IMAGE OF THE MONTH

Clinical MRI studies are typically performed with 1.5-tesla (T) magnets, though the use of 3-T systems is becoming more common. The use of ultrahigh-field-strength MRI—using 7-T magnets—remains largely the domain of major research facilities such as New York University.

Dr. Yulin Ge, a radiologist at New York University, New York, and his colleagues have been using 7-T MRI to further their understanding of the pathophysiology of multiple sclerosis.

There are two main advantages to high-field MRI over imaging with conventional field-strength magnets. The higher signal intensity-to-noise ratio (SNR) that can be achieved with a stronger magnet strength allows for greater resolution, which in turn can improve the detection of lesions. Lesion counts may be 45% greater using a 4T system with better appreciation of tissue heterogeneity within lesions as compared with a 1.5-T system.

Separately, higher field strength also boosts susceptibility effects. Magnetic susceptibility is the degree of magnetization of a material in response to an applied magnetic field. Oxyhemoglobin in arterial blood has no substantial magnetic properties, but deoxyhemoglobin, which is present in the draining veins after the oxygen has been unloaded in the tissues, is strongly paramagnetic. It can thus serve as an intrinsic paramagnetic contrast agent, the effect of which is increased with greater field strength. This in turn improves the examination of microscopic venous structures, brain iron, and microbleeds. "So venous structures can be shown very well on high-field MRI," Dr. Ge said in an interview.

The researchers have been able to directly see small vascular abnormalities—mainly small venous structures—at a very early stage of MS. "These findings have never been shown on conventional MR," he said. High-field MRI detects these changes before the blood-brain barrier breakdown that can be seen on conventional MRI.

The MS lesions appear to be centered on a small venule. "We can see the abnormal signals on and around the venous wall," Dr. Ge said. "And the lesion developed along the veins—along the venous course in the initial stage of development can be clearly seen on 7T MRI." These findings may be direct in vivo evidence of the vascular pathogenesis of lesions, he added. While it takes only 6 minutes to perform such susceptibility-sensitive imaging, slices are 2 mm thick with pixel resolution of 0.2x0.2 mm^2.

These vascular abnormalities are "not seen in one or two lesions but in many lesions," he said (as shown in image A). The number of lesions with vascular abnormalities that can be detected "gives you a very important indication of disease activity beyond the resolution of conventional MRI."

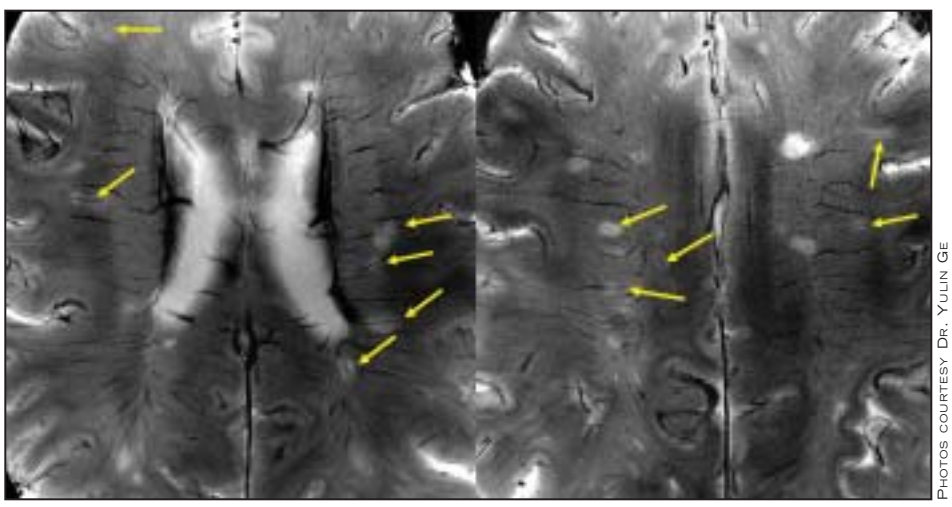
Gadolinium-enhancing lesions currently are considered the first detectable MR abnormalities in MS patients. However, the fact that vascular abnormalities detected using ultrahigh-field MRI can be seen even earlier "has important implications for treatment," said Dr. Ge.

High-field-strength MRI might allow physicians to track the early disease activity and the effectiveness of treatments. This is particularly important now that disease-modifying therapies are available.

The immunomodulatory drugs—interferon β-1a IM (Avonex), interferon β-1b SC (Betaseron) glatiramer acetate SC (Copaxone), or interferon β-1a SC (Rebif) are approved for and are currently used in the United States as first-line therapies for MS to prevent relapses or disease progression.

