Reducing costs while enhancing quality of care in MS

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ABSTRACT

The rapid escalation in prices of disease modifying therapies (DMTs) for multiple sclerosis (MS) over the past decade has resulted in a dramatic overall increase in the costs of MS related care. In this article, we outline various approaches whereby neurologists can contribute to responsible cost containment while maintaining, and even enhancing, the quality of MS care. The premise of the article is that clinicians are uniquely positioned to introduce innovative management strategies that are both medically sound and cost efficient. We describe our "top 5" recommendations, including strategies for customizing relapse treatment; developing alternative dosing schedules for Food and Drug Administration approved MS DMTs; using off label therapies for relapse suppression; and limiting the use of DMTs to those who clearly fulfill diagnostic criteria, and who might benefit from continued use over time. These suggestions are well grounded in the literature and our personal experience, but are not always supported with rigorous Class I evidence as yet. We advocate for neurologists to take a greater role in shaping clinical research agendas and helping to establish cost effective approaches on a firm empiric basis. *Neurology*® 2016;87:1617–1622

GLOSSARY

DMT = disease-modifying therapy; **FDA** = Food and Drug Administration; **MS** = multiple sclerosis; **PML** = progressive multifocal leukoencephalopathy; **UBO** = unidentified bright object.

There have been considerable advances in the treatment of multiple sclerosis (MS) over the past 2 decades, and recent evidence suggests that specialized care for patients with MS is associated with "decreased adverse events and [decreased] usage of acute and post acute health care resources."[1] At the same time, costs of MS care are rising, largely because of the rapid escalation in prices of disease modifying therapies (DMTs).[2] Insurance carriers and specialty pharmacies have responded by seeking to deny or limit payments for costly therapies, using "step edits" (a requirement to fail one or more therapies before approving and paying for an alternative approved therapy), "tiered formularies" (different copays for DMTs to treat the same disease), and escalating copays, deductibles, and coinsurance, so as to transfer more costs to the insured patient. All of these practices interfere with shared decision making between patents and their doctors and may have detrimental effects on quality of MS care.[e1] In an effort to curtail medical costs, the "Choosing Wisely" campaign[3] supported by the American Academy of Neurology put forth a list of 5 neurologic practices that could, or should, be eliminated, including use of first line DMTs in nonrelapsing, secondary progressive MS. Many in the MS community thought that this broad recommendation failed to consider the nuances of which patients with MS might benefit from continued use of DMTs.[4] An alternative, more prescriptive approach to cost containment is to introduce new strategies for managing MS that are medically and economically sound. We outline here 5 possible strategies, but many others could be proposed as well. Our suggestions, summarized in the table, should not be viewed as practice guidelines they are not always based on rigorous Class I evidence as yet but as an effort to set a patient centered, neurologist driven agenda for clinical research in MS that could help improve outcomes and decrease costs.

1. Avoid DMT in patients with "improbable MS." Misdiagnosis of MS is neither a new nor an uncommon phenomenon. It is estimated that 5% to 13% of all "MS patients" do not have MS.[5] What is new is the economic cost of misdiagnosis associated with use of expensive MS DMTs. The scope of the problem was highlighted by a survey published in 2012, in which 112 MS specialists were asked to estimate how many patients were referred to them with diagnosis of MS who "almost certainly did *not* have MS." The survey responders

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Supplemental data at Neurology.org

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Table Cost-containing strategies: Current evidence and knowledge gaps

