Levels of Evidence Required to Determine the Benefit of Treating CCSVI to Alleviate Symptoms of MS

A neurology perspective.

BY PATRICIA K. COYLE, MD, AND JACK BURKS, MD

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system (CNS) with multiple and variable clinical courses and symptoms. MS affects women more than men, younger adults (20–50 years of age) more than children or elderly, Caucasians more than other races, people with the higher society-economic status more frequently, smokers, people in temperate climates more than those in hotter climates, and more people with less Vitamin D exposure in childhood. Relapsing-remitting MS (RRMS) is the most common type (85% of MS patients). Many of RRMS patients will progress to secondary progressive MS (SPMS) after several years. Clinically isolated syndrome (CIS) denotes a first inflammatory, demyelinating event.

Primary progressive MS (PPMS) has a later age of onset and is a slowly progressive course (10%–15% of MS patients). Progressive relapsing is a disease course that begins with progression, followed by relapses (5% of MS patients). The pathogenesis involves inflammation (T-cells, B-cells, antibodies, microglia) early in the disease with degeneration and apoptosis more prominent later in the disease. The exact cause of MS is unknown. A vascular theory has been postulated for several years. To date, no scientifically rigorous data have demonstrated that vascular intervention strategies are effective. On the other hand, eight medications are FDA approved as disease-modifying therapy (DMT) for relapsing MS. No treatment for progressive types of MS (without relapses) has been successful.

MS symptoms are numerous and variable. Motor-related symptoms include weakness, spasticity, gait, balance, coordination, tremor, fatigue, speech/swallowing dysfunction, and seizures. Sensory symptoms include visual symptoms, hearing loss, vertigo, headache (migraine), numbness, and pain. Emotional symptoms include depression, hypomania, bipolar, and "pseudobulbar affect" (defined as emotional lability and inappropriate affect). Cognition problems can be detected in more than 50% of MS patients. Autonomic dysfunctions include bowel/bladder/sexual problems, heat intolerance, and hot/cold/white/blue extremities. Treatment of MS ideally requires an interdisciplinary team of neurological physicians, nurses, rehabilitation therapists, psychologists, and other subspecialty physicians to manage the multitude of issues facing those with MS.

The diagnosis of MS involves a neurological history and examination with efforts to rule out other diseases that may mimic MS. Other valuable diagnostic aids include MRI, spinal fluid evaluation, evoked potential testing, and blood tests. The diagnosis may not be made on the first visit. A disease course of CNS relapses and remissions with a changing MRI indicates possible RRMS.

The theory of venous drainage dysfunction resulting in MS or an increase of existing MS symptoms still lacks rigorous scientific clinical trails, which will be discussed later. Many past treatments for MS have failed to withstand scientific scrutiny. Over 100 previous theories have not stood the test of time. Failed MS treatments include vertebral artery surgery, snake venom, bee stings, hyperbaric oxygen, cow's milk, and many others. With this track record, neurologists are cautious (skeptical) to accept any new treatments without scientific clinical trials. These criteria begin with data that demonstrate a definite link between vascular abnormalities and clinical MS symptoms. After showing a link, the treatment must be scientifically sound with positive evidence-based medicine data.

SCIENTIFICALLY SOUND CLINICAL TRIALS

Clinical trials involve human research that follows a prespecified protocol. The studies may be intervention-

TABLE 1. CLINICAL TRIAL PHASES

Phase	Subjects	Goal
I (early clinical stage)	20–80	Safety Pharmacokinetics Dosage range Side effects
II (later clinical stage; a, pilot study; b, well-controlled study)	100–300	Short-term efficacy Further safety issues
III (final clinical stage; a, preregulatory submission; b, postregulatory submission study)	1,000–3,000	Pivotal approval studies Verify efficacy Identify rarer side effects
IV (postapproval, postmarketing stage)	Thousands	Rare adverse events Address questions that arose in earlier phase studies Expose more patients to longer therapy May look at different dose, different population

al or observational. In the case of CCSVI endovascular therapy (either angioplasty or stenting), this involves an interventional study. It would have to be decided beforehand whether a CCSVI trial would involve only angioplasty, or only stenting, or the best option based on angiographic findings and ultimately operator decision.

