Neurology® Clinical Practice

Editorial

Long-term registries

Answering tough questions with big data?

Robert J. Fox, MD; Gary Cutter, PhD

Over the past 2 decades, the treatment of multiple sclerosis (MS) has seen remarkable success in developing new therapies. Regulatory approval has been given to 9 different therapeutic entities. Given these treatment options, clinicians are faced with the challenge of deciding which therapy to recommend to individual patients.

Side-effect profiles and risk stratifications help identify the safest and best tolerated therapies for individuals, but identifying which therapy has optimal efficacy has been more difficult. Comparing efficacy across different controlled trials is problematic because of different trial structures, recruitment patterns, and disease courses among the study participants. Even trials of the same therapy, with the same inclusion criteria and study conduct, have yielded different estimates of treatment efficacy. For example, the 2 phase III trials of dimethyl fumarate twice daily found a 52.8% and 45.0% reduction in annualized relapse rate (ARR) at 2 years, despite the same inclusion criteria and endpoint adjudication.[1,2]

Head-to-head studies provide a direct comparison between therapies, but out of the potential 36 head-to-head comparison trials among the 9 therapies, only 7 have been conducted. The cost of conducting head-to-head trials makes unfeasible the conduct of every comparison. The medical community needs alternatives to compare the efficacy of MS therapies.

The MSBase Registry and industry-sponsored Tysabri Observational Program (TOP) registry provide potential collections of data to compare MS therapies in the real-world setting. Both registries utilize clinical assessments with common guidelines for assessing relapses and disability. By using a propensity-weighted analysis, known differences between treatment groups can be adjusted to provide a more apples-to-apples comparison of treatment groups. Previous analyses of these registries found that switching between injectable MS therapy (interferon-β1 or glatiramer acetate) and natalizumab was associated with a 65%–75% reduction in ARR compared to switching from one injectable therapy to another.[3] In this issue of *Neurology® Clinical Practice*, Spelman et al.[4] report a comparison of first-line use of MS therapies. Similar to their previous study, natalizumab was associated with a 68% relative reduction in ARR compared to injectable therapies. Confirmed disability progression was not significantly different between injectable- and natalizumab-treated subjects, and area under the curve (AUC) analysis of disability progression also found no difference between treatment groups.

This study affirms what clinicians have presumed from pivotal and cross-trial comparisons: that natalizumab is more effective than injectable therapies in reducing clinical disease activity in relapsing MS. A cross-trial comparison of injectables (29% reduction in ARR, relative to placebo) and natalizumab (68%) using their respective phase 3 trial results would have predicted a 58% relative difference, which is similar to the 68% reported here.

The absence of a difference in disability progression highlights a long-standing challenge with MS therapies: demonstrating long-term benefit on disability using studies of only a few

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Mellen Center for Multiple Sclerosis (RJF), Cleveland Clinic, OH; and Department of Biostatistics (GC), University of Alabama at Birmingham School of Public Health.

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Correspondence to: FOXR@ccf.org

years' duration. The true benefit from preventing inflammatory injury (i.e., clinical relapses and MRI lesions) may only manifest 10 years or later, when accelerated neurodegeneration arises from injured tissue. Very long-term registries like the North American Research Committee on Multiple Sclerosis (www.narcoms.org) may be the best and most feasible way to demonstrate the effect of therapies on the ultimate course of MS.

The Spelman et al. study highlights several of the challenges in conducting this type of research. Although over 35,000 patients with MS were registered in MSBase, the investigators utilized an industry-sponsored registry for all of the natalizumab-treated subjects, raising the possibility of differences between the patient populations. Over half of the TOP subjects enrolled after already having received natalizumab therapy.[5] Patients enrolled in an industry-sponsored registry may have different treatment expectations and results than those enrolled in an unaffiliated registry. Specifically, patients who drop off sponsored therapy may be less inclined to continue follow-up, and this could have influenced the results. The propensity score method attempted to match the 2 treatment groups, yet there were significant differences in the proportion of patients with Expanded Disability Status Scale (EDSS) ≥ 3. The consort diagram suggests different mixes of participants in each cohort, suggesting a less successful propensity score matching than expected. The subgroup analyses ideally should be pair-matched given the manner of selection and matching, but that would further reduce sample size and power. However, ignoring the matching of pairs is less effective in controlling for difference because important covariates of mismatched pairs can be diluted in the combination of covariates used to obtain the propensity scores. Despite utilizing large, well-operated registries, disability progression data were missing on 27%–51% of subjects.

In an attempt to leverage increased power from disability data, the authors have utilized an AUC analysis of EDSS, which integrates both increases and decreases in EDSS to estimate overall change in disability. This analysis assumes that EDSS is an interval scale, while it is not even an ordinal scale. The difficulty in interpreting a simple AUC is highlighted by the definition of sustained disability progression: 1.5 points for those who start at 0, 0.5 points for those at 5.5 and above, and 1 point for everyone else. The varying durations of time and number of measurements change the time-weighted average that the AUC is representing. For example, an individual who goes from 0 to 5.0 rapidly and is then censored would have a smaller AUC than a person who goes from 4.5 to 6.0 and stays there for the duration of follow-up.

Finally, an assessment of efficacy is only one part of choosing a therapy. The inherent risks of treatment (i.e., progressive multifocal leukoencephalopathy with natalizumab), side effects of therapy (i.e., skin reactions and flu-like side effects with the injectables), cost of therapy, individual disease variability, and long-term risks of suboptimal disease control are all important factors to consider. Broader models that integrate all of these components are necessary to identify the best therapy for an individual patient.

REFERENCES

1. Gold R, Kappos L, Arnold DL, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med 2012;367:1098–1107.
2. Fox RJ, Miller DH, Phillips JT, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med 2012;367:1087–1097.
3. Spelman T, Kalincik T, Zhang A, et al. Comparative efficacy of switching to natalizumab in active multiple sclerosis. Ann Clin Transl Neurol 2015;2:373–387.
4. Spelman T, Kalincik T, Jokubaitis V, et al. Comparative efficacy of first-line natalizumab vs IFN-β or glatiramer acetate in relapsing MS. Neurol Clin Pract 2016;6:102–115.
5. Butzkueven H, Kappos L, Pellegrini F, et al. Efficacy and safety of natalizumab in multiple sclerosis: interim observational programme results. J Neurol Neurosurg Psychiatry 2014;85:1190–1197.

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