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Low-dose rituximab should be used for treating MS in resource-limited settings: No

Farrah J Mateen

Correspondence to:
FJ Mateen
Department of Neurology, Massachusetts General Hospital, 165 Cambridge Street, Office 627, Boston, MA 02114, USA.
fmateen@mgh.harvard.edu

Farrah J Mateen
Department of Neurology, Massachusetts General Hospital, Boston, MA, USA

While patients with multiple sclerosis (MS) in most wealthy settings have access to more than 20 disease-modifying therapies (DMTs), patients in resource-limited settings often have access to none. This disparity in MS treatment access is extreme compared to the many diseases—neurological and otherwise—for which effective, scientifically proven treatments exist.

Many countries worldwide procure drugs according to the World Health Organization's *Model List of Essential Medicines*.[1] Since there are no MS DMTs listed, immunosuppressive agents, including rituximab and its quality-assured biosimilars, listed for other indications, should be considered for the treatment of MS. Among low-income countries that procure a limited supply of "on-label" MS DMTs, the most common are interferon beta and glatiramer acetate.[2] Patients with MS with only these two options may alternate between low-efficacy agents each time they have a disease attack. This unfortunate situation requires renewed thinking on how best to treat people with MS in resource-limited settings.

There are practical advantages to rituximab use for MS in resource-limited settings, including its appropriate use in multiple mimicking central nervous system (CNS) demyelinating disorders such as neuromyelitis optica. Semi-annual dosing of a DMT is pragmatic for highly mobile resource-limited populations, such as refugees.[3] While these pragmatic factors justify B-cell therapies as a treatment approach in general, they do not justify low-dosing. By contrast, barriers to intravenous rituximab treatment are few infusion centers, usually concentrated in large cities; scarcity of skilled personnel to treat MS; and the increased need for laboratory screening and monitoring compared to other DMTs.

People in resource-limited settings with MS—like all people with MS—deserve highly effective, safe, tolerable, and affordable treatments that have a robust evidence base. The question of whether *low-dose* rituximab is as efficacious, safer, and more affordable should be examined for people with MS.

Knowledge on the efficacy of low-dose rituximab is inadequate for people with MS to recommend it routinely as a standard of care. Importantly, no standard definition of low-dose exists, and no consensus dosing strategy of rituximab in neuroinflammatory disease has yet transpired.[4] Initial definitions of low dose range from 100 mg to 1000 mg per dose or cycle.[5–8] An observational cohort from Sweden found that patients treated with a median dose of 500 mg intravenous (IV) every 6 months was highly effective in some people with MS.[5] However, there are few long-term follow-up studies of low-dose rituximab including disability outcomes.

In all settings, rational dosing of rituximab is needed, including a focus on the therapeutic goal, which is the degree of B-cell depletion, not the overall dose.[4] It is uncertain whether dosing studies of rituximab in MS in high-income settings[6] extrapolate well to patients in resource-limited settings—who may be on average younger, of lower body mass index, and have different disease risk factors. While real-world data from low-income settings is emerging and low-dose rituximab appears promising, the picture remains incomplete. When a tiered dosing strategy of rituximab was tested in 118 people with MS in India, the authors found dosing of 500 mg IV rituximab every 9–12 months in 34 patients appeared effective.[7] Low-dosing was administered to patients with less disease activity via pre-treatment disease assessment of patients with magnetic resonance imaging (MRI) and follow-up evaluation clinically alongside serial flow cytometry for serum B-cell subsets. By contrast, a pre-print study[8] of 85 Iranian people with MS treated with rituximab (500 mg 2 weeks apart every 6 months) reported 18 patients experienced a relapse over a 4-year observation period. Notably, the initiation of rituximab in these patients was based on a poor clinical response to a first-line DMT. Financial constraints precluded the use of flow cytometry in all patients.

There remains equipoise on which patients would benefit from low-dose rituximab versus higher-dosed rituximab. Prospective, randomized studies comparing doses are required in resource-limited settings, including in children. While many people with MS would

likely benefit more from low-dose rituximab compared to interferons or glatiramer acetate, these same patients would likely benefit even more from higher-dosed B-cell therapies. Selection of the subset of MS patients who could be effectively treated with the lowest doses may require additional expenditures in laboratory tests, neuroimaging, and personnel, expenditures that could obviate the costs of lower dosing.

Beyond efficacy, there are two main arguments for the preferential use of low-dose to high-dose rituximab in resource-limited settings: (1) lower risk of serious infections and hypogammaglobulinemia and (2) lower cost.