There is an evolution in the validation of a novel therapy, starting from early single-center limited studies, to large scale global studies used to gain formal approval to market, to postapproval postmarketing studies. These studies involve distinct phases (Table 1). CCSVI endovascular therapy is now in phase 2 of trials. If these results are positive, then definitive phase 3 studies would be next to obtain governmental approval.

Design Elements

The most robust clinical trials provide what is called class I data.[1] The central components of that are outlined in Table 2. The trial should be prospective rather than retrospective. The trial should be randomized. Patients who come into the trial would be entered in a prespecified fashion into the CCSVI treatment arm or the appropriate control treatment arm. In the case of CCSVI, to minimize bias, that would likely be a sham CCSVI procedure. Another way to minimize bias is to make sure the outcome assessments are completely masked or blinded. Ideally this is a double-blind study, meaning the patients do not know whether they are in the CCSVI treatment or sham treatment arm, and neither does the assessing physician. A single-blind study, where the patient knows what they received even though the physician does not, raises the possibility that all self-reported analyses would be tainted. In addition, even the patients' belief that they are undergoing a valuable therapy could have indirect effects on the immune and endocrine systems that might provide a benefit not truly due to the therapy itself. Next, the trial should enter a representative population. In the case of MS, a decision must be made whether you are going to evaluate CCSVI therapy in all forms of MS (both relapsing and progressive) that might meet criteria for CCSVI or only a limited clinical subtype, or whether you want to focus on very early MS such as first-attack CIS CCSVI patients at high risk for MS. If CCSVI were a causal factor for MS, then you would like to treat it very early in the disease process, before there is a lot of fixed damage. However, the initial studies do not favor this because CCSVI has been most prominent in secondary progressive MS, suggesting it is a sequelae/secondary phenomenon of longstanding MS. The primary outcome must be prespecified and very clear. This is discussed in greater depth subsequently, but generally a trial must meet its primary outcome to justify further studies.

This should be chosen very carefully because the trial is judged a success or failure depending on meeting that outcome. Post hoc analyses after the fact do not count. The inclusion/exclusion criteria should be clear. In general, clinical trials typically exclude age extremes for very practical reasons. Patients should be 18 years of age or older so they can sign informed consent, and the entry age should be capped at 60 or 65 years to minimize comorbidity and aging-related deterioration concerns. Both genders should be studied, as well as all races/ethnic groups, unless there is a good reason not

TABLE 2. CRITICAL COMPONENTS FOR CLASS I EVIDENCE STUDY

- Prospective
- Randomized
- Controlled
- Blinded (masked) outcome(s) assessment
- Representative population
- Clear primary outcome
- Clear inclusion/exclusion criteria
- Adequate accounting for dropouts, crossovers
- Treatment groups are balanced/equivalent, or there is statistical adjustment for this

to. Generally, it is a good idea to exclude significant conditions that may affect how patients do or how well they will tolerate the study.

There needs to be allowance for dropouts, which occur in every study for a variety of reasons. This means that an appropriate number of patients are entered into the study to allow for these dropouts but also to allow for detection of a significant difference in the primary outcome. This is projected based on expected results, in both the treated and control arms, for the primary outcome. The study must be powered appropriately. The treatment groups need to be balanced and not significantly different. Generally, in larger trials that are doing randomization this is not an issue, but when the primary outcome may be linked to an entry feature, you must make sure that appropriate adjustments are prespecified. An example would be a primary outcome involving the number of contrast positive lesions on brain MRI. If one of the two study groups entered with a significantly higher number of enhancing lesions, that might bias the specified outcome.

The length of clinical trials is typically in terms of months to a few years, but only rarely more than 2 or 3 years. MS phase 2 trials may be 6 to 12 months, and rarely up to 2 years. Phase 3 trials are generally 2 years, rarely 1 year, and occasionally 3 years. Most clinical trials build in a long-term open-label extension, where patients originally randomized to the new therapy can choose to continue on it, and those who were randomized to the control arm have the ability to switch to the promising new therapy. This is an attractive offer to patients enrolling in a trial, where they know they may be randomized to placebo. It also allows additional data to be obtained on efficacy, safety, and tolerability. In the case of CCSVI therapy, preliminary data suggest that the intervention does not last in a good proportion of patients, and thus would need to be repeated. Therefore, the length of any CCSVI therapeutic trials should be within a timeframe where the intervention would still be expected to have corrected the anatomic abnormality.