Strategy	Supporting evidence, selected references	Areas for further research
1. Avoid DMT in patients with "improbable MS"	Observational studies[8-10] show that patients without MS typical symptoms/MRI lesions do not develop MS	Develop specific MRI criteria for MS (e.g., incorporate cortical lesions; "central vein" sign); standardize definitions of "MS typical" lesions (e.g., "Dawson fingers," juxtacortical lesion vs subcortical)
2. Customize treatment of relapses		
Use high dose oral methylprednisolone (1,000 mg) for MS relapses	Class I RCT[16]	
Consider plasmapheresis for severe MS relapses	Class I RCT for fulminant, steroid irresponsive CNS inflammatory attacks[23]	RCT of PLEX as add on to steroids for severe MS relapses with short and long term follow up
Adverse events from steroid use may outweigh benefits in mild MS relapses	No evidence for long term benefit of steroids; many relapses are self limited	RCT of steroids vs no steroids for mild relapses with short and long term follow up
3. Develop alternative dosing strategies for FDA approved MS DMTs		
Natalizumab 300 mg every 6 8 wk dosing similar efficacy to every 4 wk dosing	Multicenter observational study[34]	Ongoing studies to assess risk of PML with extended dose regimen compared to standard dose regimen
Fingolimod alternate day dosing	Case reports[28,29]	RCT comparing fingolimod 0.5 mg daily vs alternate day
Glatiramer acetate 20 mg alternate day dosing	Small scale trials[25,26]	
4. Use off label drugs as DMTs in MS		
Rituximab for relapsing MS	Three Class II studies[36-38] and several large observational studies[39,40]	
Leflunomide for relapsing MS	No published studies	RCT of leflunomide vs teriflunomide
5. Should DMTs be continued indefinitely?	Observational, propensity score matched study shows no effect in relapse rates but worse disability in previously stable patients with MS who discontinue DMT[e23]	Multicenter, randomized, discontinuation study for patients >55 y and no relapses for >5 y is set to begin recruitment in 2017

Abbreviations: DMT = disease-modifying therapy; FDA = Food and Drug Administration; MS = multiple sclerosis; PLEX = plasmapheresis; PML = progressive multifocal leukoencephalopathy; RCT = randomized clinical trial.

estimated seeing 598 such patients over a 1 year period, of whom an estimated 279 patients (47%) were receiving a DMT for MS.[6]

There are many roads to MS misdiagnosis, but one particularly common scenario involves a (poly) symptomatic, but neurologically intact patient with subcortical "unidentified bright objects" (UBOs) on T2 weighted MRI sequences. Subcortical UBOs are nonspecific and are not included as part of the formal diagnostic criteria in MS.[e2] Isolated subcortical UBOs are highly uncharacteristic of MS, yet their presence often triggers mention of "demyelinating disease" in MRI reports.[7] Reassuringly, patients without clinical history, neurologic deficits, or MRI lesions characteristic of MS rarely, if ever, progress to MS.[8,10] Therefore, such patients should not be prescribed MS DMTs, which, in addition to high costs, are associated with potentially severe side effects. Indeed, one of the first natalizumab related fatal cases of progressive multifocal leukoencephalopathy (PML) was described in a patient with no MS lesions in the optic nerve, brain, or spinal cord at autopsy.[11] Thus, while we agree with the concept of early and aggressive treatment of MS, this approach requires a high degree of diagnostic certainty at the onset of treatment.

An important contributing factor to the high misdiagnosis rates is lack of specific serum or CSF biomarkers of MS, or even of radiographic criteria for differentiating demyelinating lesions from lesions of other causes. The existing criteria for MS (Barkhof, Swanton) are designed not for diagnosing MS, but for identifying patients with clinically isolated syndrome first MS like neurologic event who are at high risk of developing MS.[5,e3] We urgently need practical radiographic criteria or other biomarkers for ruling out MS in a patient with low pretest probability of this disease and MS atypical lesions, and ruling in patients with clinically or radiologically isolated syndromes that often precede clinical MS. One promising strategy is to optimize MRI sequences for detection of features suggestive of demyelination, such as central veins within lesions. Central veins are found in more than 40% of demyelinating lesions, but rarely in microvascular disease[12] or migraine,[e4] and are thus particularly useful in distinguishing between MS and the nonspecific subcortical lesions seen in the other

conditions. Other MRI abnormalities of potential utility for MS diagnosis are cortical lesions, which are seen in 40% of radiologically isolated syndromes,[13] but not in migraine,[14] and iron deposition within lesions.[e5]

