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Editor's Spotlight/Take 5: CORR® ORS Richard A. Brand Award: Clinical Trials of a New Treatment Method for Adhesive Capsulitis

Seth S. Leopold MD

Among the nonlethal orthopaedic diagnoses, adhesive capsulitis (frozen shoulder) must be among the most frustrating. The natural history of this condition runs a painful, functionally limiting, and long course [10]. The therapy for it can be just as painful and certainly is

Note from the Editor-In-Chief: In "Editor's Spotlight," one of our editors provides brief commentary on a paper we believe is especially important and worthy of general interest. Following the explanation of our choice, we present "Take Five," in which the editor goes behind the discovery with a one-on-one interview with an author of the article featured in "Editor's Spotlight."

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time-consuming [1]. Manipulation under anesthesia and arthroscopic surgery are last resorts because the condition often resolves on its own [6], there is little comparative evidence of the efficacy of those interventions [9], and they can be associated with serious complications [7]. Many patients endure the pain and stiffness associated with this condition for more than 1 year; 2 years is not at all uncommon [10].

For these reasons, we are especially excited to present "Clinical Trials of a New Treatment Method for Adhesive Capsulitis," this year's CORR® ORS Richard A. Brand Award winning paper. The study really is a sequence of three studies—a dose-ranging proof-of-concept experiment, a technique study demonstrating the accuracy of ultrasound guidance, and a small but thoughtfully designed efficacy trial. The new treatment method evaluated by Marie A. Badalamente PhD and Edward D. Wang MD from Stony Brook University Medical

Center in New York was the extraarticular injection of *Clostridium histolyticum* collagenase, an enzyme they previously have used in the treatment of Duputryen's contractures [3].

The authors observed rather substantial gains in forward flexion and abduction for two of the studied dosing regimens, but less-consistent effects (and in many cases, no effect) on shoulder rotation. They also found clinically important improvements in VAS pain and function as measured by the American Shoulder and Elbow Surgeons (ASES) score. Adverse effects were ubiquitous—all patients reported pain, swelling, bruising, or a combination of those findings—but these reactions seemed not to be serious or long-lasting. Importantly, MRIs on these patients did not demonstrate damage to the rotator cuff, and the authors observed no shoulder instability following the collagenase injections.

Although this series of studies is exciting enough to merit the largest award in our specialty, it must be considered preliminary. Shoulder surgeons reasonably are concerned about novel interventions, given recent (and severe) problems with intra-articular local-anesthetic pumps [8] and thermal

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capsulorrhaphy [5]. Although adhesive capsulitis is frustrating, it may well be self-limiting (or nearly so), so any new intervention for it must therefore demonstrate not just efficacy but also safety; doing so will take more patients and more followup than was possible in this report. How to balance safety and efficacy is a concern all orthopaedic surgeons must share, and truly establishing safety can be difficult [4]. But the work of Drs. Badalamente and Wang certainly justifies the research to replicate and extend their findings that undoubtedly will follow.

Join me as I go behind the discovery with Marie A. Badalamente PhD and Edward D. Wang MD, the investigators on this ground-breaking study, in the Take-5 interview that follows. The implications of this work go far beyond shoulder surgery, as they deal with the questions of how big ideas get off the drawing board, how to know when an effective but novel treatment is “safe enough” to try on one’s own patients, and how to develop a research program on a new topic.

REMINDER: The deadline for this year’s CORR® ORS Richard A. Brand Award for Outstanding Orthopaedic Research is November 30, 2016. The prize of USD 25,000 will go to a paper on a topic of musculoskeletal clinical relevance deemed by the awards committee to be the strongest in terms of quality and scientific merit. See <https://abjs.member>

[clicks.net/corr-ors-richard-a-brand-award](https://abjs.member.clicks.net/corr-ors-richard-a-brand-award) for more details.

