LETTERS TO THE EDITOR

Regarding "A prospective open-label study of endovascular treatment of chronic cerebrospinal venous insufficiency"

I read with great interest the article written by Zamboni et al[1] regarding the open-label study of endovascular treatment of chronic cerebrospinal venous insufficiency (CCSVI) in patients with multiple sclerosis (MS), which was published in December 2009. The study reports significant reductions in the annualized relapse rate in 65 MS patients (10 with primary progressive, 35 with relapse remitting, and 20 with secondary progressive) who underwent treatment of central venous stenosis with measurable pressure gradients with a mean follow-up of 18 months. The percent freedom from relapse increased from 27% to 50% ($P < .0014$), and the annualized relapse rate fell from 0.9 ± 0.8 to 0.7 ± 1 ($P = .11$). All of the patients were said to be receiving treatment with a U.S. Food and Drug Administration-approved drug.

Zamboni et al[2] also published an article on CCSVI in patients with MS in the *Journal of Neurology, Neurosurgery, and Psychiatry* in 2009. That article, which was received by the journal on July 2, 2008, reports on the central venous pathology in 65 patients with MS (10 with primary progressive, 35 with relapse remitting, and 20 with secondary progressive). In this report, 28 of the 65 patients (43.1%) were *not* receiving medical treatment at the time of the evaluation.

Unfortunately, neither article gives the treatment date range, but the fact that both articles have the exact same number of MS patients and the exact same number of patients with primary progressive, relapse-remitting, and secondary progressive disease suggests that both of the articles report the same patient pool. Combining these factual concerns suggest that some, if not all, of the response to angioplasty is due to initiating medical therapy—not angioplasty.

This concern is supported by realizing that the annualized relapse rate for MS patients diagnosed with CCSVI and treated with angioplasty fell from 0.9 ± 0.8 to 0.7 ± 1.[1] This should be compared with the annual relapse rate for patients treated with interferon β-1a, which is 0.55.[3] Based on these relapse rates, patients receiving approved medical therapy have a lower relapse rate than those treated with angioplasty.

It is estimated that 350,000 people in the United States have the diagnosis of MS,[4] of those, 50% require help ambulating within 15 years. The disease is life altering; the suicide risk is high, even in young patients with mild symptoms.[5] If the above concerns are correct, presenting this procedure as an effective treatment of MS has created an unfortunate urban myth that desperate MS sufferers will cling to. The conflict of interest is obvious; the lay press is already reporting that patients with MS are seeking out physicians around the world who offer this therapy—for $10,000 per treatment.[6]

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Reply

We thank Dr Requarth for giving us the opportunity to add further data and discussion to our article. However, he certainly read with interest—but not carefully—our article, because on page 1350 line 12, we explain that the cohort of patients was the same as previously reported.[1] In the former article about these patients,[2] we described chronic cerebrospinal venous insufficiency (CCSVI), a syndrome demonstrated by the combination of Doppler ultrasound imaging and catheter angiography and characterized by outflow problems of the major extracranial cerebral veins. We also described the frequent association of CCSVI with multiple sclerosis (MS).[2]

Dr Requarth is right in reporting that the average relapse in the relapsing remitting clinical course of MS, under disease-modifying treatment (DMT), is 0.55/year. This particular clinical course was present in 35 patients of the cohort, and 33 (94%) were under DMT (Table). The other 26 patients without treatment, as correctly observed by Dr Requarth, were in different MS categories and are characterized by clinical courses without relapses, as reported in the last paragraph of page 1349. For instance, the primary progressive clinical course of MS is actually orphan of any treatment (10 patients in our cohort), and quite frequently, patients with severe disability and secondary progressive MS refuse any treatment because it is completely ineffective (16 patients in our cohort; Table).[3]

Table. Treatment used at least once during the previous 3 years in the patient cohort with chronic cerebrospinal venous insufficiency multiple sclerosis *(MS)*

Treatment	*Drug*	*MS cases, No.*
Immunosuppressants	Mitoxantrone, cyclophosphamide, azathioprine	22
Immunomodulators	Interferon-β, glatiramer acetate	31
Corticosteroids	IV high-dose methylprednisolone	95[a]
Treatment refusal		16 SP 2 RR
PP cases	No available effective treatment	10

IV, Intravenous; *PP,* primary progressive; *RR,* relapsing remitting; *SP,* secondary progressive.
[a]No. of cycles of treatment in acute exacerbations.

