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Rituximab is an acceptable alternative to ocrelizumab for treating multiple sclerosis – Commentary

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Should lower cost alternate medications with comparable mechanisms of action, but without the proof from registration studies, be used in lieu of branded medications with proved efficacy and safety? Ocrelizumab is the first United States Food and Drug Administration-approved, humanized, B cell depleting, anti-CD20 (a glycosylated phosphoprotein expressed on the surface of B cells that may act as a calcium channel) monoclonal antibody treatment for relapsing and primary progressive forms of multiple sclerosis. Rituximab is a chimeric antibody that also targets CD20 and depletes B cells with comparable efficiency. If one believes that B cell depletion is the mechanism whereby ocrelizumab exerts its beneficial effects in multiple sclerosis (MS), then both products should have similar efficacy.

Rituximab cannot be approved by some regulatory agencies due to the absence of registration studies with proof of efficacy on clinically meaningful endpoints. Regulatory agencies hold high efficacy standards so that only products with proved benefit are granted commercial license. However, clinicians may not require the same standards of proof for off-label use. Neurologists have extensive experience using medications when either there are no indicated treatments or when off-label therapies offer advantages over approved therapies.

A theoretical consideration in using branded medications over lower cost alternates is the argument that widespread use of low cost medications would reduce the incentive for industry to develop new products.

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When ocrelizumab was developed, access to rituximab as a MS treatment was limited in the United States. Had rituximab been widely available for MS, ocrelizumab might not have been assessed in three large, randomized controlled studies. However, there are other examples of lower cost alternates that had little influence on development of branded, higher priced medications. Leflunomide, a generic small molecule inhibitor of the enzyme dihydroorotate dehydrogenase (an enzyme necessary for pyrimidine synthesis), did not affect the development of teriflunomide into a leading treatment for relapsing MS. Teriflunomide is the active metabolite of leflunomide and would be expected to have the same mechanism of action but is ~100-fold more costly. Another example is cladribine whose oral formulation is approved in some markets. The identical generic molecule is available in subcutaneous or intravenous preparations at a fraction of the price of the branded oral medication but is rarely used off-label in MS.

In their article, promoting rituximab over ocrelizumab, Professors Piehl and Hillert argue that comparative effectiveness studies support use of rituximab as a MS disease modifying treatment (DMT), and that possible differences in association with malignancies found for ocrelizumab, but not associated with rituximab, make rituximab a better option. Professor Wallin takes the opposing view that ocrelizumab offers an advantage over rituximab with regard to proof of efficacy and patient access. In my opinion, the primary argument to favor rituximab (or other lower cost off-label medications) is economic. Although rituximab is not inexpensive, it is less costly than ocrelizumab. From this perspective, one could ask are there specific disadvantages in using rituximab over ocrelizumab? In my experience, patient access to rituximab for MS remains extremely limited. Most third party payers in the United States do not authorize rituximab for neurological indications. In contrast, access to ocrelizumab is widespread, although when this medication reimbursed as a first, second, or third line treatment varies from payer to payer. Prescribing clinicians inevitably favor approved, accessible medications over medications that require petitions, letter writing campaigns, or so-called peer-to-peer reviews. Moreover, payers often have resisted use of off-label medications due to lack of proof of efficacy. It seems unlikely that these same payers will reverse their off-label use policies to leverage the price differential between rituximab and ocrelizumab.

Since the approval of the interferon beta-1b for relapsing MS in 1993, the disease-modifying therapy market rapidly evolved. Thirteen disease-modifying therapies are currently available (16 if one includes three generics). Despite the maturity of the market, the predicted effect of competition on reducing prices has not occurred. Remarkably, the annual cost of MS therapies has relentlessly spiraled upward. Eventually, all manufacturers of MS DMTs will have to contend with challenges from lower cost alternates, whether this pressure comes from off-label rituximab or generic versions of branded medications such as glatiramer acetate and interferon beta-1b (generics currently available) or fingolimod (generics expected in 2019). In the United States, an act of congress will be required for federally funded programs (Medicare and Medicaid) to negotiate directly with manufacturers over pricing. As a consequence, the US taxpayer is the primary, albeit indirect, funder of global pharmaceutical development. Furthermore, taxpayers fund the National Institute of Health (NIH), a research organization that has had little interest in promoting development of lower cost treatments that compete with branded medications. Perhaps, as the high cost of specialty pharmacy medications comes into better focus, the US Congress and the NIH will no longer be able to turn a blind eye to medication pricing.