Neutralizing Antibodies to Interferon: Clinically Relevant to MS Treatment?

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The American Academy of Neurology,² the Canadian MS Clinics Network,³ and an international consensus panel⁴ also have endorsed the use of disease-modifying agents for RRMS. These guidelines are continually updated as new information becomes available.⁵ The FDA has approved 4 immunomodulators: interferon (IFN) beta-1a intramuscular (Avonex, Biogen Idec), IFN beta-1a subcutaneous (Rebif, Serono and Pfizer), IFN beta-1b (Betaseron, Berlex), and glatiramer acetate (Copaxone, Teva). In addition, mitoxantrone (Novantrone, Serono) has been approved as an immunosuppressant. Just how effective these drugs are in preventing attacks and slowing disease progression is not entirely clear. Despite compliance with disease-modifying-drug regimens, many patients still have relatively aggressive disease. Would some exacerbations happen whether or not a patient was taking a medication? Are there some unknown biologic differences that account for patients doing poorly? Are attacks part of the normal waxing and waning of the disease? Is there something in the drugs themselves that prompts an adverse immune reaction that compromises their effectiveness in some individuals? In looking for answers, investigators have been exploring immunology, genetics, molecular biology, and other factors. If these could be identified, they could help tailor available treatments. Better still, the researchers could tap this information to develop more targeted therapies that prevent attacks much earlier in the disease process than do today's disease-modifying treatments. The search for molecular markers has been a very active area of research, according to Hillel Panitch, MD, professor of neurology at the University of Vermont in Burlington. "So far the only marker we have is MRI--and that is pretty expensive," he said.

NEUTRALIZING ANTIBODIES

Numerous studies have been performed to evaluate the impact of neutralizing antibodies (NAbs) to IFN on clinical relapse, MRI relapse, and disability. The issue has been contentious, and neurologists have been debating it for close to a decade. In July, Neurology published 2 research papers⁶,⁷ and an editorial⁸ that addressed the relationship between NAbs to IFN and relapse and disease progression outcomes. One of the articles published in Neurology⁶ reported results of a post hoc analysis of the Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis (PRISMS) trial.⁹ When the manuscript was being prepared, the lead author, Gordon S. Francis, MD, was responsible for strategic direction and clinical development in neurology at Serono International, the manufacturer of Rebif. Francis is currently vice president of neurology at Elan Pharmaceuticals, a potential competitor. The 2-year analysis of PRISMS trial data that examined the impact of NAbs to subcutaneous IFN beta-1a on clinical relapse, MRI relapse, and disability revealed that use of IFN beta-1a correlated with significant positive outcomes.³ It also showed that the presence of antibodies was not associated with relapse. The 4-year reanalysis showed a different picture.⁶ Although similar relapse and disability rates were seen for patients who were either NAb-positive (NAb+) or NAb-negative (NAb2), once patients showed evidence of persistent NAbs, a decrease in pharmacodynamic response to IFN beta-1a developed and evidence of MRI relapse emerged. Francis and his team found that the impact of NAb positivity was especially striking for MRI measures--the study demonstrated that patients were functioning as well as they had been when receiving placebo. The impact on disability was less compelling. A one-point change in the Expanded Disability Status Scale was used to confirm clinical progression. Critics said that the impact on disability was marginal at best. In fact, it was only statistically significant (P < .03) for persons whose status was determined when the data were collected--that is, for those with interval-positive status.
Francis acknowledged the study's limitations in documenting increasing disability. "The studies are really too short to show disability outcomes," he said. However, Douglas S. Goodin, MD, professor of neurology at the University of California, San Francisco, couched it differently: "The effect on disability was marginal at best."

Francis stressed that the findings pointed to the need for a change in treatment. "When you see that neutralizing antibodies limit the efficacy of interferon, keeping patients on interferon simply doesn't make biologic sense."

