New Messages, New Media: ATTRACT Study Update

Renewing the commitment to find the best possible treatment for future DVT patients.

BY SURESH VEDANTHAM, MD

The Acute Venous Thrombosis: Thrombus Removal With Adjunctive Catheter-Directed Thrombolysis (ATTRACT) study is an ongoing, multicenter, randomized controlled trial (RCT) that is sponsored by the National Institutes of Health. It aims to determine whether the routine use of pharmacomechanical catheter-directed thrombolysis (PCDT) in patients with acute proximal deep vein thrombosis (DVT) reduces a patient's risk of developing post-thrombotic syndrome (PTS). Assessed clinical outcomes include 2-year PTS rates, health-related quality of life, relief of pain and swelling, safety, and cost effectiveness.

ATTRACT is being conducted in 50 hospitals in the US. As Principal Investigator of this study, I am fortunate to have broad community support that includes active collaboration with the Society of Interventional Radiology Foundation and the public endorsement of the Office of the US Surgeon General.

STUDY PROGRESS

As of November 9, 2012, the ATTRACT study had enrolled 375 patients, which is more than halfway to its accrual target of 692 patients. The study continues to progress smoothly, with a tremendous amount of work being done by talented investigators from different specialties and research coordinators nationwide.

The rate of monthly accrual improved substantially in 2012, and it is worth noting that ATTRACT is already twice as large as the only rigorous multicenter RCT that has been published to evaluate endovascular DVT thrombolysis.[1] The question now is not whether the study will be completed and published—it will—but rather, whether it will achieve the target accrual upon which its credibility will be judged. As the study progresses, the investigators' approaches to boosting enrollment evolve substantially, reflecting our now-stronger understanding of the study-specific challenges we face. In addition, the Steering Committee continues to be forward-leaning in terms of adopting innovative strategies and solutions to the enrollment dilemma and, particularly, in leveraging the recent transformation of communication capabilities that pervade modern culture. In other words, both the key messages and the media with which we deliver them have changed.

PREREQUISITES FOR SUCCESS

We continue to be concerned that DVT patients and the physician community upon whom they rely for information do not fully appreciate the benefits of participating in a study like ATTRACT. Based on previous medical-versus-surgical–type studies akin to ATTRACT and our own experience with ATTRACT enrollment at the Washington University study site, we remain convinced that a quality presentation of the study to a patient will result in consent rates of 50% to 60%. However, to date, only about 35% of patients

approached have consented, which translates to 25 patients declining per month. If even 20% of these were converted into the "yes" column, the trial would be completed in a year.

To address this issue, we have carefully examined the consenting practices of every ATTRACT site and have drawn from the published literature on research study enrollment. There are three main points of intervention: (1) ensuring that patients are approached as quickly as possible after DVT diagnosis, before they are inundated with information about DVT treatment from other providers or (as is often the case these days) the internet; (2) ensuring that the study is truly presented to patients in a balanced way without transmission of any bias the presenter may harbor consciously or subconsciously about which treatment is best; and (3) ensuring that the study investigators, the patient's primary physicians, and the patient truly understand the value to the patient of participating in this study. A fourth dimension, which could provide a tremendous boost to the study, would be for a much larger community of physicians to understand its importance, view study participation as a great opportunity for their patients, and routinely refer patients to ATTRACT sites.

IS STUDY PARTICIPATION GOOD FOR MY PATIENT?

A core issue is that many endovascular physicians harbor a strongly "pro-lysis" bias and may be concerned that referral to a study that offers a 50% chance of randomization to the (no lysis) control arm would not be in the best interests of their patients. This concern has been augmented by the 2012 publication of the results of the CAVENT study,[1] a multicenter RCT performed in Norway that found the use of drug-only CDT to reduce the risk of PTS in patients with proximal DVT. But this argument, while understandable given the typical indoctrination of endovascular physicians during their training, is nevertheless highly flawed.

To understand why, one needs to first step back and view the big picture of DVT treatment through a historical lens. In doing so, two things become clear: (1) many physicians greatly overestimate the strength of the evidence supporting the use of CDT and PCDT relative to conventional treatment approaches; and (2) many physicians greatly underestimate the value of study participation to a DVT patient.