The statistical and clinical significance of a trial is ultimately judged in its totality. All analyses need to be prespecified. The robustness of a therapeutic benefit is documented when all the outcomes are positive, or show a trend for benefit. The significance of the benefit is important. Is it clinically meaningful? Does it make a true difference in daily life? Does it ultimately affect long-term outcome? Will this aid society in general? The more the favorable outcome crosses multiple domains of the disease, the more believable is the benefit. If CCSVI therapy modestly benefits a symptom such as MS fatigue, but does nothing to affect clinical, MRI, cognitive, and other disease outcomes, it will not be a viable MS therapy.

IRB Approval

An Institutional Review Board (IRB) is a group formally designated to review and monitor biomedical research involving human subjects. In the United States, the Food and Drug Administration (FDA) has empowered IRBs to approve human research studies and monitor that the rights and welfare of human study subjects are protected. No clinical trial can be conducted without this IRB approval and ongoing monitoring. Academic institutions generally have their own IRBs. In addition, there are central independent IRBs, as well as IRBs associated with community hospitals, local and state government health agencies, and other agencies.

FDA Approval

The FDA considers balloon angioplasty devices and stents as medical devices. They have sent out a safety communication indicating that use of these medical devices in CCSVI constitutes significant risk studies, and therefore these studies require approval of an IRB, as well as approval by the FDA's Investigational Device Exemption (IDE) program. They encourage discussion of trial design in the very early preplanning phase, with involvement via the formal pre-IDE process, as well as less formal meetings.

Informed Consent

Clinical trials require formal informed consent. The form used must be approved by the IRB. It is given to a patient

to read to help them decide whether they wish to participate. It is designed to present in lay terms why the study is being conducted, the details of the study, and its risks and potential benefits. The consent form needs to be revised as new information becomes available.

Outcomes Considerations

Patient safety issues, both in the short and long term, are always a focus in any clinical trial. They may be a formal outcome or be included as a separate piece. Side effects and adverse reactions need to be evaluated and recorded. There must be a formal plan to collect and record them, as well as intercurrent illnesses. Anticipated adverse events must be clearly documented. Regular contact and various assessments, both clinical and laboratory based, are part of every trial protocol.

Disease activity-related outcomes in MS involve both clinical and laboratory measures (Table 3). These can be primary, secondary, or tertiary outcomes. Among the clinical measures, relapse is a well-documented outcome in relapsing forms of MS. Generally the relapse has to produce objective changes on neurologic examination and must meet prespecified criteria to be counted as a true relapse. Pseudorelapse (temporary worsening in the setting of infection) is always excluded because it represents reversible metabolic dysfunction rather than sequelae of a true new lesion.

Disability is manifested as objective worsening on the neurologic examination. By convention, this must be sustained (generally 3 months, sometimes 6 months), to avoid the daily fluctuations that are so common in MS. The Kurtzke Expanded Disability Status Scale (EDSS) remains the most used neurologic examination assessment for clinical trials. This is a 10-point ordinal scale, based on rating the major functional neurological systems. Zero is a completely normal examination, and 10 indicates death. EDSS 4 means the subject can walk 500 meters unassisted. EDSS 6 means they need a unilateral assistive device, EDSS 6.5 means they need a walker, and EDSS 7 means they are wheelchair bound. Disability is determined by a sustained increase of 1 point (at higher range 0.5 point) in the EDSS.

Recent studies have proposed looking at sustained EDSS improvement as a novel outcome measure. The MS functional composite is another disability assessment that involves three measures that evaluate walking (25-foot timed walk), hand function (nine-hole peg test), and cognitive processing speed (PASAT). It is often evaluated as well in MS clinical trials and has been suggested as a possible successor to the EDSS once it is further refined. Other clinical parameters that might be

TABLE 3. DISEASE ACTIVITY-RELATED OUTCOMES

Clinical

- Relapses
  - annualized relapse rate
  - time to relapse
  - proportion relapse free
  - relapse severity
- Disability (worsening on the neurologic examination)
  - sustained EDSS worsening; time to worsening
  - sustained EDSS improvement
  - MS functional composite worsening (25-foot timed walk, nine-hole peg test, PASAT)
  - transition from relapsing to secondary progressive MS
- Cognitive deterioration
  - cognitive function testing
- Visual acuity (low contrast)

Laboratory

- MRI parameters
  - contrast lesion number, volume; proportion contrast lesion free
  - new or enlarging T2 lesions; T2 lesion volume
  - T1 lesion number, volume
  - advanced MRI techniques (atrophy of whole brain or segmental; magnetization transfer imaging; MR spectroscopy; diffusion tensor imaging; functional MRI)
- Optical coherence tomography

Combinations

- Disease activity free (no relapses, sustained disability, or new/enlarging T2 or contrast lesions)

outcomes in trials include cognitive loss and very sensitive (low contrast) visual acuity loss.

