

COVER STORY

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

An interventional perspective.

BY GARY SISKIN, MD

What are the levels of evidence required to determine the benefit of treating chronic cerebrospinal venous insufficiency (CCSVI) to alleviate symptoms of multiple sclerosis (MS)? Although the answer to this question is complex, there can be no reasonable argument against the statement that level 1 evidence from prospective randomized blinded trials must be obtained for physicians to make informed decisions when evaluating and treating the cerebral outflow veins in MS patients. Therefore, the issue at hand is not whether these trials should be done—they must be done. Instead, we should focus on the ideal methodology of these trials, the guidelines that must be taken into account when designing trials, and the role that data from other, perhaps less rigorous, forms of research have when making individual clinical decisions for patients with MS.

BACKGROUND

CCSVI and the use of venous angioplasty to treat this condition is an interesting model through which to look at the role medical research plays when making decisions regarding a new treatment for a particular condition. As a theory and as a distinct medical condition, CCSVI is unproven to many and will remain that way until better studies become available and are validated in variety of settings. As recently outlined by Dake,¹ the work of Zamboni et al² revitalized an old idea regarding a possible venous contribution to MS and opened the door to this present debate. There is no doubt that much work needs to be done to validate CCSVI as a clinically relevant condition that is not only prevalent in patients with MS but possibly in others as well. To this end, the National MS Society has several projects underway, with at least one suggesting that valvular abnormalities may be present in patients with MS.³

The paucity of data supporting the etiology, pathology, and pathophysiology of this condition are significant obstacles when it comes to CCSVI. Diagnosing CCSVI using noninvasive imaging modalities has been, to say the least, inconsistent, and therefore represents another obstacle. Although studies have been published demonstrating success in diagnosing CCSVI using Doppler ultrasound^{4,5} and magnetic resonance venography,⁶ others have refuted these data,⁷⁻⁹ which has fueled the fire when it comes to CCSVI. The authors of these latter studies and related specialists have used the inconsistency of noninvasive imaging to diagnose CCSVI as a subjective means to dismiss CCSVI in its entirety. Basic studies must be performed to define CCSVI as a medical condition, and additional studies should be performed to determine the best way to noninvasively diagnose CCSVI in patients with or without MS. This article will focus on the work that needs to be done to understand the role of venous angioplasty in the treatment of these patients.

OFF-LABEL DEVICE USE

Our field has thrived in a climate that enables physicians to use medical devices off-label in the best interest of their patients according to their best knowledge and judgment. Under these circumstances, the endovascular treatment of disease has grown in ways we never would have thought possible. Many of the procedures that are commonly performed today had their start when individuals used their creativity to provide elegant solutions to complex problems with devices used in an off-label manner. When using an off-label device, physicians have the responsibility to be well informed about the product, to base its use on firm scientific rationale and sound medical evidence, and to maintain records of the product's use and effects.¹⁰ The

(Continued on page 51)

(Continued from page 40)

last criterion is particularly important because maintaining records should presumptively lead to the initial reporting of outcomes in association with off-label device use.

Appropriate record-keeping in association with off-label device use facilitates the publishing of case reports and retrospective case series, which can ultimately lead to well-designed clinical trials to better test the safety and efficacy of a medical device for this new indication. The problem, however, is that the pace of device development has frequently surpassed the pace of formal device evaluation. This fact, together with the inherent cost of designing and carrying out clinical trials, has created a disincentive to perform appropriate device trials because investigators are already thinking about next-generation devices and their potential applications before completing the cycle of evaluating earlier devices.

CURRENT RESEARCH

Assuming that physicians are well informed about the products being used for this procedure, then the other criterion requiring attention is the one asking physicians to base the use of an off-label device on firm scientific rationale and sound medical evidence. This begins to answer the question posed at the beginning of this article. At the present time, we can turn to the work of Zamboni and the early articles by Charcot, Putnam, and others^{1,2,11,12} to provide the theoretical support for venous abnormalities in this patient population and the more recent work by Diaconu et al,³ Dolic et al,¹³ Coen et al,¹⁴ Zaniewski and Simka,¹⁵ and Tucker¹⁶ to provide the pathologic and pathophysiologic basis for treatment.

The initial case series published by Zamboni et al,¹⁷ Malagoni et al,¹⁸ and Dake et al,¹⁹ as well as the abstracts presented by Mehta et al,²⁰ Zarebinski et al,²¹ Milic et al,²² Magnano,²³ Ferral et al,²⁴ and Sekhar et al,²⁵ provide some of the initial evidence supporting the potential effectiveness of venous angioplasty as a treatment for CCSVI. Finally, the case series published by Ludyga et al,²⁶ Petrov et al,²⁷ and Mandato et al²⁸ support the safety of venous angioplasty as a treatment for CCSVI. The important point is that these studies, although somewhat limited in scope, design, and/or follow-up, provide the initial rationale for the off-label use of devices in clinical practice to treat CCSVI in patients with MS.