Based on his analysis, Francis advised neurologists to do routine testing during the first 2 years of IFN treatment, regardless of the patient's health status. "Waiting for relapse before testing might be too late and gives you little option in switching drugs," he said. "If the test were only to be done once, I'd do it at 12 months." The PRISMS 4-year data demonstrated that if NAb were to develop, 50% would in 6 months, 80% would in 12 months, and 90% would in 24 months.6

Like many neurologists, Francis expressed particular concern about high titers and repeated attacks. Panitch agreed: "Neutralizing antibodies definitely have an effect on efficacy. It is best documented for MRI, followed by clinical relapse, and looking at progression of disease."

Yet Panitch would not test for antibodies if patients were doing well clinically, he said. If they were doing poorly on IFN, he said he would switch to galtiramer acetate. "It is a drug that is just as effective as interferon," he said. "Although it takes awhile to achieve its maximum dose, it is very well tolerated."

The other study published in the July issue of Neurology7 was a 4-year follow-up analysis of the European IFN-Beta-1a Dose-Comparison Study. Patients were randomly assigned to 1 of 2 treatment arms: IFN beta-1a 30 µg IM or IFN beta-1a 60 µg IM once weekly for up to 4 years. Antibodies were tested at baseline and every 3 months for the study's duration. Seropositivity was defined as a titer that was greater than or equal to 20. Negative titers were identified as values of 0 at baseline and all subsequent titers that were below 5.

The study, led by Ludwig Kappos, MD, professor of neurology and clinical neuroimmunology at University Hospital in Basel, Switzerland, demonstrated that the presence of NAb was more than 2.5 times greater in patients receiving the higher (60-µg) dose of IFN than in patients receiving the low-dose IFN (1.4% compared with 4.8%). This finding is consistent with data showing that high-dose IFNs generate a stronger antibody defense.

Kappos could not be reached for comment. However, Goodin identified limitations in the study: "The problem with the Kappos paper is that he had very few patients with antibodies--26--and he had to lump together patients on high- and low-dose interferons in the analysis."

According to Goodin, Avonex was reformulated before it entered the US market. He pointed out that studies have shown NAb to be present in 14% to 25% of patients receiving Rebif,6,9 26% to 30% receiving Betaseron,10,11 and only 2% to 6% receiving Avonex.7

Gavin Giovannoni, MBBCCh, PhD, reader in neuroimmunology in the Department of Neuroinflammation at the Institute of Neurology at University College in London, and Andrew Goodman, MD, director of the Multiple Sclerosis Center and chief of neuroimmunology at the University of Rochester, NY, wrote the companion editorial in Neurology.6 They argued that evidence provided by the studies led by Francis and Kappos lends support to using the assays. "With PRISMS [2-year], you couldn't say with any certainty whether neutralizing antibodies had any impact, but with this additional re-analysis of 4-year data, the Francis data is potentially compelling," said Goodman.

Goodman said that he was struck by the differences in MRI relapse, clinical relapse, and disability outcomes between the 2 groups, but he acknowledged that the impact on disability was not very strong. An association was found only through an interval-positive analysis when relapse data were linked to each group at the time the data were collected.

Goodman advised screening at 12 to 24 months after starting IFN or at the time of relapse. He stopped short of making recommendations about what neurologists should do when they see NAb positivity. "It's a clinical decision whether to move on to something else--and what to move to," he said. However, Goodman added that a negative test result could be telling: "If you relapse and you don't have antibodies, you might see a benefit if you either up the current drug or add another drug."

The editorialists also took up the issue of managing patients who are persistently NAb+ who are in remission. They wrote: "At present, there is little evidence to guide physicians on how to manage persistently NAb+ subjects who are doing well clinically. Ideally, these subjects should be studied to determine how to manage them appropriately."

