Interview by Jennifer Ford

Results of the PREMiSe Study on CCSVI in MS: An Interview With Robert Zivadinov, MD, PhD

In 2009, Zamboni et al described an association between multiple sclerosis (MS) and extracranial venous outflow restrictive lesions detected by extracranial and intracranial venous duplex studies. They named this venous outflow restriction chronic cerebrospinal venous insufficiency (CCSVI). In addition, they introduced an endovascular interventional treatment for CCSVI in an open-label study that included 65 MS patients with a postprocedure follow-up of over 18 months. Subsequent prospective, open-label, nonrandomized studies have investigated the safety and efficacy of venous angioplasty in MS. Findings from these studies have generated considerable controversy but remain unproven.

Dr. Robert Zivadinov from the State University of New York at Buffalo was one of the lead investigators in a pilot study, the Prospective Randomized Endovascular Therapy in MS (PREMiSe) trial, which is believed to be the first prospective, randomized, double-blinded, controlled study of balloon angioplasty for the treatment of MS performed with Institutional Review Board approval in a rigorous fashion in the United States with safeguards in place to ensure careful determination of risks and benefits. All screening, diagnostic, interventional, follow-up procedures, and visits were performed at no cost to the patients.

Vascular Disease Management spoke to Dr. Zivadinov at the annual VEITHsymposium about his presentation of results of the pilot study.

Q: Please give us a summary of your talk at the VEITHsymposium so we can share your work with readers.

A: I presented preliminary results from the PREMiSe Study, which was a sham-controlled, double-blinded randomized trial to investigate the safety and efficacy of percutaneous transluminal venous angioplasty (PTVA) for correcting CCSVI in MS that included 30 MS patients in 2 phases.

Phase 1 of the study included 10 patients and it was open label to gain experience with the procedure as well as to ensure the proper blinding and assess its initial safety. It was a 6-month duration in time, and after that we proceeded with the sham-controlled, double-blinded, randomized portion of the study, which included 20 patients. Patients were screened with a duplex ultrasound to meet the criteria for chronic cerebrospinal venous insufficiency and then those findings were confirmed invasively using catheter venography and intravascular ultrasound before the angioplasty occurred. Clearly, they had to have at least 50% stenosis of their extracranial pathways, including internal jugular or azygous veins. Out of 20 patients, 19 entered the randomized phase of the study: 10 in the sham arm and 9 in the treatment arm. They received multiple evaluations over the 6 and 12 months including clinical assessments, MRI assessments, duplex assessments, blood assessments, cognitive quality of life and neuropsychological assessments.

The primary endpoint of the study was safety at 24 hours and 1 month. There were really no serious adverse events—neither over the 6 month period nor now at the 12 month mark of the study. The other endpoint was the restoration of the blood flow, which was measured immediately postprocedure on catheter venography. One of the criteria was that blood flow should be restored at least by 50% after the procedure and that was achieved at 1 month, as measured by duplex; the restoration should have reached 75% of the flow improvement and there was no difference between the treated and not treated patients.

There are different things that could have contributed to that. First, the venous angioplasty is just not the right
procedure to correct these types of problems. Second, by using invasive catheter venography and IVUS, the mechanical changes in their veins could have been introduced also to the sham arm to some extent. Additionally, all patients received aspirin and heparin therapy, which could have influenced the extracranial narrowings.

In terms of other primary or secondary efficacy endpoints, we looked at one of the hallmarks of any efficacy of treatment in MS, which is the accumulation of new lesions over the follow-up and surprisingly we found that there were actually more lesions in the patients who were treated than those who were in the sham arm with 19 new lesions in 9 patients developing in treatment vs only 3 in 10 patients in the sham arm. This almost reached statistical significance and may suggest that this type of treatment may actually increase the perfusion in the brain, which may lead to a short-term increase in the inflammation. This is our best explanation for the observation.

There were also clinical signs of more activity in the treated arm with 4 relapses developing in these 9 patients vs only 1 in the sham arm. So there were no differences in any cognitive, clinical, or other outcomes that we saw over the follow-up. So, all in all, this was the first double-blind sham randomized control study that clearly showed that the amount of abnormalities shown with invasive imaging was even larger than with the screening we did. It also showed that we need to figure out the right way of treatment, because doing angioplasty to enlarge these veins, which then collapse again, is probably not the right treatment. So until we develop new strategies and methods including safe-stenting, which at the moment does not exist, we will work to treat those veins.

The challenge is that when treating arteries, you open the artery and the artery should stay open, but with veins, they should not stay open all the time. The internal jugular vein is the most important vein and in the supine and erect positions, these veins need to change in diameter. If the vein can’t change in diameter, there is

Q: Were the results surprising to you?

A: Very surprising. They were clearly opposed to our hypotheses 100%. Absolutely. We would not start a study if we didn’t want to see a benefit from this type of treatment. So it was surprising that we showed exactly the opposite.

Q: So perhaps this has shown you where not to look. Have other avenues opened up as a result?

A: We published results of the multimodal pilot study (Zivadinov R. Multimodal noninvasive and invasive imaging of extracranial venous abnormalities indicative of CCSVI: results of the PREMiSe pilot study. BMC Neurol. 2013;13[1]:151). It certainly showed that the amount of abnormalities shown with invasive imaging was even larger than with the screening we did. It also showed that we need to figure out the right way of treatment, because doing angioplasty to enlarge these veins, which then collapse again, is probably not the right treatment. So until we develop new strategies and methods including safe-stenting, which at the moment does not exist, we will work to treat those veins.

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blood flow when there should not be. So clearly, we have not found an appropriate treatment and this could be one of the reasons that our treatment failed.

Robert Zivadinov, MD, PhD, is a professor of Neurology at the State University of New York at Buffalo. He is also Director of the MR Imaging Center at The University’s CTRC (Center for Translational Research) as well as Director of The Buffalo Neuroimaging Analysis Center. Dr. Zivadinov was one of the lead investigators of the PREMiSe study. Dr. Zivadinov reports gifts to the State University of New York at Buffalo from Jacquemin Family Foundation; grants from Biogen Idec, Teva Neuroscience, Sanofi-Genzyme, Novartis, and EMD Serono; and honoraria for speaking and consultation from Teva Neuroscience, Biogen Idec, EMD Serono, Bayer HealthCare, Sanofi-Genzyme, Novartis, Claret, and General Electric.