2. Customize treatment of relapses. Corticosteroids are the mainstay for treatment of acute attacks of MS, usually delivered as methylprednisolone 1,000 mg per day IV for 3 to 5 days, sometimes followed with an oral taper. Inadequate oral dosing of corticosteroids for acute optic neuritis (prednisone 1 mg/kg for 14 days) appears to be ineffective, and even detrimental,[15] but when oral steroids are given in doses that are (near) equivalent to IV, there appears to be no significant difference in outcomes of relapses. A recent randomized trial showed that high dose methylprednisolone 1,000 mg given orally for 3 days was noninferior to the same dose given IV.[16] The clinical equivalence is biologically plausible as 82% of oral methylprednisolone is bioavailable.[17] Oral delivery eliminates the relatively high cost of IV infusions ($799.35 for 1 hour of nonchemo outpatient infusion at the University of Colorado Hospital) and is patient friendly. One logistic difficulty is the lack of prepackaged oral high dose steroid preparations. To circumvent this problem, one could use compounding pharmacies (up to 500 mg of methylprednisolone could be compounded in a single capsule at a cost of $264 for a 5 day, 10 capsule course; Pine Pharmacy, Buffalo, NY), or mix 1,000 mg of lyophilized methylprednisolone intended for IV infusion ($56.75 per dose at the University of Colorado Hospital) with juices or other flavored drinks to make the concoction more palatable. However, there is no evidence that Acthar gel (adrenocorticotropic hormone) is in any way superior to methylprednisolone for MS relapses indirect comparisons suggest that it may be associated with more adverse events[18] and its current average wholesale price of $40,840.80 for a 5 mL/400 unit bottle[e6] makes routine use of this product for MS relapses difficult to justify.

All relapses are counted as equal for purposes of calculating annualized relapse rates in clinical trials, but in practice they vary widely in severity. Some relapses are mild and self limited, and may be difficult to differentiate from the transient worsening due to physiologic or psychologic stressors (pseudo relapses). It is uncertain whether risk of an adverse event from steroids outweighs potential benefits of treatment in such instances. However, approximately half of relapses result in persistent deficits, and nearly a third in marked neurologic deterioration (sustained ≥1 point increase on the Expanded Disability Status Scale).[19,20] Clearly, there is room for improvement in managing steroid nonresponsive MS relapses. IV immunoglobulin has been subjected to rigorous trials with disappointing results. IV immunoglobulin did not benefit recovery from acute optic neuritis when used as a solo agent,[21] and it did not appreciably improve postrelapse outcomes when used as an add on to steroids.[22] Plasmapheresis, however, has shown benefit for fulminant, steroid unresponsive CNS inflammatory attacks in a Class I, randomized, sham controlled trial.[23] It would be worthwhile to conduct a similar trial for severe MS relapses to determine whether plasmapheresis can improve long term outcomes in MS, thereby potentially justifying the initial investment.

3. Develop alternative dosing strategies for Food and Drug Administration–approved MS DMTs. Efficacy of Food and Drug Administration (FDA) approved DMTs has been demonstrated in large randomized trials, but dose and schedule selection for these agents has not always been evidence based. For example, glatiramer acetate is now believed to exert its action through a broad range of mostly long term effects[24] that would not necessarily require daily administration as in the pivotal trials. Indeed, 2 small scale studies of glatiramer acetate 20 mg every other day suggest similar efficacy, but better tolerability, of alternate day dosing compared to daily dosing,[25,26] and glatiramer acetate is now marketed as 40 mg 3 times weekly based on similar outcomes as 20 mg daily.[e7] Another candidate for frequency reduction is fingolimod, whose half life for a 0.5 mg capsule taken daily is 6 to 9 days, and its presumed mechanism of action is via sequestration of lymphocytes within lymph nodes.[27] There is anecdotal support for fingolimod's efficacy at lower frequency (e.g., every other day) based on our experience and case reports.[28,29] The ongoing, industry sponsored trial of 0.25 mg vs 0.5 mg daily dosing of fingolimod vs glatiramer acetate 20 mg daily[30] will address the question of whether each fingolimod pill could be halved without sacrificing efficacy, but not whether the number of pills could be halved. From a cost of care perspective, however, a noninferiority trial of alternate day vs daily dosing of fingolimod would be preferable. Absent such a trial, clinicians could systematically collect and publish observational data on their patients receiving fingolimod on an alternate day schedule.

