Might Misdiagnosis of Multiple Sclerosis Compromise Outcomes of Clinical Trials?

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Introduction

Multiple sclerosis (MS) is a neurological disorder characterized by inflammatory demyelination and abnormal neurological function. The histopathologic hallmarks of MS are plaques of demyelination restricted to the central nervous system (CNS). Magnetic resonance imaging (MRI) is the diagnostic technique of choice, and provides an essential component of modern diagnosis of MS based on the McDonald criteria. These guidelines have been periodically revised. The most current criteria state that a patient must present with signs or symptoms “of an acute inflammatory demyelinating event in the CNS … with duration of at least 24 hours, in absence of fever or infection,” coupled with standardized MRI findings, which include evidence of dissemination in lesions in space (DIS) and time (DIT).1 While these criteria work well for most patients, some patients present with atypical MRI lesions. MS can be a difficult disease to recognize and diagnose, due to the variety of patient presentations encountered by physicians. This, when coupled with MRI findings that can be misleading, can be a challenge for even experienced neurologists. Patients who present with atypical MRI findings, yet may be diagnosed with MS, may skew MS clinical trial results. This study was designed to categorize and quantify lesion patterns in patients enrolled into a phase III clinical drug trial for MS. We suspected that patients with atypical lesion patterns upon entry into the trial might have different on-study outcomes than those with more typical MRI findings.

Materials

This project utilized the resources of the University of Texas MS MRI Analysis Center (UT MRI-AC). MRI databases from a phase III MS clinical trial (CombiRx) that spanned 7 years of preplanned follow-up was kindly provided by Idec and Teva.

Methods

MRI scans from 1008 randomized and 98 non-randomized patients were reviewed. The scans were processed in the UT MRI-AC. They consisted of a dual echo T2-weighted, FLAIR, and pre and post gadolinium (Gd-enhanced) T1-weighted image series for each patient. Scans were reviewed, lesion categorized and counted, and any “special features” were noted. Lesions were grouped into categories as prescribed by the McDonald criteria and calculations were made to determine whether a particular patient met the 2005 and/or 2010 McDonald criteria. Scans were also categorized as either “typical” or “atypical” lesion pattern on MRI. “Atypical” lesion presentation included patients who presented with any of the following primary special features: leukodystrophy-like, NMO-like, normal brain, “Atypical” lesion presentation for MS patient.

Typical MRI presentation for MS patient

This short echo T2-weighted scan is a normal-appearing brain without evidence of inflammation or T2 hyperintense lesions of the type seen in MS.

Typical MRI presentation for MS patient

An example of a patient with a “lumbarative” type lesion in the right posterior frontal lobe.

Atypical MRI presentation for MS patient

These findings are very consistent among MS patients. Many lesions present periventricular and olbing (“Dawson Fingers”), and others reach out into the subcortical white matter.

Typical MRI presentation for MS patient

Example of a patient with possible small vessel disease, i.e. hypertension. The lesions do not surround the ventricles and do not touch the cortical “U-fibers”.

Results

2010 McDonald Criteria

Table 1: Subgroup comparison of MRI and Clinical parameters met 2005 and 2010 McDonald criteria.

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<thead>
<tr>
<th>Subgroup</th>
<th>Value</th>
<th>Significance</th>
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<td>Met 2005 criteria</td>
<td>85.54%</td>
<td>p&lt;0.0001</td>
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<tr>
<td>Met 2010 criteria</td>
<td>62.38%</td>
<td>p=0.0047</td>
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Atypical MRI presentation for MS patient

With Gd+ Lesions

Mean BOD (95% CI) 14.01 (12.13-15.88)

New CUA on Study 64.92%

DAMS on Study 23.07%

Results comparing CAFS, PDEs and PROG on study did not differ significantly.

2010 McDonald Criteria

Table 2: Subgroup comparison of MRI and Clinical parameters met 2005 and 2010 McDonald criteria.

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Conclusions

In the 1008 patients who were randomized, having Gd enhancements and a higher BOD at baseline corresponded with meeting both 2005 and 2010 McDonald criteria more often. Thus, more stringent entry criteria may assure more on-study events, a finding consistent with an analysis of an earlier independent trial.1 This was also evident when evaluating comparisons between the 2005 and 2010 McDonald criteria. The MRI component of the 2010 criteria is less stringent, enabling subjects with less MRI-defined disease, earlier in their clinical disease course to enter trials and as a consequence may lower their proportionate contribution to on-study events. However, having more MRI features at study entry did not correspond with differences in on-study clinical events (as evidenced by the pure clinical measures of CAFS, PDEs, and PROG). In addition, having more MRI features considered typical of MS at study entry corresponded with more on-study activity in the face of partially effective therapies. This held true for MRI-based on-study activity (CUA) and a combination of MRI and clinical-based activity (DAMS). It did not correspond with differences in on-study purely clinically defined events (CAFS, PDEs, and PROG). Furthermore, the between-subjects analysis of 2005 and 2010 McDonald criteria being met more often, had Gd enhancements, and a higher BOD at baseline. These results suggest that although patients with atypical lesion patterns sometimes showed more on-study or MRI activity, they did not show any difference in clinical disease progression.

Of the 98 patients who were not randomized, those with more features at screening (including Gd enhancements and higher BOD) and typical cerebral MRI lesion patterns more often met both the 2005 and 2010 McDonald criteria. As these patients did not enter the study no on-study data was gathered.

Acknowledgements

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References

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