Is this adequate? Do the studies mentioned here provide the evidence to support the performance of this procedure on their own? Although I believe that

this evidence supports the clinical use of these devices for an off-label indication, we must acknowledge that additional studies need to be performed to better understand CCSVI and the role of endovascular treatment. It remains important for physicians performing this procedure as part of their clinical practice to retrospectively report their outcomes as a critical means for understanding if further study makes sense and if physicians are acting responsibly when performing this procedure. However, it is equally critical to understand that retrospective studies alone do not provide the evidence needed to answer the questions that persist about CCSVI.

FUTURE STUDIES

In order to gather higher levels of evidence with the hope of gaining additional support for this treatment, well-designed prospective studies are required. For this to happen, an understanding of the guidelines for an investigational device exemption (IDE) must be understood by both investigators and institutional review boards that wish to be involved with research in this area. As previously mentioned, the devices used for this procedure are off-label when utilized for angioplasty of the internal jugular and azygos veins in MS patients with CCSVI. That is not a debatable point. Given the fact that significant complications have been reported in association with this procedure (and therefore with these devices),^{19,29} the angioplasty balloons and stents used for this procedure are considered significant-risk devices.

One point of confusion is the fact that the previously noted studies have concluded that venous angioplasty in this setting is a safe procedure with a very low risk of major complications. Some have interpreted that as meaning no risk for major complications and therefore think of these devices as nonsignificant-risk devices. This is an important distinction because significant-risk devices require an IDE when used in a prospective research study but nonsignificant-risk devices do not. The May 2012 communication issued by the US Food and Drug Administration (FDA) regarding CCSVI confirms this point.³⁰ The FDA reviews proposed research protocols to ensure that the scientific rationale is sound, that the protocols are designed to answer the questions being posed, and that the rights, safety, and welfare of patients are protected. In this way, the FDA is taking the necessary steps to make sure that the devices are being studied appropriately and responsibly.

The exact methodology for any proposed clinical trial remains a question in the minds of those involved in this area of study. One significant issue is whether a trial

COVER STORY

should be designed to evaluate this procedure as an MS treatment or as a treatment for venous disease. As an MS treatment, we should acknowledge that the neurology community has certain standards and expectations in place that must be met for such a trial to stand on its own and to enable appropriate comparison to other therapies for this condition. This will dictate the enrollment criteria (type of MS, disease-modifying drug regimens, etc.), the duration of follow-up (months vs years), and the means by which patients are evaluated during the follow-up period (ie, contrast-enhanced magnetic resonance imaging, objective criteria such as the Expanded Disability Status Scale or Multiple Sclerosis Functional Composite, patient-reported outcomes such as the Multiple Sclerosis Impact Scale-29 or Multiple Sclerosis Quality of Life-54, etc.).³¹⁻³³ As a treatment for venous disease, the expectations are not as established, and therefore, we may or may not be sure of the exact outcome measures that will be needed to confirm or refute a study hypothesis. Given this uncertainty, both avenues should be further explored.

What is more certain, however, is the need for these studies to be conducted in a randomized, blinded fashion. This means that venous access needs to be achieved in every patient even though the actual intervention procedure would only be performed in patients meeting certain criteria and then randomized to a treatment group. The other patients may have diagnostic tests performed but will not be treated.

Many have attributed positive effects reported in association with this procedure to a placebo effect. Although a more detailed discussion of this is again outside the scope of this paper, it is critical for those investigating this procedure to take the placebo effect into account as part of their study design.³⁴ By ensuring that the patients and the physicians responsible for evaluating these patients during the follow-up period are blinded as to whether a patient was actually treated with angioplasty, the placebo effect is removed as a potential explanation for the symptomatic improvement that may be reported after this procedure.

CONCLUSION

By issuing their recent communication, the FDA has made it clear that good medical care needs to be provided to patients who choose to undergo this procedure.²⁸ Physicians must make sure that patients are appropriately informed about the potential risks and benefits of the procedure, as well as the questions surrounding CCSVI and venous angioplasty for this indication. The FDA has also made it clear that questions regarding the safety and efficacy of angioplasty exist

and will need to be answered before this procedure earns a place in the treatment of patients with MS. To answer these questions, the appropriate rules governing research on medical devices being used in an off-label fashion need to be followed. However, the FDA specifically stated in this communication that they “do not regulate the practice of medicine and that physicians may choose to use a legally marketed device, based on their clinical assessment, for purposes other than the cleared or approved use.” It is my hope that practitioners choosing to use these devices off-label will report their outcomes so that we can continue to gain an understanding of CCSVI.

Interventionists interested in this procedure have an obligation to gather level 1 evidence to support performance of this procedure. Although the studies published to date seem to provide the necessary support for the off-label use of these devices in clinical practice, they do not adequately answer the safety and efficacy concerns raised by the FDA and the neurology community. If we are going to consider this as a treatment for patients with MS, then it is my opinion that we must design trials that meet the standards and expectations set forth by neurologists, as it concerns the work they have done with other MS therapies. If we are going to consider this as a treatment for venous disease, then the nature of this disease must be better characterized so that trials can be developed that can clearly attribute symptoms to the venous abnormality and symptomatic improvement to treatment. Either way, prospective randomized blinded trials, approved through the FDA’s IDE program and demonstrating safety and efficacy, will be required if the treatment of CCSVI is ever going to be acknowledged as an option that might improve the lives of these patients. ■

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