A particularly important example of a DMT for which alternate dosing may not only be cost saving, but also life saving is natalizumab, a monoclonal antibody that blocks lymphocyte attachment to vascular cell adhesion molecule receptors on endothelial surfaces, thereby blocking entry of activated T and B lymphocytes into the CNS. Natalizumab is approved for every 28 days dosing, yet vascular cell adhesion molecule receptor saturation of >50% is maintained for

8 weeks or more after infusion.[31] This observation may help explain why disease reactivation is virtually never seen less than 8 weeks after the last natalizumab infusion.[32,33] An investigator initiated, multicenter observational study compared efficacy of natalizumab dosing interval extended up to 8 weeks and 5 days in 905 patients with standard, every 28 days natalizumab dosing in 1,093 patients.[34] Both groups had excellent response to natalizumab, and the extended dose group had even fewer relapses and new T2 lesions than the standard interval dose group. Despite higher risk factors for development of PML in the extended dosing group (e.g., higher percentage on individuals exposed to the JC virus that causes PML, longer exposure to natalizumab, and higher use of prior immunosuppression), no cases of PML have been observed in the extended dose group to date, while 4 cases were seen in the standard frequency group. Thus, preliminary evidence suggests that less frequent dosing of natalizumab may be a safer, yet highly effective approach that also reduces the cost of this very expensive therapy by up to 50%.

4. Off-label use of DMTs for MS. Presently, the main driver of MS costs is the direct costs for the DMTs,[2,35] whose sales have more than doubled in the last few years.[2] The average annual DMT price in the United States now exceeds $60,000 per patient year.[2,e1] A highly effective and significantly less expensive alternative for relapse suppression in MS is rituximab, a monoclonal, anti CD20 antibody that is FDA approved for treatment of certain malignancies (non Hodgkin lymphoma) and autoimmune conditions (rheumatoid arthritis and others). Rituximab's impressive efficacy in relapsing remitting MS was demonstrated in HERMES, a randomized clinical trial,[36] and confirmed in 2 other trials,[37,38] numerous observational studies,[e8,e9] and the authors' personal experience.[e10] A recent Swedish study comparing fingolimod vs rituximab in patients with relapsing MS who switched from natalizumab because of JC virus antibody positivity showed superiority of rituximab over fingolimod regarding both efficacy (relapses in 1.8% of rituximab treated patients vs 17.6% on fingolimod; hazard ratio of 0.10) and safety (5.3% adverse event rate in rituximab patients vs 21.1% for fingolimod; hazard ratio of 0.25 in favor of rituximab).[39]

At the Rocky Mountain MS Center at the University of Colorado, we infuse rituximab 1,000 mg once and repeat with 500 mg IV every 6 months thereafter (unless there is reconstitution of CD20 cells, in which case we use 1,000 mg every 6 months). While costs vary by location and may change over time, the current cost for 1,500 mg spread over 2 doses, including the infusions themselves, is approximately $20,000 at a Walgreen's infusion center in Colorado near our institution, well below the average wholesale prices, or wholesale acquisition costs of the standard DMTs.[2] It should also be noted that the above dosing strategy utilizes 50% or less of rituximab compared to the standard rheumatoid arthritis dosing of this drug (1 g 4 times a year).

A partially humanized version of rituximab, ocrelizumab, completed 4 phase II and III trials for relapsing and primary progressive MS. The 2 phase III trials of ocrelizumab in relapsing MS were reported at the 2015 ECTRIMS (European Committee for Treatment and Research in Multiple Sclerosis) meeting, and showed 46% reductions in annualized relapse rates and 95% reductions in new enhancing lesions in comparison to thrice weekly interferon beta 1a.[e11] The placebo controlled trial of ocrelizumab for primary progressive MS became the first primary progressive MS trial to meet its primary endpoint in reducing disability.[e12] Its predecessor, a 2 year trial of rituximab vs placebo in primary progressive MS, was overall negative, but participants younger than 51 years and with enhancing lesions on their baseline brain MRI had a significant reduction in likelihood of sustained disease progression.[e13] Ocrelizumab's maker has filed for FDA and other regulatory approvals for relapsing and progressive forms of MS in 2016 and is expected to receive a decision by January 2017. In our view, rituximab has 2 important advantages over ocrelizumab in relapsing MS: an established long term safety record (an estimated 312,000 patients with rheumatoid arthritis alone were treated with rituximab since its approval in 1997 [Genentech, data on file]), and a considerably lower projected price. Counting a phase II trial of another anti CD20 monoclonal antibody, the completely humanized ofatumumab,[e14] there are now 8 successful phase II and III studies supporting the use of anti B cell therapy in MS. The time has come for insurance companies to routinely approve payment for the highly efficacious anti CD20 monoclonal antibody therapy in MS, presently as rituximab.

