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The RESTORE trial: What did we learn about multiple sclerosis?

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WHY WAS THE TRIAL CONDUCTED? In their article "MS disease activity in RESTORE: A randomized 24-week natalizumab treatment interruption study,"[1] Fox and colleagues carefully evaluated a very specific question: what happens if a specific treatment for multiple sclerosis (MS) is temporarily stopped? To many people, this would seem an unusual question. It does not seem logical. Why would a treatment, if it were working, be stopped? The answer is that some treatments can have long-term side effects. In others, like natalizumab, it has been observed that long-term treatment, which is aimed at the immune system, can cause problems with the way that our bodies respond to certain viruses.

In some people, natalizumab has been associated with progressive multifocal leukoencephalopathy (PML), a potentially fatal neurologic illness. PML is caused by the JC virus. If a person has had the JC virus, his or her immune system forms antibodies to the virus. These antibodies would continue to be present in a person's blood even after the infection had occurred. Basically, once exposed, the person will continue to make antibodies against the virus.

When exposed to natalizumab, a medication that targets a specific part of the immune system, a person's ability to respond to certain viruses, like JC, changes. Studies have shown that the people who were at the highest risk for developing PML were those who had antibodies in their blood. In other words, they had been exposed to JC virus at some time in the past. In addition, people who had the antibodies and had also tried other immune system medications were at a high risk. The risk increased with duration of treatment with natalizumab.[2]

Because there is an association between the length of treatment and the occurrence of PML, some have proposed a "drug holiday." In short, when the MS was better, a person would temporarily stop taking natalizumab. By stopping the treatment, it has been proposed that the risk of developing PML would decrease. However, a study was needed to determine whether this idea (a "drug holiday") was correct. The biggest worry regarding a temporary interruption of treatment was the possibility of the MS becoming worse. It was for these reasons that the RESTORE trial occurred.

HOW WAS THE STUDY DONE? The study was performed at 31 medical centers in the United States and Europe. A total of 175 people were in the trial, which lasted 6 months. During the trial, people were randomly assigned to be in one of 3 groups: (1) continue natalizumab, (2) take placebo (in other words, no treatment at all), and (3) replace the natalizumab with another MS treatment. If assigned to the last group, the patient and his or her neurologist decided whether to switch to an interferon, glatiramer acetate, or methylprednisolone, all of which have been shown to be effective in the treatment of MS. If the patient's illness worsened, natalizumab was restarted.

Each patient had MS. There were more women than men. Most patients had tried another therapy before they started taking natalizumab. In order to be in the trial, each person had to be on natalizumab. Patients had to be free of MS relapses for more than 1 year.

During the trial, each person was followed very carefully to look for any change that would indicate a worsening of MS. Illness was evaluated in 2 main ways. First, the patients were seen frequently, asked about new neurologic symptoms, and examined carefully. Second, each person had an MRI scan once a month to assess for any change in neuroimaging. The researchers used 2 methods rather than one because some people can have a change in the examination without a change on MRI and others can have a change on MRI without obvious changes on examination. By performing both, the study doctors used every available tool to determine whether the MS was getting worse without natalizumab.

As mentioned, one group of patients switched to a different MS treatment. However, the study was not designed to determine whether one treatment was better than another. Instead, the main point was to determine whether people with MS got worse when not taking natalizumab. If so, the risk of worsening would have to be weighed against the risk of developing PML. In short, the study tried to answer the question: should a person with MS taking natalizumab go on a "drug holiday?"

WHAT WERE THE RESULTS? Fox and colleagues first evaluated the MRI results. Forty percent of the people who received placebo or an alternative therapy had recurrence of their MS by MRI criteria. This

was in comparison to 0% of those who continued natalizumab. No changes occurred on MRI until the group had been off natalizumab for 12 weeks or more. Most did not develop changes until the fourth or fifth month off natalizumab. To be more specific, 6% showed changes at week 12, 76% at weeks 16 to 20, and 18% after week 20. Remember, everyone had an MRI once a month to make these determinations.

The rates of MS relapse were based on clinical criteria. Nineteen percent of those who stopped taking natalizumab had a relapse, compared to 4% of those who remained on the drug. Eight percent of the relapses occurred between the first and second month (week 4–8) off natalizumab, 44% occurred between the second and fourth month off the therapy, and the remainder of relapses (56%) occurred thereafter.