Richard Ransohoff, MD, commented on the studies. "This work is a service for the community of MS..."
patients and their physicians. We neurologists felt uncertain about the significance of neutralizing antibodies for many years because none of the individual efficacy trials were powered sufficiently to demonstrate an effect of developing persistent neutralizing antibodies. Now all the data taken together make a compelling argument that interferon-beta injections lose their effectiveness for treating MS when persistent neutralizing antibodies are present." Ransohoff is professor of molecular medicine and director of the Neuroinflammation Research Center at the Cleveland Clinic Lerner Research Institute.

In an e-mail, he added, "It is now timely to undertake research to define how to reduce the likelihood of developing NAb and how to optimize therapy for NAb-positive patients. Some trials are already under way. This research will help make us more effective at using interferon beta for our patients and also stimulate the search for new treatments."

But not all neurologists viewed IFN as necessarily ineffective in the presence of NAb. Avertano Noronha, MBBS, MD, associate professor of neurology at the University of Chicago, said, "You would expect the presence of antibodies to block everything, including natural interferons present in the body. Yet there is plenty of evidence that shows that the antibodies disappear all the time and that circulating immune complexes in interferon beta-1b activate suppressor cells and turn off the immune attack." Noronha added, "Only 7% of patients who worsen have high-titer antibodies."

Furthermore, Noronha pointed out that head-to-head studies of IFNs have shown better outcomes with high-dose, high-frequency IFNs than with once-weekly IFN. He explained that antibodies have less of an effect in the high-dose group because of antigen excess (a lot more IFN).

Denmark, which has a national health service, has had a countrywide MS Treatment Register since 1996, when IFN-beta treatment for RRMS was initially approved. Also, in the July issue of Neurology, Per Soelberg Sorensen, MD, and colleagues analyzed the proportion of patients who have persistently positive, negative, and fluctuating antibodies over a 6- to 78-month period. Blinded investigators performed the antibody studies.

The study revealed that among 455 patients, 52.3% were consistently NAb2, 40.9% became definitely NAb+, and 6.8% had fluctuating antibodies. Consistent with other studies, more patients who were taking low-dose IFN beta-1a intramuscularly remained negative for NAb.

Panitch credited the Sorensen paper with providing the "best-documented evidence" on the NAb issue. The Danish Health Ministry stipulated that all patients be entered into the registry and tracked on a routine basis. The registry has records of more than 400 patients.

Asked about the relevance of his study, Sorensen responded by e-mail, stating that the European Federation of Neurological Societies Task Force on Guidelines has adopted clinical practice guidelines concerning the NAb issue. In contrast to official guidelines in the United States, the federation has developed stringent guidelines, recommending that therapy with IFN-beta be discontinued in patients when high titers of NAb are sustained. The guidelines call for repeating the test at 3- to 6-month intervals and discontinuing the test at 24 months if the results remain negative. The group also recommended measuring binding and NAb in specialized laboratories with a validated assay. For patients found to have NAbs, measurements should be repeated every 3 to 6 months.

As much as possible, the federation tried to use a high standard of evidence, namely randomized controlled trial data, in making its recommendations. The recommendations that Sorensen described are based on such data, but he did not identify those studies. The Task Force found slightly weaker evidence to recommend the discontinuation of screening of patients who have negative antibodies during the first 2 years of therapy, but the federation still included that recommendation in the guidelines.

ECRI (formerly the Emergency Care Research Institute), an independent evidence-based practice center and World Health Organization Medical Technology Evaluation Center, in Plymouth Meeting, PA, conducts research on the evidence to back use of new diagnostics and treatments. So far, the data are too inconsistent to make a judgment, noted Karen Schoelles, MD, medical director: "Nobody is really sure how to use this data." She questioned sorting out the normal ups and downs of a relapsing, remitting disease from the adverse effects of treatment. In addition, she pointed to the absence of standardized assays. "That makes it difficult to compare results across studies," she said.