While rituximab has the most evidence in support of off label use in MS, other agents merit mention as well. Leflunomide is a readily available and inexpensive generic drug. Upon ingestion, leflunomide is almost entirely converted into teriflunomide, a moderately effective FDA approved agent for relapsing remitting MS.[e15] As such, leflunomide has been used off label for MS, although, to our knowledge, no studies of this drug in MS have been published. Monthly cost of leflunomide ranges from $24.85 to $65.68 (GoodRx.com), well below the cost of teriflunomide marketed as Aubagio (Sanofi Genzyme, Cambridge, MA). A head to head comparison of leflunomide with teriflunomide would be instructive. Other oral generic immunosuppressants, such as azathioprine[e16] and methotrexate,[e17] have a long history

in MS, but are regarded as much less efficacious for relapse prevention as the newer agents, such as natalizumab or rituximab.

5. Should DMTs be continued indefinitely? The question posed in the section title cannot be answered at present. All clinical trials that led to FDA approval of DMTs for relapsing MS typically had an age cutoff of 55 years or younger. Studies in progressive MS, often including those up to age 60 or 65, have generally been negative, unless one looks at subanalyses by age or recent inflammatory disease activity (relapses or enhancing lesions). The subanalyses show that younger patients with recent active inflammation do appear to benefit, regardless of placement into a "relapsing" or "progressive" phenotype category.[e13,e18] Thus, while it is clear that younger patients with recent inflammatory disease activity benefit from presently available DMTs, it is not clear whether the same is true in older patients without recent inflammatory activity.

Discontinuation of interferon beta 1a[e19,e20] or natalizumab[32,33] in patients with highly active disease before therapy leads to disease reactivation within months of stoppage. But in older patients, who are at lower risk of relapses[e21] and new enhancing lesions,[e22] or in patients with no relapses or inflammatory MRI activity for prolonged periods, the benefits of continuing relapse suppressive therapies are uncertain. A recent observational study compared the risk of relapse and disease progression among patients with no relapses for 5 years or more, some of whom stopped DMT and others who continued on DMT.[40] The 2 groups were propensity score matched from a large MS database, MSBase. Their average age was 45 years. No difference in relapse rate was observed between the 2 groups, suggesting that stopping DMT in a nonrelapsing patient in this context does not increase risk of subsequent relapses. However, disability progression rates were higher among patients who stopped DMT. This difference was largely attributable to faster rate of progression among a subset of stoppers with no prebaseline disease progression compared to stayers with no prebaseline disease progression. Thus, it is unknown whether continuation of DMT in the older, nonrelapsing patients is warranted. The uncertainty provides justification, perhaps even an imperative, to conduct a randomized discontinuation trial,[e23] in which some patients are randomized to continue on treatment and others to stop therapy. Such trials have been successfully conducted in oncology,[e24] rheumatoid arthritis[e25] and other fields, but not in MS. We have recently received funding to conduct a randomized discontinuation trial in MS.[e26] The 2 year, multicenter trial is scheduled to open enrollment in early 2017 for 300 patients who are 55 and older and have had no relapses or new MRI activity for at least 5 years while maintained on DMT. The results of the trial should help patients and clinicians make an informed decision as to whether and when it may be safe to stop DMT.

CONCLUSIONS

Clinical trial agendas in MS are, to a large extent, set by the pharmaceutical industry. In this article, we argue for greater clinician involvement in shaping the clinical research agenda for our field, with special emphasis on developing, and bringing to mainstream clinical practice, strategies that may decrease costs while enhancing the quality of care. We identified a number of possible therapeutic strategies that make medical and economic sense, including alternative dosing of FDA approved DMTs; off label use of highly effective relapse suppressants; customizing treatment of relapses; performing a randomized DMT discontinuation trial; and improving specificity of MRI criteria for MS and development of alternative biomarkers to enhance diagnostic accuracy (table). Some of these strategies do not, as yet, have sufficiently high level of evidence, and we advocate for high quality research that would put these cost effective approaches on a firm empiric basis.

AUTHOR CONTRIBUTIONS

Ilya Kister: study concept and design, drafting of the manuscript, critical revision of the manuscript for important intellectual content, study supervision. John R. Corboy: study concept and design, drafting of the manuscript, critical revision of the manuscript for important intellectual content, study supervision.

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