UT SOUTHWESTERN MEDICAL CENTER NEWS

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MS drug may reduce immunity, UT Southwestern researchers find

DALLAS – Dec. 15, 2008 – A drug used to treat multiple sclerosis might make some patients vulnerable to brain infection by reducing the number of immune cells there, UT Southwestern Medical Center researchers have found.

The findings also suggest that the drug, natalizumab, might be safer and more effective when given with treatment "holidays" instead of continuously over long periods, the researchers said.

"Natalizumab is very effective in keeping pro-inflammatory cells out of the brain to reduce damage from MS," said Dr. Olaf Stüve, assistant professor of neurology at UT Southwestern and senior author of the study, which appears in the December issue of *Archives of Neurology*.

But the potential downside is interference with immune surveillance against infection, he said. Thus, infections of the brain or spinal cord may go undetected until they become a serious problem.

"However, our study has limitations because of the small number of autopsies that were involved," Dr. Stüve said.

"Whether or not treatments other than prolonged, uninterrupted dosing may benefit patients with MS should be tested in controlled clinical trials," he said.

Natalizumab was introduced in 2004 and almost immediately withdrawn after three people developed a brain infection called progressive multifocal leukoencephalopathy, or PML. Two of those patients died.

The drug, known as Tysabri, returned to the market in 2006 under stricter monitoring guidelines and label warnings about the risk of developing PML. Only five other drugs are approved for treating MS.

"It's a very effective drug, and it's clear that the vast majority of patients are greatly benefiting from its use," said Dr. Stüve, who is also an assistant professor at the Dallas Veterans Affairs Medical Center.

MS is an autoimmune disease in which a person's own body attacks the fatty coating surrounding nerve cells. Natalizumab is designed to prevent that autoimmune attack.

"Unlike other immunosuppressant drugs, natalizumab was specifically designed to interfere with the migration of immune cells into organs," Dr. Stüve said. Most MS experts believe that these cells play a major role in the disease and that their ability to enter the central nervous system should be reduced.

"This type of infection has also been reported with several other types of immunosuppressant

(MORE)

drugs that are being used to treat MS," he said.

About 43,000 people have taken natalizumab since it was reintroduced in 2006, Dr. Stüve said, with three more people having developed PML. Because of the increased monitoring, these cases of PML were detected relatively early, he said.

The researchers previously have shown that natalizumab significantly reduces the number of immune cells in the cerebrospinal fluid, which bathes and protects the spine and brain. In particular, the number of CD4+ T cells dropped 10 times more than the other types of immune cells. Activation and rapid division of CD4+ T cells are vital for many immune responses.

In the current study, the researchers focused on the number of immune cells within the open spaces of the brain itself, known as cerebral perivascular spaces. Cells around these spaces are believed to be crucial in mounting autoimmune attacks on the body.

They examined postmortem brain tissue from one of the patients with MS who had died while taking natalizumab. Controls included tissue from patients with MS who were not treated with natalizumab, and from patients with PML who had not been treated with natalizumab. Natalizumab caused a significant reduction in immune-related cells in the perivascular spaces of the person with MS, including a total depletion of CD4+ T cells and the cells that activate them.

"The challenge will be to identify biomarkers that will help patients at risk for breakdown of immune surveillance," Dr. Stüve said.

Other UT Southwestern researchers involved in the study were Dr. Maria del Pilar Martin, a former postdoctoral fellow; Dr. Petra Cravens, instructor of neurology; Ryan Winger, summer student; Dr. Elliot Frohman, professor of neurology; Dr. Todd Eagar, assistant professor of neurology; and Dr. Nitin Karandikar, associate professor of pathology.

Researchers from Ohio State University Medical Center; the University of California, San Francisco; Klinkim Rechts der Isar in Munich, Germany; and the University of Colorado, Denver, also participated.

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