Prospective randomized trial of venous angioplasty in MS (PREMiSe)

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ABSTRACT

Objective: We report the results of the investigation of safety and efficacy of venous angioplasty in patients with multiple sclerosis (MS) with findings of extracranial venous anomalies, considered hallmarks of chronic cerebrospinal venous insufficiency (CCSVI), in a 2-phase study (ClinicalTrials.gov NCT01450072).

Methods: Phase 1 was an open-label safety study (10 patients); phase 2 was sham-controlled, randomized, and double-blind (10 sham procedure, 9 treated). All study patients fulfilled venous hemodynamic screening criteria indicative of CCSVI. Assessment was at 1, 3, and 6 months post-procedure with MRI, clinical, and hemodynamic outcomes. Primary endpoints were safety at 24 hours and 1 month, venous outflow restoration >75% at 1 month, and effect of angioplasty on new lesion activity and relapse rate over 6 months. Secondary endpoints included changes in disability, brain volume, cognitive tests, and quality of life.

Results: No perioperative complications were noted; however, one patient with history of syncope was diagnosed with episodic bradycardia requiring placement of a pacemaker before discharge. Doppler evidence-based venous hemodynamic insufficiency severity score (VHISS) was reduced >75% compared to baseline in phase 1 (at 1 month) but not phase 2. In phase 2, higher MRI activity (cumulative number of new contrast-enhancing lesions [19 vs 3, $p = 0.062$] and new T2 lesions [17 vs 3, $p = 0.066$]) and relapse activity (4 vs 1, $p = 0.389$) were identified as nonsignificant trends in the treated vs sham arm over 6 months. Using analysis of covariance, significant cumulative new T2 lesions were related to larger VHISS decrease ($p = 0.028$) and angioplasty ($p = 0.01$) over the follow-up. No differences in other endpoints were detected.

Conclusion: Venous angioplasty is not an effective treatment for MS over the short term and may exacerbate underlying disease activity.

Classification of evidence: This is a Class I study demonstrating that clinical and imaging outcomes are no better or worse in patients with MS identified with venous outflow restriction who receive venous angioplasty compared to sham controls who do not receive angioplasty. This study also includes a Class IV phase 1 study of safety in 10 patients receiving the angioplasty procedure.

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GLOSSARY

AE = adverse event; **ANCOVA** = analysis of covariance; **ANOVA** = analysis of variance; **CCSVI** = chronic cerebrospinal venous insufficiency; **CE** = contrast-enhancing; **CV** = catheter venography; **EDSS** = Expanded Disability Status Scale; **IJV** = internal jugular vein; **IVUS** = intravascular ultrasound; **MS** = multiple sclerosis; **MSFC** = MS Functional Composite; **PREMiSe** = Prospective Randomized Endovascular Therapy in MS; **QoL** = quality of life; **VH** = venous hemodynamic; **VHISS** = venous hemodynamic insufficiency severity score.

Multiple sclerosis (MS) is characterized by demyelinating lesions affecting the CNS. An association between MS and extracranial venous outflow restrictive lesions detected by venous duplex studies, named chronic cerebrospinal venous insufficiency (CCSVI), has been described.[1] There is controversy as to the nature of these structural and functional extracranial venous anomalies and whether they even represent pathologic findings, and certainly no agreement exists as to whether there is any etiologic relationship with MS. Several recent prevalence studies that used

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Supplemental data at Neurology.org

From the Departments of Neurosurgery and Radiology, The Jacobs Neurological Institute (A.H.S., Y.K., M.L.H., E.I.L., L.N.H.), and the Departments of Neurology (R.Z., R.H.B.B., D.W.H., B.W.-G.), Biostatistics (J.Y.), and Pharmaceutical Sciences (M.R.), University at Buffalo, State University of New York; and the Buffalo Neuroimaging Analysis Center (R.Z., K.L.M., V.V., C.L.K., D.P.R., K.D., E.C.), NY.

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different imaging techniques have reported large discrepancies in the prevalence of extracranial venous anomalies characterized as CCSVI findings in patients with MS.[2–7]

Endovascular treatment for these venous anomalies was introduced in an open-label study that included 65 patients with MS with postprocedure follow-up of >18 months.[8] Several subsequent prospective open-label, nonrandomized studies investigated safety and efficacy of venous angioplasty in MS.[9–18] Findings from some of these studies have generated considerable controversy over potential treatment benefit, which remains unproven, whereas others showed a potential increase in disease activity.[9,10,19]

We investigated safety and efficacy of venous angioplasty in patients with MS exhibiting findings of extracranial venous outflow restrictive anomalies described as hallmarks of CCSVI in the setting of a prospective, double-blind, sham-controlled, randomized pilot trial. Primary study endpoints were safety, venous outflow restoration, and effect of angioplasty on MRI lesion activity and relapse rate.

