NEUROSCIENCE TODAY, NEUROLOGY TOMORROW

IL-7 Level May Mark Interferon Responsiveness

BY JEFF EVANS

FROM SCIENCE TRANSLATIONAL MEDICINE

Serum levels of interleukin-7 helped determine which patients with relapsing-remitting multiple sclerosis would benefit from treatment with interferon-beta in a series of experiments involving human sera and mice with experimental autoimmune encephalomyelitis.

Patients with high IL-7 levels had a T helper cell type 1 (T_H1) form of MS that has been shown to respond better to interferon-beta therapy than does the T_H17 form of MS.

"These results not only help to clarify our understanding of a genetic risk factor associated with MS but also suggest new predictive, mechanism-based measurements for MS patient stratification," wrote Li-Fen Lee, Ph.D., of Pfizer, and her colleagues (Sci. Transl. Med.2011;3:93ra68).

The study brings together findings from earlier reports that in totality suggested that IL-7 and its receptor, IL-7R-alpha, may be involved the pathogenesis of MS. Several genome-wide association studies have pointed to a single nucleotide polymorphism in the gene encoding IL-7R-alpha that confers increased susceptibility to MS. In another study, patients with MS had higher levels of both IL-7R and IL-7 mRNA in cerebrospinal fluid than did patients with noninflammatory neurological diseases. And other studies have shown that IL-7/IL-7R-alpha signaling is necessary for the survival of T lymphocytes in humans and animal models.

Using cells from 26 patients with relapsing-remitting MS and mice with experimental autoimmune encephalomyelitis (EAE), Dr. Lee and coauthors found that in both cases, IL-7 promotes the differentiation of naive T cells into T_H1 cells, but not T_H17 cells. Mice that were given IL-7 after EAE was established and paralysis had begun experienced worsened symptoms, whereas those that were given an antagonist IL-7R-alpha antibody had reduced disease severity.

Previous studies have suggested that interferon-beta (IFN-beta) treatment prevents EAE in mice with pathogenic T_H1 cells before symptom onset, yet it exacerbates the disease when given to mice with the T_H17 form of EAE.

The investigators examined the relationship between MS type and response to IFN-beta treatment in the 26 patients.

The level of IL-7 in serum was significantly associated with the rate of relapse. In the 2 years after treatment with IFN-beta, there were no relapses in 5 of 5 patients with an IL-7 level greater than 150 pg/mL, compared with no relapses in 7 of 21 patients with an IL-7 level less than 150 pg/mL.

"Our finding of a role for IL-7 in directing and promoting the generation of human T_H1 cells … is entirely consistent with the elevated IL-7 levels seen in patients with the IFN-beta-responsive form of MS," the investigators wrote.

They concluded that "it is possible that serum IL-7 level may be useful for predicting clinical benefit from IFN-beta treatment in [relapsing remitting MS] patients. It is conceivable that patients with high levels of serum IL-7 might directly benefit from potential new therapies targeting either IL-7 or its receptor."

The study was funded by grants from the National Institutes of Health and a National Multiple Sclerosis Society fellowship. Dr. Lee and eight other authors are employees of Pfizer, which has filed a patent application titled, "Antagonist Anti-IL-7 Receptor Antibodies and Methods" with three of the authors. Stanford University and two of the authors have filed a separate patent application for "Markers for Determination of Patient Responsiveness." The remaining seven authors declared having no competing interests. ■

ADVISER'S VIEWPOINT

Validation, Additional Data Needed

This manuscript explores the role of IL-7 in MS and experimental autoimmune encephalomyelitis (EAE) in mice. The authors present data showing that high serum levels of IL-7, especially in association with low levels of IL-17F, predict a good clinical response to interferon-beta (IFN-beta) therapy in MS. They also show that IL-7 can induce T_H1, but not T_H17, cell differentiation in both humans and mice. They postulate a "T_H1-driven" form of MS responsive to IFN-beta and a "T_H17-driven" form of MS not responsive to IFN-beta. Use of IL-7R-alpha-blocking antibodies in EAE before or after onset of paralysis resulted in reduced severity of EAE, reductions in peripheral naive and activated T cells, and reduced lymphocyte infiltration into the central nervous system.