Newer compounds approved by the Food and Drug Administration for use in MS include mitoxantrone (Novantrone) and natalizumab (Tysabri). Last year, natalizumab was reintroduced for the treatment of relapsing forms of MS with a black box warning about the risk of progressive multifocal leukoencephalopathy associated with treatment. The drug had previously been voluntarily suspended from the market following the development of PML in three patients treated with the drug (two for MS and one for Crohn's disease).

—Kerri Wachter



PHOTOS COURTESY DR. YULIN GE

Ultra-high-field MRI shows an intimate relationship between lesions and centered small veins (arrows), suggesting a primarily vascular pathogenesis of MS lesions.

Early Interferon Lessened Disability in Multiple Sclerosis

BY ELIZABETH MECHCATIE
Senior Writer

Early treatment with interferon-beta in patients who have experienced a clinical event suggestive of multiple sclerosis can delay disability progression, said Dr. Ludwig Kappos of University Hospital, Basel (Switzerland).

The study, conducted in several European countries, was the follow-up of the initial phase of the BENEFIT (Betaferon/Betaseron in Newly Emerging Multiple Sclerosis for Initial Treatment) study of 468 people (mean age 30 years) with a first event suggestive of MS and at least two clinically silent MRI lesions. In the first 2-year phase of the study, 292 patients were randomized to start treatment with interferon beta-1b (250 mcg subcutaneously every other day) within 60 days of developing the event, and 176 received placebo. The follow-up study analyzed patients 3 years after the beginning of the 2-year placebo-controlled phase and enrolled nearly 90%—418—of the patients who had completed that phase; 378 chose to take interferon-beta starting at 2 years, and 392 completed the 3-year follow-up. At that time, 16% of patients in the early-treatment group had confirmed progression on the Expanded Disability Status Scale (EDSS), versus 24% of patients in the delayed treatment group. Treatment was tied to a 40% reduced risk. The number needed to treat early to avoid one additional confirmed case of EDSS progression was almost 12, the authors wrote (Lancet 2007;370:389-97).

Also at 3 years, 37% of patients in the early-therapy group developed conversion to clinically definite MS (CDMS) vs. 51% of those who received delayed treatment, a 41% risk reduction. The number needed to treat early to avoid one additional CDMS conversion was seven. Over the 3 years, patient-reported functional assessment scale scores were high and stable.

The early-treatment group was exposed to interferon-beta for a median of 1,080 days over 3 years, versus a median of 364 days in the delayed treatment group.

The impact on the EDSS 3 years after the onset of the first MS-type event indicates that "a delay of such treatment by, essentially, just one event, even at this early stage of the disease, has an effect on later accumulation of disability," Dr. Kappos and his associates wrote.

Adverse events were typical of the side effect profile; flulike symptoms and injection site reactions were reported in about half of all patients.

The authors noted that in three multicenter, placebo-controlled studies, CDMS was delayed in patients who received treatment with interferon-beta for a first episode of neurologic symptoms that were highly suggestive of MS. But to date, they said, there had been no controlled evidence that early initiation of treatment with interferon-beta affects the development of confirmed disability, compared with delaying treatment. A 5-year follow-up of the participants is planned.

In an accompanying editorial, Dr. Sean J. Pittock of the departments of neurology and laboratory medicine and pathology at the Mayo Clinic, Rochester, Minn., said that though the study presents the first evidence of interferon beta-1b's benefit, the magnitude of benefit, though statistically significant, is clinically small (Lancet 2007;370:363-4).

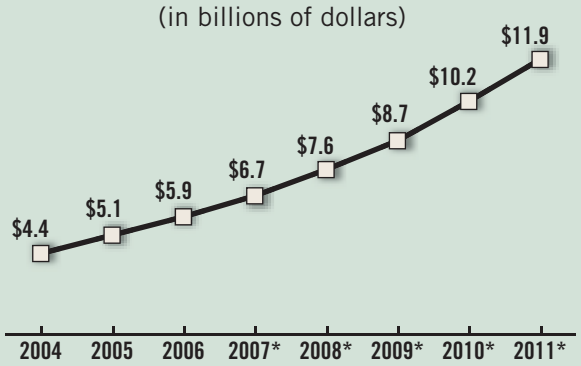
Interferon beta-1b is marketed in the U.S. by Bayer HealthCare Pharmaceuticals Inc. as Betaseron, with approval for treating relapsing forms of MS to reduce the frequency of clinical exacerbations. The approved label includes the statement that patients with MS "in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with" MS.

Dr. Pittock disclosed no conflict of interest. Some of the study's authors were from Bayer Schering Pharma AG. The disclosure statement for the other authors, including Dr. Kappos, listed several as having received research support and having served as consultants to Bayer Schering and other pharmaceutical companies. ■

DATA WATCH

Rise Expected to Continue in World Market For Multiple Sclerosis Treatment

(in billions of dollars)



*Projected data.
Note: Market focuses on glatiramer acetate and interferon beta-1a and -1b.
Source: Kalorama Information

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