METHODS

Study design and patient selection. Prospective Randomized Endovascular Therapy in MS (PREMiSe) (ClinicalTrials.gov NCT01450072) was planned in 2 phases. Phase 1 was an open-label safety study of endovascular venous angioplasty with an intended enrollment of 10 patients with MS with extracranial venous anomalies consistent with criteria utilized for describing CCSVI and was conducted to strengthen procedural protocols and work out blinding methodologies. Phase 2 was sham-controlled, randomized, and double-blind, including up to 20 patients with MS with CCSVI type venous anomalies undergoing either angioplasty or sham procedure. The sample size was restricted owing to the pilot nature of this study because there were no previous studies evaluating effects of angioplasty in patients with MS with control subjects. We assumed a 50% treatment effect to keep a small sample size in view of the pilot nature of the purported effects published at the time this study was designed. Both phases were of 6 months' duration. Patients were enrolled between June 2010 and March 2012.

Standard protocol approval, registrations, and patient consents. The study was approved by our Institutional Review Board and overseen by a data safety monitoring committee consisting of physicians not involved in the care or treatment of patients with MS at the University at Buffalo. Written informed consent was obtained from all subjects. Screening, diagnostic, interventional, and follow-up procedures and visits were performed at no cost to the patients. Data were collected by the investigators and analyzed by an independent statistician.

Inclusion criteria for phase 1 were as follows: age 18–65 years, Expanded Disability Status Scale (EDSS) score[20] 0–8.5, diagnosis of clinically definite MS,[21] and fulfilling at the time of screening ≥2 CCSVI venous hemodynamic (VH) duplex criteria.[22] Inclusion criteria for phase 2 were refined further to identify patients most demonstrative of structural and hemodynamic dysfunction described as CCSVI and most likely to benefit from intervention: age 18–65 years, EDSS score[20] 0–5.5, active-relapsing MS,[23] and fulfilling, at the time of screening, ≥2 VH extracranial duplex criteria.[22] Details of venous duplex screening are provided in appendix e-1 on the *Neurology®* Web site at Neurology.org. Active-relapsing disease was defined as 1 relapse within the past 12 months or presence of contrast-enhancing (CE) lesions on postcontrast MRI within the previous 3 months and concomitant treatment with disease-modifying treatments excluding natalizumab.

Exclusion criteria (either phase) included acute relapse, disease progression, or steroid treatment within 30 days preceding study entry, preexisting medical conditions known to be associated with brain pathology (e.g., neurodegenerative disorder, cerebrovascular disease, history of alcohol abuse), severe peripheral chronic venous insufficiency, severe contrast media allergy (anaphylaxis), and abnormal renal function.

Patients were also required to fulfill screening criteria on catheter venography (CV), defined as azygous vein or internal jugular vein (IJV) luminal diameter reduction ≥50%. CV findings were confirmed by intravascular ultrasound (IVUS); both studies were performed under conscious sedation with local anesthesia preceding the endovascular venous angioplasty or sham procedure. CV was conducted using the method previously described[8] and interpreted by interventional neurosurgeons (A.H.S., E.I.L., L.N.H.). Diagnostic CV is described briefly in appendix e-2 and in detail elsewhere.[24]

In phase 2, randomization was performed by an independent statistician in 1:1 fashion and is described in appendix e-3. All study personnel, with the exception of the interventional neurosurgeons, were blind to the assigned procedure, as were the patients. Blinding is described in appendix e-3.

Sham and venous angioplasty. The goal of angioplasty was to restore venous outflow of stenotic IJVs and azygous vein to >50% of normal proximal venous diameter at the time of intervention. Angioplasty was performed only in the treated, not in the sham, arm. To ensure proper blinding, all patients received a rigorous sternal rub (painful stimulus) upon insertion of the angioplasty balloon, but the balloon was inflated only in the treated arm; all were prevented from observing fluoroscopic images. A detailed description of these procedures is provided in appendix e-4.

Endpoints and follow-up assessment. The primary endpoint was safety at 24 hours and 1 month. A serious adverse event (AE) was defined as an untoward medical occurrence that was life-threatening, resulted in persistent disability or required intervention to prevent it, caused prolongation of hospitalization, or resulted in death. Nonserious AEs were all others. Preliminary efficacy outcomes were venous outflow restoration of >75% at 1 month compared to baseline, as measured by changes in venous hemodynamic insufficiency severity score (VHISS), and effect of angioplasty on new MRI-based lesion activity and clinical relapse rate over 6 months. Additional endpoints included changes in EDSS, brain volume, cognitive tests, 6-minute walk, and quality of life (QoL), as well as MS Functional Composite (MSFC) scores. A detailed description of study endpoints is provided in appendix e-5.