WHY IS THIS IMPORTANT? The information from the RESTORE trial helped to clarify an important question about whether or not natalizumab can be used intermittently. The results suggest that a planned interruption of treatment results in a worsening of the MS. Clinical worsening occurred in as little as 1 month, whereas MRI changes did not occur until after the third month without natalizumab.

Although some of the alternative therapies helped to prevent MS relapse, the study was not designed to compare these treatments. Further study would be needed to make that determination.

REFERENCES

1. Fox RJ, Cree BAC, de Sèze J, et al. MS disease activity in RESTORE: a randomized 24-week natalizumab treatment interruption study. Neurology 2014;82:1491–1498.
2. Olek MJ. Natalizumab for relapsing-remitting multiple sclerosis in adults. Available at: http://www.uptodate.com/contents/natalizumab-for-relapsing-remitting-multiple-sclerosis-in-adults. Accessed February 24, 2014.

About multiple sclerosis

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WHAT IS MULTIPLE SCLEROSIS? Multiple sclerosis (MS) is an inflammatory disease that affects the central nervous system (the brain and spinal cord). It affects women about twice as often as men. It is usually diagnosed around age 30.

The cause of MS is unknown. However, there are several clues about how MS begins. For instance, MS occurs more often in people who live in northern latitudes. Some have proposed that northerners are exposed to an infection in childhood. The immune system forms antibodies to the infectious agent (a bacteria or virus).

Later in life, for reasons that are unclear, the antibodies attach to a protein in the myelin coating of the axons. The body becomes confused and begins destroying the much-needed myelin. Without myelin, nerve cell signals travel much more slowly. This results in weakness, numbness, and other neurologic symptoms.

Something in our genes may be responsible for MS. For instance, a person is more likely to get MS if he or she has a first-degree relative (mom, dad, brother, or sister) with MS. Twenty-five percent of identical twins, who have identical genetic makeup, develop MS if their twin has MS. In comparison, only 2% of fraternal twins, whose genetic makeup is like a brother or sister, develop MS if their twin has MS.

Some genetic research in MS focuses on how our bodies are able to recognize foreign substances. For instance, in organ transplantation, the immune system may see the transplanted organ as "foreign" and "reject" it. Research into the genetics of MS may show how some people's bodies become "confused." This would help us to identify who is more likely to develop illnesses like MS, where the body attacks its own myelin.

HOW MS AFFECTS THE BRAIN Most people think MS is an illness that mostly affects white matter. Studies show that MS affects gray matter as well. When MS affects gray matter, the nerve cells die. Nerve cell death causes a decrease in the volume of the gray matter. A reduction in volume is called atrophy. Years ago, before MRI, an autopsy might show atrophy. Today, MRI can identify atrophy in the living brain. Newer MRIs are able to detect subtle changes even more easily.

If MS primarily affects the white matter, why do nerve cells die? Some scientists believe that an attack on myelin also affects the axon. Some nerve cells cannot live without their axons. When a nerve cell dies due to axonal injury it is called wallerian degeneration.

Others have proposed that MS affects the nerve cell body directly. In other words, the nerve cell body is destroyed first. Which is correct? Is it the axon first, or is an attack on the cell body the beginning of what we call MS? The answer to this question could lead to a cure for this illness.

As MS affects different parts of the brain, neurologic symptoms appear. Depending on the brain region, these symptoms can be weakness, numbness, or changes in vision or balance. Often the symptoms come and go (relapsing-remitting). In other people, the symptoms appear and gradually worsen over time (progressive). The treatments for MS are designed to prevent new symptoms, slow or halt the progression of disease, and reverse the injury that has occurred, if possible.

Most textbooks describe 2 "types" of MS. In one, the symptoms come and go. In between the symptoms, the person may feel fine. This type of MS is called relapsing-remitting MS. The other main type is called progressive MS. This type slowly worsens, resulting in a gradual loss of neurologic function. Some have observed that white matter is more involved in the relapsing-remitting type, while gray matter may be more involved in the gradually progressive form.

More recent literature has made the distinction between these 2 types less clear. Are they separate illnesses? Does one type turn into the other? How do they overlap? The answers to these questions remain unclear.

FOR MORE INFORMATION

AAN Patients and Caregivers site
http://patients.aan.com/go/home

Multiple Sclerosis Association of America
http://www.msassociation.org

Multiple Sclerosis Foundation
http://www.msfocus.org

National Multiple Sclerosis Society
http://www.nationalmssociety.org

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