The authors propose that such IL-7R-alpha-blocking antibodies may be effective in treatment of MS. These results are exciting, and suggest that we may be able to predict an individual's response to treatment with IFN-beta or other MS therapies by looking at induction of specific cytokines. This would be a major advance in a field where we treat patients with a variety of disease-modifying therapies with very little knowledge of how individual responses to therapy may vary.

However, there are a few cautions to keep in mind when reviewing these results. The results are preliminary, and based on a retrospective sample of 26 patients treated with IFN-beta for at least 12 months. Two blinded neurologists classified the patients as responders or nonresponders based on historical data on the number of relapses and steroid treatments in the 2 years before initiation of therapy, compared with 2 years after starting therapy. No MRI data were reported to assess for subclinical disease activity, and neutralizing antibody status to IFN-beta was also not reported. The "high IL-7, low IL-17F" group comprised only five patients, who had an average of two relapses in the 2 years preceding treatment and no relapses in the 2 years during treatment with IFN-beta.

These results obviously need to be validated in a larger, prospectively determined cohort with appropriate MRI monitoring for subclinical MS disease activity. Past experience with MS clinical trials and our evolving knowledge of the complexity of the immune alterations in MS suggest that focusing on changes in one or two cytokines and concepts such at "T_H1-driven" and "T_H17-driven" forms of the disease are likely oversimplifications, although they may serve as useful constructs for future investigation.

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Multiple Sclerosis Does Not Hurt Pregnancy, Birth Outcomes

BY KERRI WACHTER

FROM ANNALS OF NEUROLOGY

Women with multiple sclerosis can be reassured that should they choose to become pregnant, they are generally not at any greater risk of adverse pregnancy or birth outcomes than are similar women without the disease, according to a retrospective cohort study.

The findings should have important clinical implications for this group of patients, because about three-quarters of people with MS are women and the clinical onset of the disease most often occurs in early adulthood, just when many are considering starting a family, Mia L. van der Kop and her coauthors wrote.

Studies have shown that one-fifth to one-third of women with MS bear children after disease onset.

Ms. van der Kop and her coinvestigators at the University of British Columbia, Vancouver, linked clinical data from the British Columbia (BC) MS clinics' database with outcomes data from the BC Perinatal Database Registry (BCPDR) to examine whether maternal MS was associated with adverse neonatal and delivery outcomes and what factors, if any, were associated with risk (Ann. Neurol. 2011 June 27 [doi: 10.1002/ana.22483]).

Of 7,056 female patients who were registered at one of the four MS clinics in BC from 1980 through 2008, the investigators found links for 321 women (432 births) with laboratory-supported or clinically definite MS whose with births occurred between April 1998 and March 2009 in the BCPDR. These births were compared with 2,975 births from a random sample of 2,958 women in the general population who were frequency-matched for age, local health authority, and delivery year. The clinics' database is estimated to capture 80% of the MS population in BC. Patients' names and dates of birth were used to confirm the accuracy of linkage.

A greater proportion of births in the MS group were to women who were nulliparous, primigravid, hypertensive, or had smoked during pregnancy. A greater proportion of births in the comparison group were to mothers with diabetes during pregnancy and a history of multiple therapeutic abortions.

Maternal MS was not associated with assisted vaginal delivery (odds ratio, 0.78) or cesarean section (OR, 0.94). The proportion of elective cesarean sections was similar in both the MS and comparison groups (18.6% vs. 16.1%, respectively), and the indication for cesarean delivery did not differ between groups. Delivery outcomes were not associated with either an older age at MS onset or longer duration.

The degree of disability in MS mothers was not significantly associated with higher odds of a cesarean section or an assisted vaginal delivery, compared with women with a normal neurologic exam.

Among nulliparous women, there was no significant difference in the median duration of the second stage of labor between those with MS and those in the comparison group. Duration of the second stage of labor was not associated with age at MS onset.

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