Statistical analysis. Statistical analysis was performed using the Statistical Package for the Social Sciences (version 17.0; SPSS, Chicago, IL) and Statistical Analysis System (Version 9.3; SAS, Cary, NC). The normal assumption was inspected using the normal quantile plot and histogram based on the residuals from respective models used. To handle digresses from the normal distribution, alternative methods based on nonparametric methodologies (e.g., Mann-Whitney *U* test and a previously described

Table 1 Baseline demographic, clinical, and duplex characteristics of patients enrolled in the PREMiSe study

	Phase 1 (n = 10)	Phase 2: Sham arm (n = 10)	Phase 2: Treatment arm (n = 9)	*p* Value[a]
Female	5 (50)	8 (80)	5 (55.6)	0.350
Age, y	46.5 (9.4); 47 (25/57)	44.8 (10.5); 47 (20/56)	43.3 (8.2); 44 (26/51)	0.741
Age, y, at onset	34.9 (11.3); 31.5 (18/52)	34 (10.2); 35 (12/46)	32 (10.4); 35 (18/46)	0.644
Disease duration, y	11.6 (7.7); 11 (2/22)	10.8 (4.5); 10 (5/18)	11.6 (9.7); 9 (2/31)	0.827
Disease course				
RR	6 (60)	5 (50)	7 (77.8)	0.350
RP	0 (0)	5 (50)	2 (22.2)	
SP	3 (30)	0 (0)	0 (0)	
PR	1 (10)	0 (0)	0 (0)	
No. of relapses in the year prior to study entry	0 (0)	0.4 (0.7); 0 (0–2)	1 (0.9); 1 (0–2)	0.113
EDSS	4.4 (2.2); 4.8 (1.0/8.5)	4.0 (1.5); 4.0 (2.0/5.5)	3.8 (1.5); 3.5 (1.5/5.5)	0.720
MSFC	0.06 (0.7); 0.08 (−1.6/0.8)	0.04 (0.4); −0.02 (−0.5/0.7)	−0.4 (0.9); −0.3 (−0.2/0.7)	0.198
Distance, ft, walked in 6 min	1,539.3 (727.6); 1,245 (795/3,215)	1,339.2 (505.5); 1,092 (755/2,130)	1,242.7 (725.5); 1,626 (253/2,050)	0.738
Type of DMT				
Interferon-β	4 (40)	7 (70)	7 (77.8)	0.638
Glatiramer acetate	2 (20)	2 (20)	2 (22.8)	
Natalizumab	2 (20)	0 (0)	0 (0)	
Rituximab	0 (0)	1 (10)	0 (0)	
Mitoxantrone	1 (10)	0 (0)	0 (0)	
Combination	1 (10)	0 (0)	0 (0)	
Months on DMT	37.7 (30.4); 32 (3/96)	81.5 (52.6); 78 (6/156)	47.4 (31.2); 43 (12/106)	0.109
VH CCSVI criterion				
VH1	10 (100)	5 (50)	3 (33)	0.566
VH2	9 (90)	10 (100)	8 (88.9)	
VH3	8 (80)	10 (100)	9 (100)	
VH4	2 (20)	6 (60)	7 (77.8)	
VH5	6 (60)	3 (30)	1 (11.1)	
≥2 CCSVI VH criteria	10 (100)	10 (100)	9 (100)	1.000
≥2 CCSVI VH extracranial criteria	10 (100)	10 (100)	9 (100)	1.000
VHISS	5.9 (2.2); 5.5 (2/10)	6.1 (2); 5.5 (4/10)	6 (1.3); 6 (5/9)	0.842

Abbreviations: CCSVI = chronic cerebrospinal venous insufficiency; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; MSFC = Multiple Sclerosis Functional Composite; PREMiSe = Prospective Randomized Endovascular Therapy in MS; PR = progressive relapsing; RP = relapsing-progressive; RR = relapsing-remitting; SP = secondary progressive; VH = venous hemodynamic; VHISS = venous hemodynamic insufficiency severity score.

Values are mean (SD); median (min/max) or n (%).

[a] *p* Value represents statistical analysis between sham and treated arms of phase 2. Analysis between these groups was performed by using χ^2 test, Student *t* test, and Mann-Whitney rank sum test, as appropriate.

method[25]) were used. Statistical analyses included comparisons between only the 2 treatment arms in phase 2. For demographic, clinical, and MRI differences between the 2 groups, Student *t* tests, χ^2 tests, and Mann-Whitney *U* tests were used as appropriate.