MRI parameters are generally key components in MS clinical trials. They can be primary outcomes in phase II, but not phase III, trials. Contrast lesion activity (which marks new current disease activity) is seen especially with younger age patients, in the early years of relapsing MS. When contrast lesions are being evaluated, one generally does frequent MRIs (as often as monthly) for a period of time. This would not be a good outcome with progressive MS, where contrast lesions are much less common. T2 hyperintense lesion number and volume are routinely evaluated. T1 hypointense lesions

TABLE 4. ADDITIONAL PATIENT OUTCOME MEASURES

- Quality-of-life measures
- Symptom improvement
  - fatigue; depression; bladder, bowel, sexual dysfunction; spasticity; pain; gait; heat sensitivity; cognition

are most common in secondary progressive MS and correlate with greater tissue matrix destruction so long as they are chronic (new contrast positive lesions also appear as hypointense on T1).

There are many advanced MRI techniques that can be used to evaluate the MS damage process (particularly microscopic injury that is invisible on conventional MRI), but they are technically more demanding to perform and require that centers be experienced and skilled in their use. Recently, a composite clinical and laboratory measure, disease activity free, has generated excitement as a potential way to analyze an optimal response, although it does not evaluate microscopic injury.

Optical coherence tomography (OCT) is a way to evaluate the retinal nerve fiber layer, a pure axonal region. Preliminary studies in MS have been promising that OCT may evaluate neurodegenerative injury within the eye, and possibly the brain, in MS.

PATIENT-REPORTED OUTCOMES

Improvement in symptoms and quality of life are important. Often these outcomes rely on self-report measures. There is clearly value in looking at the decrease in symptoms and increase in quality of life in MS clinical trials (Table 4). More objective scales to demonstrate functional improvement of symptoms are now standardized and validated. The clinical and MRI disease activity measures remain the main focus in trying to determine a therapy that can change the course of the disease. Without documentation of an effect on these measures of disease injury/damage, you are looking at a symptomatic therapy as opposed to a disease modifying-therapy.

OTHER CLINICAL TRIAL ISSUES

MS patients entered into clinical trials typically show a placebo response; they do better than expected even though they are not receiving the active agent. The explanation for this is not clear, but it needs to be taken into account. This means that an optimized CCSVI trial should have a blinded control group in order to show that any response is better than what a placebo treatment would produce.

MS trials also are affected by what type of MS is being studied. The signature marker of relapsing MS is clinical attacks. However, as milder patients are entered into trials, the attack rate even in placebo arms is quite low, making it more difficult to show a statistical difference on this outcome.[2] When disability is the outcome, generally there is a specified requirement that patients show a certain degree of worsening/disease activity in the 1 to 2 years before entry. This is done to try to select patients who are actively worsening for the trial, rather than very stable patients who might show little to no change. No disease-modifying therapy has yet been proven for progressive (slow worsening) MS. To show an impaction on this progression, trials typically have to be longer (a minimum of 2, and often 3 years). Unfortunately, progressive patients may clinically stabilize for up to several years at a time.

Finally, none of the current outcomes are ideal. Clinical relapses are the tip of the iceberg. EDSS disability measurements show intra- and inter-rater variability and are relatively insensitive in many areas. Conventional MRI measures only detect macroscopic lesion activity, while the advanced MRI techniques have very limited availability. This has fueled attempts to develop new outcomes such as the composite freedom from disease activity, sustained disability improvement, a more sensitive MS Functional Composite, and novel clinical and MRI outcomes noted in Table 3. Patient-reported outcomes are also receiving a new emphasis, and give an additional dimension to evaluate the benefit of a therapy for the patient.