Despite the use of DMT in 94% of patients with a relapsing remitting course (Table), they had experienced a higher than expected relapse rate of 0.9/year. However, the patients in our population had MS associated with CCSVI. For this peculiar association, we measured in our pilot study if angioplasty treatment of CCSVI could modify the neurologic outcome of MS.

The endovascular treatment, despite the 47% restenosis rate recorded in the internal jugular veins, reduced, although not significantly, the annualized relapse rate from 0.9 to 0.7. Relapse did recur in 50% of patients compared with 77% registered in the previous 2 years ($P = .0014$). As stated in the article, relapses as well as new T1 gadolinium-positive lesions did not occur in patients with patency of the major cerebral veins: two objectively measured facts and not a sham effect. Actually, we are conducting long-term follow-up of the same cohort.

We think it would be highly irresponsible to not report to colleagues such preliminary results. The excitement is understandable for patients and is linked to two reasons. The first is the awareness that MS, ranging from 56% to 100% of cases, can be associated with a major vascular problem.[2,4-6] The second is that the latter may have a resolution through a minimally invasive surgery.

Knowing if this is a sham or a real therapeutic effect for MS is a precise responsibility of the medical community, and not an opinion expressed in a scientific letter. As stated on page 1357 line 35, a randomized, controlled, double-blind study is the only tool that can answer the question of Dr Requarth. This will start in the next months involving several centers in Italy.

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Regarding "A prospective open-label study of endovascular treatment of chronic cerebrospinal venous insufficiency"

In the article "A prospective open-label study of endovascular treatment of chronic cerebrospinal venous insufficiency," by Zamboni et al,[1] the authors compared pre- and post-therapy outcomes with two-sample statistical analyses as though the outcomes arose from independent groups of patients (page 1351 of the article). They did not present within-patient results or use paired statistical tests for change in venous pressure or neurologic outcomes. Their reported use of Fisher exact test to analyze annualized relapse rates is not appropriate because those data are not proportions or numbers of patients. Tables IV and V fail to state the number of patients included in these results. One might suspect that not all 35 relapsing remitting patients contribute to Table IV, as no counts yield percentages of 27% (9: 26%, 10: 29%) or 50% (17: 49%, 18: 51%), for example.

Given the attention that Dr Zamboni's results have received, the reader would welcome an addendum with clarification and information that is more complete. It is possible that the appropriate paired testing would provide similar or greater degrees of statistical significance, bolstering hope for the effectiveness of percutaneous transluminal angioplasty in treating multiple sclerosis patients.

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Reply

Our study is a pilot study with promising results. It shows two main shortcomings: the lack of a control group and blinded clinical assessors. We chose to use statistical tests to underestimate rather than exalt our findings, precisely because of the above limitations. The tests suggested by you, as you noted at the end of your letter, provide even greater degrees of statistical significance. Our policy is to be as prudent as we can, waiting for randomized control trial angioplasty results. The main message of our study is the safety and the feasibility of venous angioplasty in patients affected by chronic cerebrospinal venous insufficiency associated with multiple sclerosis (CCSVI-MS).[1]

However, differences in quality of life and multiple sclerosis functional composite among neurologic outcomes were re-assessed also with paired t test, as you requested in your letter, and were significantly different. For instance, MSFC in relapsing remitting patients by comparing baseline with 18 months value showed a highly significant improvement of the motor and cognitive function expressed by such functional composite test ($P < .0001$).

Differences in preoperative and postoperative pressure were assessed with the two-tailed Mann-Whitney test, as reported at page 1351 of our article.[1]