"Good outcomes data is going to take at least 20 years to collect, looking at disability over years and decades," Schoelles said. "Ideally, answers should come from well-designed clinical trials. Absent these studies, patients are bearing the brunt of side effects in the face of expensive treatment."

One of the problems with interpreting much of the data that have been collected is that a standardized assay does not exist. Therefore, findings are inconsistent, which makes it hard to draw conclusions. It is extremely difficult to determine what the threshold for a high titer should be. The
reformulation of Avonex before it entered the US market also could account for problems in replicating results in the United States.

As an example of international differences, Panitch pointed out: "When I have tested patients, I rarely find them positive." He questioned the utility of performing the test when, for him, the likelihood of finding antibodies was 1 in 20 or less. "An important idea is that neutralizing antibodies do tend to disappear. Routine testing every 4 to 6 months like it is done in Denmark is not productive." Widespread use of a standardized assay could change that, according to Panitch and others.

CLINICAL UTILITY

Will the new studies lead to broader use of the assay? Lauren Krupp, MD, said that she viewed the new data as "providing pretty good support for using the assay," at least in some instances. Krupp, director of the pediatric MS program and codirector of the Multiple Sclerosis Center at State University of New York in Stony Brook, said that she would probably not use the assay unless patients were not doing well.

Although Krupp was impressed with the new data, she pointed to several caveats in interpreting it. One concern she raised is the design of the PRISMS 4-year study, namely that it used a post hoc design. "That is most useful for suggesting areas for future analysis, not for guiding practice," she said. She also noted that the data on progressive disability had some problems, namely that disability progression was only demonstrated by one measure: the interval-analysis measure. She also questioned whether adding an immunosuppressive agent might minimize the neutralization of IFN.

Other neurologists also indicated that they would most likely use the test when faced with patients who have relapsed--but not routinely during the first 2 years of treatment. For example, Steven Cavalier, MD, a neurologist in Baton Rouge, LA, said that perhaps he would perform the test when a patient wasn't doing well. Asked what would he do with a positive finding, he said that he might give some consideration to switching to glatiramer acetate.

Although Goodin opposed using the test, he had this to say: "I could imagine a scenario where I might use the drug. If you have a patient on Avonex and the patient is not doing well, you might test for antibodies. If they have high titers, it would make no sense to move them up to Betaseron or Rebif. I'd probably move them to Copaxone." Goodin disagreed strongly with discontinuing therapy in patients with persistently high titers who were doing well. However, he took exception to the Danish guidelines that call for taking all patients off the drug no matter how they are doing. "If you pull a drug for a test, patients are going to go nuts. If I got worse after they pulled the drug, I would sue."

CLINICAL PRACTICE GUIDELINES

At present, many health plans won't cover the test; patients who want it must pay at least $500. How long will it be before the test is adopted or is discarded as another assay of limited value? Both proponents and naysayers say that evidence to back or question its use is now on their side. Ransohoff would like to see the American Academy of Neurology and the National Multiple Sclerosis Society endorse new clinical practice guidelines that integrate the assay into practice for patients treated with IFN. So far, the National Multiple Sclerosis Society has posted a link on its Web site that discusses the latest findings (www.nationalmssociety.org/Clinup-Antibodies.asp), but it has not given recommendations for or against using the test or guidance about situations in which testing might be helpful.

According to John Richert, MD, vice president of research and clinical programs at the Multiple Sclerosis Society, the issues are complex. "Some variables to consider are how elevated a titer is it, is it reproducible at 3 months, how is the person clinically, and how long has the patient been on the drug," he said. "What the presence or absence of antibodies dictates is not straightforward." That said, Richert acknowledged that the studies in the July issue of Neurology "helped cement the perspective that persistently high titers are associated with adverse effects."

Yet neurologists want guidance now. "The bigger question is, do you start a medicine that is least likely to produce antibodies?" Goodin asked, "or do you weigh reported evidence of improved outcomes with given therapies and use them?" *

REFERENCES


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