CCSVI COLLABORATIVE RESEARCH INITIATIVE

Endovascular therapy physicians, neurologists, diagnostic experts, scientists, trial design experts, patients, and others are beginning to collaborate to develop trials and set standards for CCSVI research to ensure an accurate diagnosis as well as definitive laboratory/clinical/patient-related outcomes, adequate patient safety, and appropriate disclosure to patients considering the procedure.

The exact process is still being developed but will likely start with a review of the theory and evidence to date. Questions to be addressed are included in the *Considerations for the CCSVI Collaborative Group* sidebar. A well-conceived plan of action will answer many important questions. Resource acquisition and prioritization are important initial steps. The MS patients, health care professionals, payors, and the general public await these answers.

In May 2012, the FDA expressed serious concerns about the efficacy and safety of CCSVI procedures, as well as the lack of evidence to support a link between CCSVI and MS—or any symptom or disease. Further,

CONSIDERATIONS FOR THE CCSVI COLLABORATIVE GROUP

1. What do we know already?

A. MS diagnosis, disease course, symptoms, response to, and safety issues related to immunologically based DMTs and location of MS damage, which include perivenular lesions.

B. Treatments involving stenosis of the CNS venous system is still a "pilot phase" and will require rigorous research before commercialization is appropriate.

C. Interdisciplinary collaboration is imperative to delineate both diagnostic and therapeutic issues.

2. What are some of the disputed findings?

A. CNS venous drainage is impaired in MS.

B. Impaired venous drainage is the cause of MS or is related to symptom severity.

C. CNS venous stenosis can be diagnosed accurately.

D. Reducing venous stenosis is beneficial to most MS patients, especially pain, mood, cognition, heat intolerance, bowel/bladder/sexual dysfunction, and quality of life.

E. Restenosis is unlikely and is (or is not) related to increasing symptoms.

F. Iron deposits occur from venous stenosis, and this iron-induced damage causes inflammation and MS symptoms.

G. Relieving venous stenosis is a safe procedure with minimal risks.

H. The outcomes of fully established CCSVI treatments are well defined and adequate.

3. What is not known about CCSVI and its treatment?

A. The diagnostic algorithm for the definite diagnosis of CCSVI has not been fully delineated.

B. The prevalence of CCSVI in other diseases and "normals."

C. The efficacy and safety outcomes of CCSVI-treated patients. Much data have not been collected or published.

D. Is CCSVI treatment a disease-modifying therapy, a symptom management therapy, a quality-of-life treatment, and/or a placebo response? What type of MS would respond to CCSVI treatment?

E. Is CCSVI a hereditary condition?

F. Does MS create CCSVI or vice versa?

G. When, if ever, are stents indicated in CCSVI? Are they safe?

H. What is the risk/benefit ratio and what should MS patients be told before undergoing treatment?

I. What are the long-term benefits/risks of CCSVI treatment?

they emphasized the necessity for those conducting clinical trials in CCSVI to comply with FDA regulations. Current use is off label. Recently, a US study was voluntarily closed and a Canadian study did not show any benefit. Nonetheless, patients insist on their right to receive CCSVI treatments. Physicians' responsibility is to bring more science to the equation.

The collaborative group has the challenge of implementing the design and outcomes as stated in this article. These studies will lead to better understanding of CCSVI and its potential treatments—and possibly a better understanding of MS. ■

Patricia K. Coyle, MD, is Professor with the Department of Neurology at Stony Brook University in Stony Brook, New York. She has disclosed that she has received compensation for consultative and education-related activities in MS from Acorda, Bayer, Biogen-Idec, EMD Serono, Novartis, Pfizer, Roche, Sanofi Aventis/Genzyme, and Teva Neurosciences. Dr. Coyle may be reached at (631) 444-8188; patricia.coyle@stonybrookmedicine.edu.

Jack Burks, MD, is a clinical neurologist and Chief Medical Officer of the Multiple Sclerosis Association of America, Cherry Hill, New Jersey. He has disclosed that he has no financial interests related to this article. Dr. Burks may be reached at (775) 826-4171.

1. Goodin DS, Frohman EM, Garmany GP, et al. Disease modifying therapies in multiple sclerosis. Ann Neurol. 2002;58:169-178.
2. Uitdehaag BM, Barkhof F, Coyle PK, et al. The changing face of multiple sclerosis clinical trial populations. Curr Med Res Opin. 2011;27:1529-1537.