Consider first the record of anticoagulant therapy (AC) alone. This form of DVT therapy has been evaluated in many well-constructed clinical trials totaling more than 20,000 patients enrolled during a 50-year period. The findings—that AC prevents pulmonary embolism and recurrent DVT—have been consistent across many studies. The risk of major nonfatal bleeding for initial AC using low-molecular-weight-heparin in "all-comers" is 1.5%; major bleeds are rare in patients who would be considered for thrombolysis (0% in the no-lysis arm of CAVENT), and fatal or intracranial bleeding from initial heparin-based AC therapy alone is exceedingly infrequent.[2,3] Moreover, AC drugs are administered orally or by parenteral injection in a uniform way, increasing the likelihood that clinical trial results truly represent the therapy as it is delivered in clinical practice. Although AC alone has not been perfect in terms of PTS prevention, studies have found recurrent DVT (which AC prevents) to be a major risk factor for PTS.[4] Good-quality, long-term AC has been associated with reduced PTS rates. Hence, AC is very safe, prevents PE, and probably reduces PTS,[5] and the level of certainty that net benefit outweighs the risks in our patients is outstanding.

In contrast, consider CDT and PCDT. Most studies have major methodological flaws that potentially introduced a great deal of bias into the results, including nonrandomized study design, small sample size, lack of blinding, and lack of use of validated outcome measures. CAVENT, the only rigorously performed RCT with blinded assessors and midterm (2-year) follow-up, reported outcomes in just 189 patients, of whom, only 90 patients received CDT. CDT was delivered in a manner akin to US practice 15 to 20 years ago: 1- to 4-day drug infusions through a multisidehole catheter, without use of thrombectomy devices and with limited use of stents. Furthermore, the results of CAVENT were somewhat underwhelming—a 28% relative risk reduction in PTS at 2 years, at a price of a 3% additional risk of major bleeding. But, no venous ulcers occurred in either treatment arm, so it is not clear if CDT just prevented mild PTS cases, as opposed to clinically important PTS.

So, is the treatment studied in CAVENT the same treatment we provide in US practice? Is a 3% risk of major bleeding (for perspective, if 100,000 DVT patients per year are lysed, that is 3,000 extra major bleeds per year) really worth it without proof that CDT prevents severe PTS? No fatal or intracranial bleeds occurred in the 90 patients studied, but surely, this risk still exists (a risk of 0.1% translates to 100 deaths/strokes per year). Could initially successful CDT be undermined by late recurrent DVT episodes that inevitably cause PTS anyway? There is major statistical uncertainty regarding the efficacy and safety estimates that favor CDT—would you risk your life based on a study of 90 lysed patients?

In contrast, consider what a patient entering the ATTRACT study will receive. All ATTRACT subjects receive all evidence-based DVT treatments that are currently known to work: AC and compression therapy. Study patients are monitored closely and receive a number of items for free, including compression stockings, follow-up visits, an ultrasound exam, and the thrombolytic drug. They have the confidence that the treatment protocols being used to treat them have been endorsed by national DVT experts and the National Institutes of Health. They know that PCDT is being delivered in a careful way with many safeguards put in place by a diverse team that included physicians who are not necessarily "advocates" of PCDT. Because a motivated research nurse coordinator is assigned to monitor their care, they can more easily access the health care system for help and information (including questions about their DVT).

Studies have shown that in DVT patients receiving warfarin, those who are enrolled in a clinical trial are much more likely to have International Normalized Ratio values that are within the therapeutic range than patients treated in clinical practice. Hence, enrolling in ATTRACT is likely to enhance the quality of care given to a patient. Although 50% of study patients do not receive thrombolysis, it continues to be uncertain if that really improves long-term outcomes, and there is certainly inconvenience and risk.

Hence, participation in ATTRACT is a terrific way for a DVT patient to receive an outstanding level of care while also helping other patients. We ask every physician reading this article to click on the "Why Should I Join This Study" page of the study website (www.attract.wustl.edu) and start providing the great opportunity of ATTRACT participation to his or her patients. Providers can page (314) 360-5565 any time for quick assistance in assessing eligibility and finding a nearby study site.

The Steering Committee is aware that many people, and in particular the younger generation, are highly visual and prefer video over other forms of media presentation when learning new health information. As such, we are currently developing a YouTube video to succinctly convey the study's importance and the opportunity it offers to patients for a much larger audience in the hope of driving patient self-referrals to our investigator network. We are also exploring the use of a smartphone application to provide the ability to quickly refer patients to ATTRACT into the pockets of community health providers. Once the required regulatory approvals are obtained, these items will become available to the community.

CONCLUSION

The ATTRACT study continues to offer a once-in-a-generation opportunity to properly test the ability of endovascular thrombolysis to improve DVT patient outcomes. As always, a hefty dose of community support will be required for success to be achieved, and we remain hopeful that the readers of this article will refresh their commitments to supporting this study. ■

ATTRACT is led by a Steering Committee comprising the following individuals:

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