Multi-timepoint longitudinal changes over 6 months in clinical, MRI, QoL, and cognitive outcomes were analyzed by using mixed-effects analysis of variance (ANOVA) models that include different treatment groups, month (as a categorical variable), and their interaction as factors. Mixed-effects ANOVA included baseline outcomes as dependent variables so that a significant interaction between month and treatment arms would indicate treatment differences. With no presence of the interaction, the *p* value for month in the mixed-effects ANOVA was used for overall time effect (based on all phase 2 patients). Means and confidence intervals in figure plots are based on raw data. To test whether relapse rate and MRI lesion activity outcomes were dependent on venous outflow restoration success in phase 2, we applied logistic regression analysis or analysis of covariance (ANCOVA), in which VHISS and treatment status were used as covariates. Given the exploratory pilot nature of the study, a nominal *p* value of <0.05 was considered significant using 2-tailed tests.

Table 2 Adverse events in patients enrolled in PREMiSe over 6 months

	Phase 1 (n = 10)	Phase 2: Sham arm (n = 10)	Phase 2: Treatment arm (n = 9)
Description of AE	1. Rash due to Doppler sonography at screening	1. Immune thrombocytopenic purpura treated with 100 mg prednisone once daily	1. Cardiac event treated with pacemaker installation
	2. UTI treated with antibiotics for 10 days	2. Bladder infection treated with antibiotics over 10 days	2. Swelling and soreness at left side of the neck; no treatment required
	3. UTI treated with antibiotics for 5 days	3. Diagnosis of shingles treated with Valtrex (GlaxoSmithKline) three times daily for 7 days	3. Hospitalization for scheduled transobturator sling procedure
	4. Intercourse pain (condom-related) that prompted hospitalization for 2 days		
	5. Neck pain due to car accident		
Severity of AE	1. Nonserious	1. Serious	1. Serious
	2. Non	2. Non	2. Non
	3. Non	3. Non	3. Non
	4. Non		
	5. Non		
Timepoint of AE	1. Baseline	1. 6 months	1. 24 hours
	2. 6 months	2. 6 months	2. 6 months
	3. 6 months	3. 6 months	3. 6 months
	4. 6 months		
	5. 6 months		
Relationship of AE to treatment or invasive diagnostic procedure	1. Unrelated	1. Unrelated	1. Unrelated
	2. Unrelated	2. Unrelated	2. related
	3. Unrelated	3. Unrelated	3. Unrelated
	4. Unrelated		
	5. Unrelated		

Abbreviations: AE = adverse event; PREMiSe = Prospective Randomized Endovascular Therapy in MS; UTI = urinary tract infection.
AEs are listed in chronological order with individual AEs assigned an increasing number.

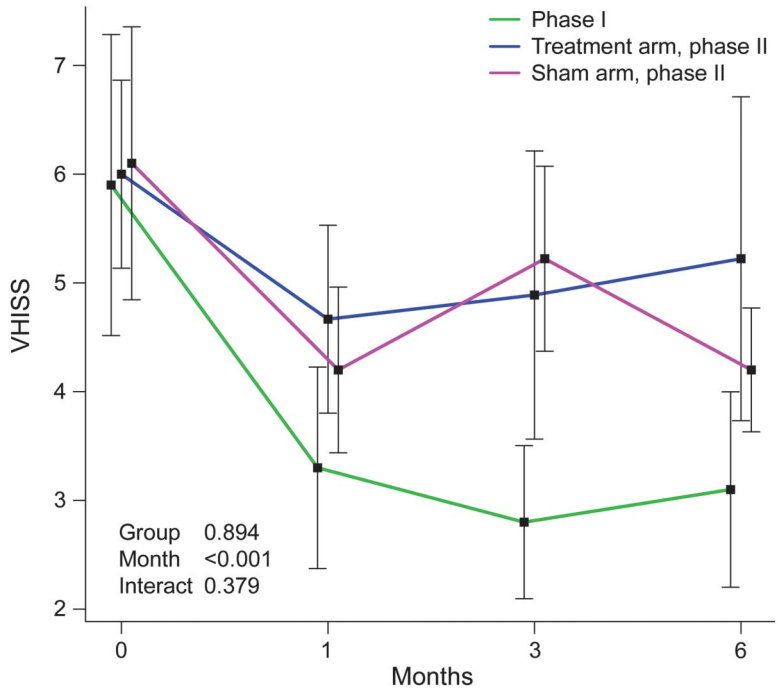
RESULTS **Screening, randomization, and blinding.** In total, 15 patients signed informed consent in phase 1 and 30 in phase 2 after prescreening qualification procedures were completed. Of those, 5 in phase 1 and 10 in phase 2 did not fulfill noninvasive screening procedure requirements on duplex examination. As preplanned, 10 patients were enrolled in phase 1 and 20 in phase 2. Of those, 1 patient in phase 2 did not fulfill invasive screening criteria for endovascular intervention. Hence, 10 patients were randomized to the sham treatment arm and 9 to the angioplasty treatment arm and received the allocated intervention in phase 2 (figure e-1).

