Iranian setting.**
- **Time horizon of 5 years: Whereas Pharmacoeconomics guidelines mostly suggest longer time-horizons for chronic disorders(22), due to lack of long-term follow-up data longer time-horizons would have increased uncertainties of results.**

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