Take Five Interview with Marie A. Badalamente PhD and Edward D. Wang MD, coauthors of “CORR® ORS Richard A. Brand Award: Clinical Trials of a New Treatment Method for Adhesive Capsulitis”

Seth S. Leopold MD: *Congratulations on this exciting work. It raises so many issues that go far beyond shoulder surgery. Perhaps most importantly is the idea of safety; lysing palmar fascia, as one does in Duputryen’s contracture, may be quite different from lysing the shoulder capsule, which plays a critical role in shoulder stability. What gave you the confidence that this would be safe to do?*

Edward D. Wang MD: The main concern with our injection technique was ensuring that the collagenase remained extraarticular to prevent damage to the articular cartilage. At the outset, we tried to focus on maximizing the margin of safety. We obtained fine blunt needles commonly used by anesthesia to perform epidural injections. Then we tested them during live arthroscopic surgery and on cadavers. As a result, we became convinced that these blunt-tip needles, which bent easily, would have a difficult time penetrating the pathologically thickened capsule seen with adhesive capsulitis. We thought all of these factors collectively would provide an acceptable margin of safety to proceed.

Marie A. Badalamente PhD

Edward D. Wang MD

Since instability is uncommon following surgical release of adhesive capsulitis, we did not think postinjection instability

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would be an issue with our treatment. So far, this seems to be holding true.

Dr. Leopold: *One can establish efficacy with a few dozen or couple hundred patients, but establishing safety requires many hundreds or even thousands of patients [3], since rare but severe problems of a treatment can quickly change one's perspective on the risk-reward calculus. How will we know that this approach is truly safe?*

Dr. Wang: I think there will always be risk associated with this procedure. The goal will be to continue to demonstrate that the incidence of adverse events is as low as or lower than alternative treatment options currently available for adhesive capsulitis. The only way I know how to do that is by continuing to treat study patients, relying on the execution of proper technique to give us an adequate margin of safety. Hopefully, the data will ring true after more studies are completed.

Dr. Leopold: *Talk to us about the birth of this idea; every joint is different, and the causes of joint stiffness can vary from joint to joint. How did you decide to take C. histolyticum collagenase from the hand to the shoulder, and where else might it "go"?*

Marie A. Badalamente PhD: The idea to test collagenase *C. histolyticum* in adhesive capsulitis took place as our clinical trials of this enzyme in

Dupuytren contracture still were ongoing. We were aware that adhesive capsulitis is approximately eight times more common among patients with Dupuytren contracture. Also, work of other investigators suggests that both disorders may share a common pathobiology, one in which myofibroblasts produce excessive amounts of collagen in the palmar fascia of the hand [3] and in the shoulder capsule [2]. It is possible that injectable collagenase *C. histolyticum* may have merit in a wide range of fibroproliferative disorders where collagen synthesis outweighs collagen degradation.

Dr. Leopold: *One question about the study design itself: It looks like you did a dose-ranging evaluation in patients with adhesive capsulitis (Study 1 in your paper) prior to doing your test on volunteers with "healthy" shoulders (Study 2). Why did you do it in this sequence?*

Dr. Wang: In our first study, the injections were performed without the use of ultrasound guidance. I personally administered all of those injections. Then, we planned on having investigators at other study centers administer some of the injections in our multicenter studies, so we added ultrasound guidance as a further refinement in order to make the technique transferable while maintaining our margin of safety. Study 2 was designed to evaluate the ultrasound-

guided injection technique, specifically to confirm the extra-articular location of our injection using that technique.

Dr. Leopold: *Many readers will not know the full extent of the process an intervention like this goes through from conception to FDA approval. Would you share a bit about the timeline (when you had the idea, when it might be ready for clinical use outside of trials), the hurdles you've faced and those you have yet have to clear, and what it is like to go through this process as an investigator developing a new treatment?*

Dr. Badalamente: The FDA approval process for injectable collagenase *C. histolyticum* for Dupuytren contracture took 15 years of "lab bench to bedside" studies. We now are in the midst of phase-2 trials as part of the FDA approval process for injectable collagenase *C. histolyticum* in the treatment of adhesive capsulitis of the shoulder. Because there now is an extended "human experience" in Dupuytren disease, not only from clinical trials but also from clinical practice since 2010, much is known about the safety of the enzyme. This information is important to the FDA development of the treatment in adhesive capsulitis and may serve to shorten the approval process. At present, we anticipate one more phase-2 study and one pivotal phase-3 study before data may be

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submitted to the FDA for approval. Extreme patience and meticulous attention to detail are attributes investigators need to undertake such studies. My motto has become “there is no elevator to success, you have to take the stairs”! The reward of an FDA approval with the potential to help patients around the world is one I cherish in Dupuytren contracture and hope to see again in adhesive capsulitis.

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