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Rituximab is the way forward for managing Multiple Sclerosis (MS) in Sri Lanka

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For

Multiple Sclerosis (MS) is a chronic autoimmune demyelinating disorder of the central nervous system (CNS) causing significant neurological disability in young adults.[1] The global median prevalence is estimated to be 36 cases per 100,000 affecting over 2.9 million adults with a higher predilection for females.[1] MS has several clinical phenotypes including relapsing-remitting MS (RRMS), secondary progressive MS (SPMS) and primary progressive MS (PPMS). RRMS accounts for the vast majority of clinical presentations.

Over the last two decades the landscape for the treatment of MS has greatly evolved with the advent of several novel disease modifying treatments (DMTs).[1] An updated understanding of the MS immunopathogenesis revealed B cells to play a more central role in mediating acute MS attacks through antibody independent mechanisms such as antigen presentation, T cell activation and proinflammatory cytokine production.[2] Therefore, depletion of B cells by anti-CD20 therapies significantly reduced ongoing CNS inflammation and clinical relapses.[2, 3] Rituximab is a chimeric mouse/human IgG 1 monoclonal antibody that binds specifically to CD20 expressing B lymphocytes thereby disrupting memory B-cell function and inhibiting plasma cell production.[2, 3] Although rituximab has not received approval from the Food and Drug Administration (FDA) for use in MS, it is extensively used in European, African and Southeast Asian health care sectors as the off-label, drug of choice for highly active MS.[1, 3, 4]

The 'Helping to Evaluate Rituxan in Relapsing-Remitting Multiple Sclerosis' (HERMES) trial was a landmark randomized double blind placebo-controlled study which clearly demonstrated the significant reduction in relapse rates and cumulative gadolinium enhancing CNS lesions in RRMS patients treated with rituximab compared to placebo.[3] Furthermore a cohort study by Granqvist et al., (2018) highlighted that rituximab markedly lowered relapses in RRMS in comparison to other injectable DMTs like interferon β and dimethyl fumarate (DMF).[4] Several major retrospective cohort studies have displayed a superior clinical efficacy of rituximab as the preferred alternative in abating the annual relapse rates (ARR) and expanded disability status score (EDSS) of severe RRMS patients refractory to standard injectable DMTs.[4] In contrast to approved platform DMTs, rituximab has a better safety profile with only mild to moderate infusion reactions and minor infections as evidenced by the major clinical trials and observational studies.[1,3] Interestingly rituximab induced infusion reactions mostly occur with the first dose and drastically diminish in subsequent infusions when coupled with premedication prednisolone.[1,3,5] Hence, there is a markedly greater drug compliance and patient satisfaction corollary to the robust safety and tolerability of rituximab.[1,3, 5]

Systematic review and meta-analysis by Tian et al have solidified the fact that rituximab is effective at significantly lowering the ARR, disease progression and neuroradiologic disease activity in RRMS.[1,6] The pivotal OLYMPUS trial subgroup analysis illustrated a pronounced delay in confirmed disease progression and lower contrast enhancing CNS lesions in younger PPMS patients (<51 years) treated with rituximab.[1,3] Moreover a retrospective cohort study by Naegelin et al., revealed SPMS patients treated with rituximab had a significantly lower EDSS and delayed disease progression up to 10 years compared to the matched control group.[3,7]

A recent local case series by De Alwis et al., further emphasized rituximab as a cost-effective treatment strategy for MS in developing countries such as Sri Lanka.[8] In conclusion, multiple randomized controlled trials and real-world data have provided irrefutable proof of the high efficacy, safety and affordability of rituximab as a potential first line therapy in most forms of active MS.[1,3,5,8]

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While rituximab has shown promise in the treatment of multiple sclerosis (MS),[1] there are several reasons why it may not be the definitive way forward for the condition.

1. Lack of sufficient evidence for recommendations:

Despite its off-label use, rituximab lacks the extensive clinical trial data and regulatory approval specifically for MS.[1] Guidelines for MS treatment often rely on evidence-based practices, and the absence of conclusive studies may limit its inclusion as a recommended treatment option.

2. Regulatory concerns:

The off-label use of rituximab raises regulatory concerns. Regulatory bodies, such as the Food and Drug Administration (FDA) or its equivalent in different countries, have not officially approved rituximab for the treatment of MS.[1] This absence of regulatory approval may deter some healthcare professionals from prescribing it, especially in regions with strict adherence to regulatory guidelines.

3. Legal implications for off-label prescribing:

The lack of specific laws in Sri Lanka to protect doctors prescribing medications off-label can pose legal challenges. Doctors may be hesitant to use rituximab due to the potential legal consequences, making it a less favourable option in regions without clear guidelines on off-label use.

4. Insurance reimbursement challenges:

The cost of rituximab is often substantial, and without an official indication for MS, insurance companies may be reluctant to honour claims for reimbursement. This can create financial barriers for patients who may not be able to afford the medication without insurance coverage.

5. Emerging alternative treatments:

The landscape of MS treatment is dynamic, with ongoing research and the development of new therapies. There may be alternative treatments with stronger evidence and official approvals that offer better efficacy and safety profiles for MS patients.

6. Potential side effects and risks:

Rituximab, like any medication, carries potential side effects and risks.[2] In the absence of comprehensive MS-specific studies, the full spectrum of risks associated with rituximab for MS patients may not be fully understood.

7. Varied response among MS patients:

Responses to rituximab can vary among MS patients. Some may experience significant benefits, while others may not respond as favourably. The lack of a consistent response profile can make it challenging to determine its effectiveness for the broader MS population.

In conclusion, while rituximab shows promise in the treatment of MS,[3] the lack of sufficient evidence, regulatory approval, legal protections for off-label prescribing, insurance reimbursement challenges, emerging alternative treatments, and potential side effects raise valid concerns about its status as the definitive way forward for MS treatment. Continued research, regulatory support, and comprehensive clinical trials are necessary to establish rituximab's efficacy and safety for MS and to address the broader issues associated with its off-label use.

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Commentary

Given its effectiveness and good tolerability, rituximab has been used as an alternative treatment in patients with Multiple Sclerosis (MS), particularly Relapsing Remitting Multiple Sclerosis (RRMS). From observational data, rituximab was effective in both treatment naive and treatment-switching patients. However, it has not been approved by the Food and Drug Administration (FDA) for MS due to the lack of phase III randomized, controlled trial data.

Currently, two randomized, non-inferiority trials comparing rituximab and ocrelizumab in patients with active MS are ongoing.[1,2] Future results from these trials might pave way for the FDA approval of rituximab for the treatment of MS.

MS patients in many Asian countries still have limited access to standard treatments due to their high cost.[3] Since anti-CD20 B-cell depletion therapies have been shown to be effective for the treatment of MS, rituximab is a promising alternative therapy for MS patients in resource-limited settings.[3] Although studies on the off-label use of rituximab in MS were mainly conducted in North America and Europe, particularly in Sweden,[4] there were a number of studies in the Asian population in India, Iran, Lebanon, and Cyprus. Those studies demonstrated that rituximab consistently lowered the Annual Relapse Rate (ARR) and Expanded Disability Status Scale (EDSS) progression in Asians with RRMS. The safety and tolerability of rituximab in the Asian population was also favourable. However, more data in the East and Southeast Asian populations are awaited.

Rituximab is used widely off label in the treatment of RRMS. Though definitive clinical trial data are still awaited, off label use has shown significant benefit in open label studies. Adverse events profile too, seem to be acceptable in comparison to other Disease Modifying Drugs (DMDs). If cost effective, its use can be justified in treatment naive patients and also when switching treatment.

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