The risks of infection during immunosuppression could be higher in resource-limited settings for a variety of reasons, including the wide range of pathogens found in tropical zones and the impact of poverty on infectious diseases. However, limited data substantiate the hypothesis that low-dose rituximab leads to lower rates of serious infection in people with MS compared to typically used higher doses.[5] Serious infections have not been disproportionately reported in MS patients treated with rituximab in resource-limited settings.[6–9]

The second main argument to lower dose is cost. Assuming an average cost of 23USD per 10 mL vial of rituximab (10 mg/mL) in resource-limited settings,[10] a dose of 1000 mg would cost ~2,300USD per cycle or 4,600USD annually if dosed every 6 months. Since many patients in resource-limited settings pay for medicines out of pocket, only ultra-low-dose rituximab (<500 mg every 6 months) could be affordable without additional financial support. The World Bank estimates 40 countries have a gross national income (GNI) per capita of <1500USD per year. Notably, these costs do not include laboratory screening, administration by skilled health care workers, additional medicines to improve tolerability, or patients' transportation costs. Moreover, since MS affects disproportionately young women, a demographic group already disadvantaged in several resource-limited settings in terms of education, employment opportunity, personal income, and social safety nets, cost almost certainly remains a major determinative factor in treatment choice for most people living with MS in the poorest settings.

When cost of an effective drug is the most critical factor in making a dosing determination for a disabling and life-threatening disease, more must be done by the global community than recommend a lower dose. One must question whether lower doses of any effective drug can be ethically recommended based on cost alone in MS. In other diseases, including HIV/AIDS, insulin-dependent diabetes, and chronic myeloid leukemia, re-negotiation of drug pricing and ensuring adequate supply chains of life-sustaining treatments have occurred. Although not straightforward, political will, advocacy, and science have come together to improve cost. People with MS in resource-limited settings should not be subject to no treatment, less-adequate treatment, less robust data for their DMT use, or fewer treatment options due to issues of cost alone. The MS field can achieve rational drug pricing and evidence-based drug dosing for patients in resource-limited settings.

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ORCID iD

Farrah J Mateen https://orcid.org/0000-0002-4293-8115

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Claudia Cárcamo and Ethel Ciampi

Correspondence to:
C Cárcamo
Departamento de Neurología, Diagonal Paraguay, 362, 5° Piso Pontificia Universidad Católica de Chile, Santiago, 8330077, Chile.
ccarcamo@med.puc.cl

Claudia Cárcamo
Departamento de Neurología, PontificiaUniversidad Católica de Chile, Santiago, Chile

Ethel Ciampi
Departamento de Neurología, Pontificia Universidad Católica de Chile, Santiago, Chile; Servicio de Neurología, Hospital Sótero del Río, Santiago, Chile

We are facing a tempting but complex controversy.

Anti-CD20 antibodies have revolutionized classic concepts of multiple sclerosis (MS). Their high efficacy was shown since the first MS trials led to reconsidering the role of B lymphocytes in the pathophysiology of the disease.[1,2]

Likewise, the evidence in favour of the use of highly effective therapies in the early stages of the disease to reduce the conversion to progressive forms and the consequent burden of disease has changed the paradigms of therapy from general stepwise treatment to a personalized one,[3] reversing in recent years the proportion of patients treated with high-efficacy versus moderate-efficacy therapies in high-income countries.

Rituximab was the first chimeric anti-CD20 antibody developed and showing its high efficacy in relapsing MS, encouraged the development and approval of Ocrelizumab (humanized) and Ofatumumab (human) for the treatment of MS. However, their high cost limits their use, as well as other disease-modifying therapies, in countries with insufficient resources.

The proposal to use low doses is mainly based on large real-life cohorts of patients, as described by Fredrik Piehl and Thomas Mathew, in studies of high-income countries, where doses between 100, 500, and 1000 mg every 6 months have been used.[4–6] However, the evidence of the effect of these doses on reducing costs is insufficient, as argued by Farrah J. Mateen, taking into account laboratory tests, neuroimaging, personnel, and travel expenses. Furthermore, limited data are available on the reduction of risks, such as infections, hypogammaglobulinemia, and lymphopenia.

Structured systems with appropriate health policies can significantly lower costs to provide adequate access to highly effective therapies. In our experience in Chile, a developing middle-income country, the two main health systems are divided into private health (20% of the population, corresponding to the higher socioeconomic status), and public health (80% of the population, corresponding to the lower socioeconomic status). Access to Relapsing-Remitting MS diagnosis has been universal for both health systems since 2010. Public health patients may be eligible for high-efficacy disease-modifying therapy (DMT) only from 2016 while private health patients may access high-efficacy DMT at least from 2010. Public health patients were associated with a higher probability of progressive MS and a higher risk of Expanded Disability Status Scale $\geqslant$ 6.0, and longer diagnostic delay and being diagnosed before 2016, as a proxy of high-efficacy DMT delay were also risk factors for a more severe course. On the other hand, current treatment with high-efficacy DMT was a protective factor.[7]