Baseline characteristics. The phase 2 treatment arms were reasonably well-matched for various demographic, clinical, and duplex characteristics with no statistically significant between-group differences (table 1). Phase 1 patients were also well-matched to phase 2 patients, except for inclusion of 3 secondary-progressive patients and lower number of relapses in the previous year. All groups were also well-matched with respect to MRI and clinical metrics (table e-1 and table e-2).

Safety and tolerability of treatment procedures. All patients in phases 1 and 2 tolerated the endovascular procedure well. No operative or postoperative complications (vessel rupture, thrombosis, or side effects to contrast media) were identified. No serious AEs were detected at any timepoint in phase 1 (table 2). Half the phase 1 patients reported a nonserious AE; none was related to the treatment procedure (table 2).

In phase 2, 1 patient in the treated arm presented with a serious AE at 24 hours (table 2). The patient experienced an episode of symptomatic bradycardia that was confirmed by telemetry; consequently, a cardiac consultation recommended pacemaker installation. During pretreatment screening, bradycardia was not noted on electrocardiography or by history. However, before pacemaker installation, the patient confirmed previous similar episodes not reported to any physicians. Further follow-up was uneventful for this patient. Although considered preexistent, this event

Figure 1 Graphic representation of venous outflow dilation outcomes



Changes in venous hemodynamic insufficiency severity score (VHISS) at 1, 3, and 6 months, compared to baseline, in phases 1 and 2 plotted by using mixed-effect model analysis. *p* Values in the plot are based on comparison between phase 2 groups. Time effect *p* values within groups are phase 1 ($p < 0.0001$), phase 2 treated arm ($p = 0.02$), and phase 2 sham arm ($p = 0.04$), respectively.

could be possibly related to venous angioplasty. Another patient, in the sham arm, presented with a serious AE at 6 months. The event was a viral infection causing immune thrombocytopenic purpura that was treated with prednisone (100 mg/day) and was unrelated to the study.

Radiographic venous outflow dilation outcomes. We evaluated radiographic evidence of luminal enlargement following venous angioplasty. We noted that venous outflow could achieve at least 50% of proximal venous diameter in all phase 1 and 2 patients at the time of intervention as demonstrated by angiography. In phase 1 (figure 1), there was improvement of VHISS ($p < 0.0001$) over 6 months that resulted in >75% restoration of venous outflow compared to baseline. In phase 2, improvement was observed also in treatment ($p = 0.02$) and sham ($p = 0.04$) arms at month 1 but did not reach >75% restoration of venous outflow compared to baseline. No differences in VHISS improvement were detected between phase 2 treated and sham groups ($p = 0.894$).

Changes in clinical outcomes. No relapses occurred in phase 1. In phase 2, there were 4 relapses in the treated arm (among 3 patients) and 1 in the sham arm ($p = 0.389$). The relapses occurred at 1, 3 (2 relapses), and 6 months in the treated arm and at 5 months in the sham arm. There was no statistical evidence that a higher number of relapses in the treated arm was related to VHISS changes ($p = 0.183$) or angioplasty vs sham treatment status ($p = 0.401$). The relapse risk for phase 2 patients is shown by Kaplan-Meier plot in figure e-2.

No significant changes in EDSS, MSFC, or 6-minute walked distance were detected in phase 1 patients (figure e-3). In phase 2, no significant within- or between-group changes in EDSS, MSFC, or 6-minute walked distance were detected, except improvement of MSFC in the sham treatment arm ($p = 0.04$, figure e-3).

No significant between-group changes in cognitive or QoL outcomes were detected in phase 2 patients (figure e-4). However, in both phases, there were within-group changes in Symbol Digit Modalities Test ($p = 0.009$ for phase 2 treated arm), Beck Depression Inventory Fast Screen ($p = 0.01$ for phase 2 sham arm), Fatigue Severity Scale ($p = 0.03$ for phase 2 sham arm), MS Neuropsychological Screening Questionnaire ($p = 0.008$ for phase 2 sham arm), and Multiple Sclerosis Quality of Life–54 physical ($p = 0.02$ for phase 1, $p = 0.0008$ for phase 2 treated arm, and $p = 0.001$ for phase 2 sham arm) and mental health ($p = 0.003$ for phase 2 sham arm) composites (figure e-3).

Changes in MRI outcomes. Two patients in phase 1 had MRI findings indicative of disease activity (table 3). Of 9 patients in the phase 2 treated arm, 5 showed new CE lesions, with 2 accounting for most of the lesion activity, and 4 of those 5 patients had new T2 lesions (table 3), whereas only 2 in the sham arm showed new lesion activity. There was a trend for higher cumulative number of new CE lesions ($p = 0.062$) and new T2 lesions ($p = 0.066$) in the treated compared to the sham arm over 6 months (figure 2).

