An older dog with newer tricks
Predicting efficacy of IFN-β treatment for multiple sclerosis

Gregory F. Wu, MD, PhD
Erin E. Longbrake, MD, PhD

Correspondence to
Dr. Wu
wug@neuro.wustl.edu

Neurology Neuroimmunol Neuroinflamm
2016;3:e218; doi: 10.1212/NXI.0000000000000218

A building optimism for individually tailored therapy has been integrated into the burgeoning landscape of treatment options for multiple sclerosis (MS). In spite of ongoing advances in imaging and the understanding of MS pathogenesis, predicting which therapies will be most effective for individuals with MS has remained elusive. In this issue, Hegen et al. report on the use of serum cytokine analysis to explore predictors of MS patient responses to interferon-β (IFN-β) therapy. They perform Luminex cytokine quantification from serum of patients with either clinically isolated syndrome or relapsing MS before and 3 months after treatment with IFN-β. Using hierarchical clustering analysis, they stratify patients into 6 groups according to baseline cytokine expression and find that these groupings provide meaningful discrimination between patients’ subsequent clinical responses to IFN-β treatment.

As an extension of the authors’ prior studies in experimental murine systems and in human patients with MS, the results undoubtedly promote the notion that there could be clinical utility in quantifying circulating cytokines before the initiation of disease-modifying therapy. Before this is incorporated into clinical practice, it will be important to determine whether the classification of patients into groups according to baseline cytokine phenotypes is stable over time. The authors base their classification on a single blood draw before initiating IFN-β therapy. However, intra-individual variability in circulating cytokines can occur, as circulating immune markers vary for many reasons, including the overall health of the individual and exposure to other medications. Assay technique can also be a limiting variable. In this article, the authors make no mention of patients’ prior exposure to other disease-modifying therapies for MS, but other work using this patient cohort suggests that not all patients were treatment-naïve. As illustrated by the reported results, exposure to disease-modifying therapy changes the profile of circulating cytokines. Hence, longitudinal data demonstrating that patients consistently fall into the same cytokine group should be taken into consideration before clinical utility can be seriously considered.

The current study used several definitions for IFN-β nonresponders, which are worth noting. One definition was based on annualized relapse rate (ARR) for the 2 years before IFN-β treatment compared to the 2 years after treatment. Relapses were defined based only on history; no objective demonstration of a neurologic deficit was required. It should also be noted that the ARR was higher for IFN-β nonresponders than for responders during the 2 years before the study. This raises the question as to whether nonresponders simply had more active MS in general. The reported data may thus distinguish between patients with more active vs less active MS, as opposed to indicating an effect of IFN-β treatment. The authors alternatively defined nonresponders as patients who experienced a 1-point increase in Expanded Disability Status Scale (EDSS) score between baseline and 2 years post-IFN-β treatment. Nonresponders had lower baseline EDSS scores than responders, and both groups had mild disability, with mean scores of 1.8 for responders and 1.2 for nonresponders. Because the EDSS is a nonlinear scale, a clinically insignificant neurologic change can result in a 1-point increase on the low end of the scale. This may have biased the categorization of patients as responders or nonresponders. Careful selection of patient groups, and an expansion of the number of participants, will undoubtedly be useful in validating the observations made regarding IFN-β responsiveness to date.

In summary, Hegen et al. report on an important approach for subdividing patients with MS based on their baseline level of circulating cytokines. This classification correlated with patients’ subsequent clinical outcomes. Should these findings be reproduced with a larger number of observations and increased rigor of...
defining outcomes, this strategy would have a substantial influence on the way treatment decisions are made for patients with MS. Furthermore, the use IFN-β, which has been decaying in the face of a rapid expansion of therapeutic options,9 may be reinvigorated by a more precise indication specific to this class of disease-modifying therapy. On the other hand, the approach of preassessing the likelihood of responsiveness to disease-modifying MS therapy is not exclusive to IFN-β. Indeed, several studies on predictors of efficacy for other disease-modifying treatments have been reported. A report on the factors associated with responsiveness to natalizumab serves as one example, which notably examined MRI and CSF features in a prospective trial.10 It is not unreasonable to speculate that these additional variables in combination with serum cytokine levels could provide even greater resolution for predicting response to disease-modifying treatment in MS. Once it becomes possible to discern the critical elements driving responsiveness to individual disease-modifying therapies, understanding of the pathogenesis of MS will certainly be enhanced and tailored therapy for individual patients with MS can truly be realized.

STUDY FUNDING
No targeted funding reported.

DISCLOSURE
G. Wu has served on scientific advisory boards for Biogen, serves on the editorial board of N2, has served on speakers’ bureaus for Pfizer, and has received research support from NIH (R01NS083678). E. Longbrake served on the scientific advisory board for Genzyme, received speaker honoraria from Genzyme and Biogen, and received research support from National MS Society, Sylvia Lawry Physician Fellowship. Go to Neurology.org/nn for full disclosure forms.

REFERENCES
An older dog with newer tricks: Predicting efficacy of IFN-β treatment for multiple sclerosis
Gregory F. Wu and Erin E. Longbrake
*Neurol Neuroimmunol Neuroinflamm* 2016;3; DOI 10.1212/NXI.0000000000000218

This information is current as of April 7, 2016

<table>
<thead>
<tr>
<th>Updated Information &amp; Services</th>
<th>including high resolution figures, can be found at: <a href="http://nn.neurology.org/content/3/2/e218.full.html">http://nn.neurology.org/content/3/2/e218.full.html</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>References</td>
<td>This article cites 9 articles, 2 of which you can access for free at: <a href="http://nn.neurology.org/content/3/2/e218.full.html##ref-list-1">http://nn.neurology.org/content/3/2/e218.full.html##ref-list-1</a></td>
</tr>
<tr>
<td>Subspecialty Collections</td>
<td>This article, along with others on similar topics, appears in the following collection(s): All Immunology <a href="http://nn.neurology.org/cgi/collection/all_immunology">http://nn.neurology.org/cgi/collection/all_immunology</a> Multiple sclerosis <a href="http://nn.neurology.org/cgi/collection/multiple_sclerosis">http://nn.neurology.org/cgi/collection/multiple_sclerosis</a></td>
</tr>
<tr>
<td>Permissions &amp; Licensing</td>
<td>Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: <a href="http://nn.neurology.org/misc/about.xhtml#permissions">http://nn.neurology.org/misc/about.xhtml#permissions</a></td>
</tr>
<tr>
<td>Reprints</td>
<td>Information about ordering reprints can be found online: <a href="http://nn.neurology.org/misc/addir.xhtml#reprintsus">http://nn.neurology.org/misc/addir.xhtml#reprintsus</a></td>
</tr>
</tbody>
</table>