Using mixed-effects ANOVA models, no significant interactions between month (postprocedure) and group or group effects were found. In separate analyses based on cumulative number of new lesions using ANCOVA, there was evidence that higher cumulative number of new T2 lesions was related to larger decrease in VHISS ($p = 0.028$) and treated arm ($p = 0.01$) over the follow-up. There was a higher accumulation of T2 lesion volume ($p = 0.04$) in the treated compared to the sham arm (phase 2) over 6 months (table 3). No differences in brain volume changes over 6 months were found (table 3). The safety profile should be interpreted with caution given the pilot nature of this study.

DISCUSSION We performed venous angioplasty of extracranial venous outflow restrictions in patients with MS safely. This safety profile is diminished by the trial's pilot nature and small sample size. However, the procedural correction of venous outflow

Table 3 Changes in MRI measures in the PREMiSe study over 6 months

	Phase 1 (n = 10)	Phase 2: Sham arm (n = 10)	Phase 2: Treatment arm (n = 9)	*p* Value[a]
Cumulative no. of new T2 lesions, sum	0.2 (0.4); 0 (0/1) 2	0.3 (0.7); 0 (0/2) 3	2.1 (2.9); 1 (0/8) 17	0.066
T2-LV absolute change	0.4 (1); 0.01 (−0.09/3.4)	−0.2 (0.4); −0.06 (−0.8/0.6)	0.5 (1.5); 0.06 (−0.3/4)	NA
T2-LV % change	1.3 (10.3); 0.6 (−15.9/23.4)	−4.7 (11); −1.5 (−21.4/12.2)	13.9 (22.8); 2.9 (−10.6/45.8)	0.04
Cumulative no. of T1 lesions, sum	0	0.2 (0.6); 0 (0/2) 2	0.8 (0.9); 0.5 (0/2) 6	0.144
T2-LV absolute change	0.1 (0.3); (0.009) (−0.4/0.8)	−0.2 (0.2); −0.06 (−0.6/0.3)	0.2 (0.5); 0 (−0.1/1.2)	NA
T1-LV % change	−2.9 (32.7); 2.5 (−73/28)	−14.6 (33.6); −5.3 (−100/14.1)	−10.2 (30.9); −8.3 (−50/32.9)	0.811
Cumulative no. of CE lesions, sum	0.1 (0.3); 0 (0/1) 1	0.3 (0.7); 0 (0/2) 3	2.4 (3.2); 1 (0/9) 19	0.062
CE-LV absolute change	−0.04 (0.1); 0 (−0.4/0)	−0.04 (0.1); 0 (−0.4/0)	−0.03 (0.08); 0 (−0.1/0.1)	NA
CE-LV % change	−100 (0); −100 (−100/−100)	−94.1 (8.3); −94.1 (−100/−88.3)	34.4 (186.3); −44 (−100/247.1)	0.262
Active T2 lesion scan	2 (20)	2 (20)	4 (44.4)	0.321
Active T1 lesion scan	2 (20)	0	4 (44.4)	0.118
Active CE lesion scan	2 (20)	1 (10)	5 (55.6)	0.145
PBVC	−0.64 (0.66); −0.65 (−1.86/0.24)	−0.74 (0.93); −0.56 (−2.5/0.51)	−0.23 (0.84); −0.45 (−1.1/1.1)	0.257
GMVC	−2.1 (1.2); 2 (−4.4/−0.1)	−1.84 (3.1); −2.3 (−6.5/3.3)	−0.53 (1.6); −0.65 (−2.6/1.99)	0.320
WMVC	0.9 (1.5); 0.51 (−0.96/4.3)	0.4 (2.9); 1.2 (−3.8/4.4)	0.12 (2.6); 0.22 (−4/4)	0.841

Abbreviations: CE = contrast-enhancing; GMVC = gray matter volume change; LV = lesion volume; NA = not available; PBVC = percentage brain volume change; PREMiSe = Prospective Randomized Endovascular Therapy in MS; WMVC = white matter volume change.
Values are mean (SD); median (min/max) or n (%). Sum = total number.
[a] *p* Value represents statistical analysis between sham and treated arms of phase 2. The analysis between these groups was performed by using Student *t* test. Statistical analysis between T2-LV, T1-LV, and CE-LV was performed only for percentage changes. Changes between baseline and follow-up scans for whole brain, gray matter, and white matter volumes were calculated using the direct measurement technique; hence, no absolute, but only percentage volume changes are available. The absolute lesion volumes are presented in milliliters. Statistical analyses between phase 2 sham and treated arms were also adjusted for age, sex, disease duration, relapse rate in the year prior to study entry, and number of CE lesions at baseline. No significant differences were found between these arms, except for T2-LV % change ($p = 0.05$). Of the 5 patients with active multiple sclerosis assigned to the treated arm in phase 2, cumulative numbers of CE lesions per patient over 6 months were as follows: 9, 5, 3, 1, and 1 (respectively). In the sham arm, one patient had 2 CE lesions and one had 1.

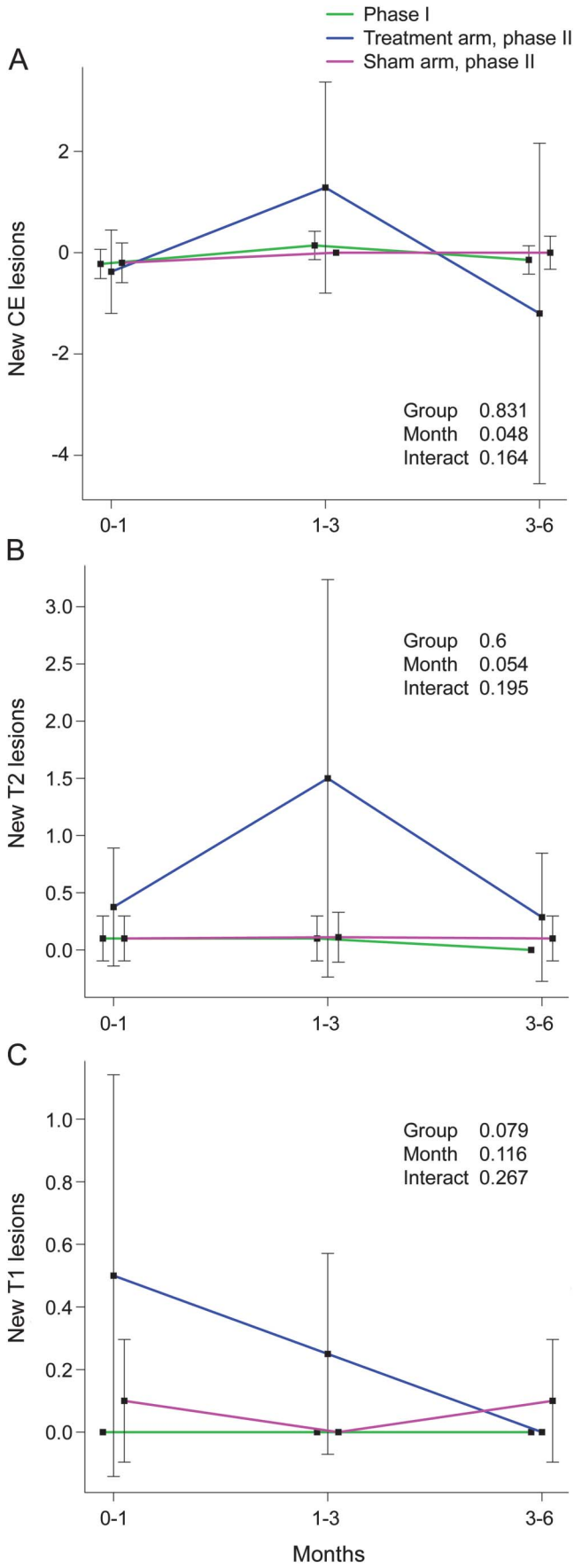
restriction appears transient and not associated with durable improvement in VHISS at 6 months. Further, there appears to be no significant improvement in clinical disease following angioplasty. Rather, there was a trend towards increasing disease activity in treated patients as measured by MRI outcomes and relapses. Our findings may be skewed by the limited sample size; however, numerous pilot phase 1/2a treatment trials in MS included similar sample size,[26–29] before the decision was made to proceed with phase 2b trials on the basis of safety and preliminary efficacy findings.

Extracranial venous outflow anomalies describing the CCSVI theory have generated tremendous controversy, with sizeable peer-reviewed data arguing both merits and faults with the hypothesis.[30,31] There has been a massive clinical rush towards employing venous angioplasty for the treatment of MS despite the lack of evidence for this intervention. Most opinions in favor of the treatment are based on sudden and robust improvement as self-reported by patients.[8,11,12,17,18]

We have previously reported on extracranial venous anomalies.[24,32,33] Our studies, though suggestive of a venous role in many chronic neurologic diseases including MS, were not quite as strongly supportive as initially reported,[1] nor quite as dismissive as results recently reported.[34] However, given the initial remarkable results,[8,11,12,16,17,35] we attempted to design a study that could address critical aspects of the venous outflow restriction playing a role in MS pathogenesis (CCSVI hypothesis). Therefore, we designed PREMiSe with a double-blinded, sham-controlled design—which was unique for CCSVI interventional studies—knowing that many aspects of this hypothesis remained unsubstantiated but with clearly established biases among physicians and patients.

Our phase 2 results suggest that these previous self-reported findings are largely related to placebo effects. Similarly, one potential explanation for improved VHISS in phase 1 as compared to phase 2 could be that duplex examiners knew this was an open-label phase in which all patients were treated. However, in phase 2, sham patients also slightly improved in VHISS (figure 1). Potential explanations for this finding include (1) modest reproducibility, even among highly trained technicians[32,33]; (2) functional and

Figure 2 Graphic representation of MRI lesion activity



Changes in accumulation of mean new contrast-enhancing (CE) lesions (A), mean new T2 lesions (B), and mean T1 lesions (C), between 0–1, 1–3, and 3–6 months in phases 1 and 2, by using mixed-effect model analysis. Some means for new T2 and T1 lesions have standard error = 0 since only values of 0 are presented. *p* Values in the plot are based on comparison between the phase 2 groups. Time effect *p* values within these groups are for mean new CE lesions: phase 1 ($p = 0.198$), phase 2 treated arm ($p = 0.593$), and phase 2 sham arm ($p = 0.766$), respectively; for mean new T2 lesions: phase 1 ($p = 0.617$), phase 2 treated arm ($p = 0.254$), and phase 2 sham arm ($p = 0.991$), respectively; and for mean new T1 lesions: phase 2 treated arm ($p = 0.057$) and phase 2 sham arm ($p = 0.776$), respectively.

hemodynamic changes over time, possibly related to use of CV and IVUS during diagnostic procedures; and (3) administration of aspirin and enoxaparin sodium with ongoing pro/antithrombotic changes and potential effects on flow.

For the open-label component (phase 1), we were primarily focused on safety rather than efficacy. However, to target patients most likely to benefit from venous angioplasty, we restricted enrollment criteria for phase 2 by including patients who were less disabled (EDSS score ≤5.5) with active disease (relapse in the last 12 months or recent MRI activity) who demonstrated ≥2 extracranial VH criteria. This rigor has not been applied in previous studies[8,9,11–15,17,18] and despite our intention, it failed to demonstrate benefit of venous angioplasty.

Contrary to the proposed CCSVI hypothesis, analysis of VHISS changes suggests that a decrease in venous outflow restriction (i.e., improved venous outflow) correlated significantly with an increase in MRI activity. Due to the small sample size, only a trend in increase in clinical disease activity was noted with a reduction in VHISS scores. We have previously reported that lesion activity was increased after endovascular treatment for CCSVI in patients with MS.[18] In line with these early observations, PREMiSe showed that of the 5 patients with MS in the treated arm (phase 2) with active MRI scans, 2 patients accounted for most lesion activity during the trial (table 3). Four possible hypotheses for explaining this paradoxical effect are as follows: (1) the patients did not respond to angioplasty; (2) reopening of the veins simply increases perfusion of the microcirculation of the brain parenchyma, which resulted in short-term increase in inflammation; (3) the observed azygous vein or IJV stenosis is a secondary compensatory response, such as in response to chronic venous reflux, that is exacerbated following venous angioplasty and results in increased disease activity; or (4) variability secondary to chance. In line with our findings, 2 recent retrospective studies show an increase in disease activity irrespective of adherence to disease-modifying

therapy in patients with MS presenting with CCSVI who underwent venous angioplasty.[9,10]

No differences in cognitive or QoL outcomes were observed between the 2 treatment arms in sham-controlled phase 2. However, various outcome measures showed within-group improvements over 6 months in both phases and need further analysis.

In this first double-blind, sham-controlled, randomized trial evaluating venous angioplasty to address extracranial venous anomalies characterized as CCSVI in patients with MS, we found that the procedure was reasonably safe. However, it failed to provide any sustained improvement in venous outflow as measured through duplex or clinical and MRI outcomes. To the contrary, more sizeable change in venous outflow was associated with increased disease activity primarily noted on MRI. This study was a limited pilot trial not powered to detect possible safety concerns observable only with a larger population and longer follow-up; however, the results caution against widespread adoption of venous angioplasty in the management of patients with MS outside of rigorous clinical trials. It also provides validation for conduct of sham-controlled, double-blind trials in the evaluation of novel interventions in complex diseases.

AUTHOR CONTRIBUTIONS

Conception and design: Dr. Siddiqui, Dr. Zivadinov, Dr. Weinstock-Guttman, Dr. Karmon. Acquisition of data: All authors. Analysis and interpretation of data: All authors. Drafting the manuscript: Dr. Siddiqui, Dr. Zivadinov. Critically revising the manuscript: All authors. Final approval of the manuscript: All authors. Statistical analysis: Dr. Yu. Administrative, technical, or material support: Dr. Siddiqui, Dr. Zivadinov, Dr. Karmon. Study supervision: Dr. Siddiqui, Dr. Zivadinov, Dr. Weinstock-Guttman, Dr. Karmon.

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