VOLUME 9, ISSUE 8 | MARCH 12, 2013

Orthopedics This Week

The Passion of Chris Centeno

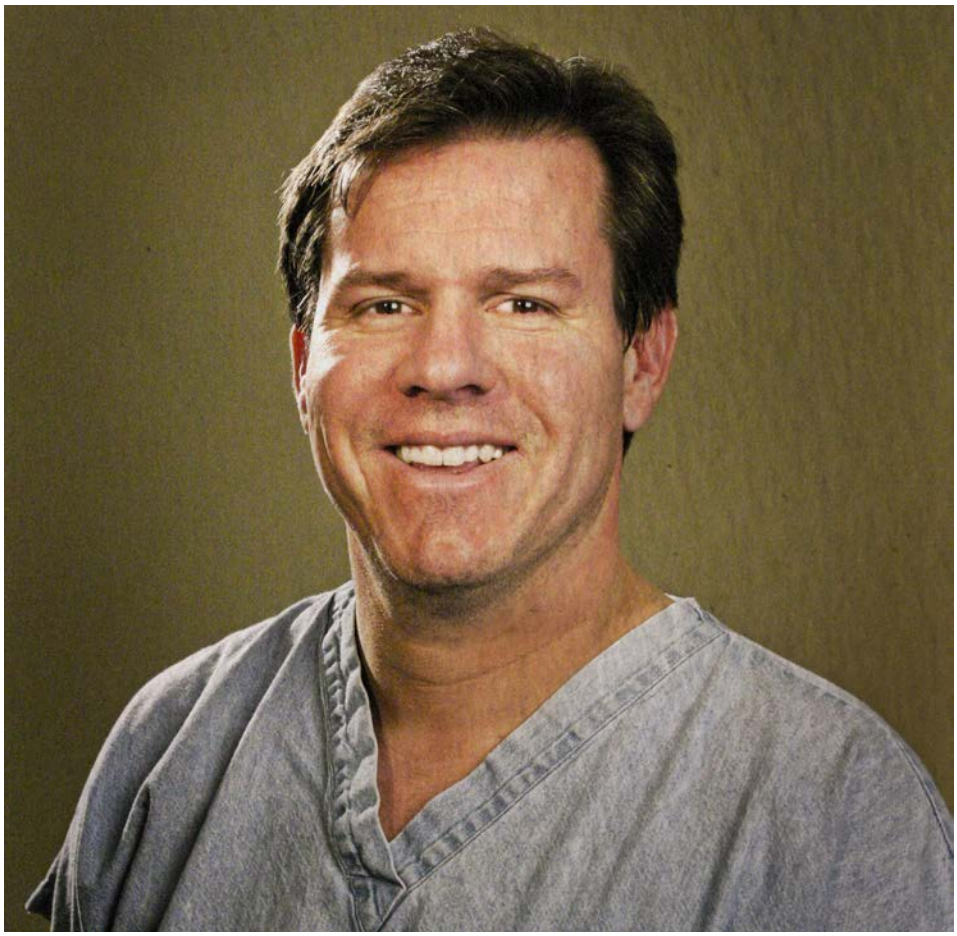
By Robin Young

To paraphrase Oliver Wendell Holmes, medical innovation is great when it is greatly pursued.

Harrington, Charnley, Kirk, Bunnell, Shands, Panjabi, Ilizarov, Michelson, Campbell and Kuntscher. To a man they peered into the recesses of the human body and saw a future very different from the one taught in medical school. Why, they wondered, did patients have to suffer because of the parochial science of the time?

Greatly pursuing a vision of better tools, procedures and patient outcomes often comes at a price. John Charnley famously had more than 300 failed hip replacements before perfecting his materials and procedure. Harrington's idea to implant a rod and attach it to the spine at the top and bottom of a scoliotic curve with hooks was considered an abomination when first presented at AAOS in 1958. At his hospital, residents were discouraged from scrubbing in with him.

Chris Centeno, M.D., who is greatly pursuing a vision of autologous biologic therapies, has an ever growing registry of stem cell treated orthopedic patients (now more than 4,300 patients) as well as the dubious honor of having been forced to sue the FDA twice before being sued over one of his five autologous stem cell therapies.



Chris Centeno, M.D.

Dr. Centeno trained at the Baylor College of Medicine, Texas Medical Center and the Institute for Rehabilitation Research.

Resisting Autologous Biologic Therapies?

"Resistance comes when you forge new ideas that are ahead of their time. The nice part is that eventually, when the rest of the world catches up, the resistance turns into acceptance." – Chris Centeno.

Why would autologous therapies be controversial? Because, in the case where the patient's cells are cultured over the course of several weeks, the FDA has decided that they should be 'drugs.'

Centeno, who is board certified in physical medicine, rehabilitation and pain management through the American Board of Anesthesia, has been treating patients for joint pain and arthritis with their own platelets, stem cells and growth factor proteins since 2005. He takes very strong exception to the FDA's conclusions. In his view, using autologous therapies on patients falls within the practice of medicine guidelines.

The procedure that triggered the FDA action is Centeno's Regenexx C procedure for collecting and then expanding the patient's own mesenchymal stem cells over the course of about 2weeks. That culturing of the patient's cells caught the attention of FDA in the form of an untitled letter to his practice in 2008. The battle over whether a patient's own cells should be a drug has gained much attention, with both a Former FDA chief and deputy director (Andrew von Eschenbach, M.D. and Scott Gottlieb) writing separate Wall Street Journal Editorials that the FDA has its position on this issue (that cultured cells are drugs) dead wrong. In the meantime, Centeno has published two favorable papers on the cultured technique on the complications seen in 339 patients and on the outcome of 155 patients with severe knee arthritis.

Centeno has had no FDA issues with his four other autologous methods. His family of autologous procedures is: Regenexx-SD, Regenexx-AD, Regenexx-SCP and Regenexx-PL-Disc. All are same-day procedures.

Unique Methodology

First, you probably wouldn't recognize parts of the Centeno-Schultz clinic in Broomfield, Colorado, just outside of Denver. While all of the usual bits and pieces are there: exam rooms, procedure rooms, imaging equipment, etc… there's also a large state of the art clean room lab facility. There a team of PhD's and lab workers who not only process cells for re-injection, but also use many tools that are usually only found in university labs. Machines for analyzing gene expression, cell surface markers, fluorescent markers inside cells, and cartilage components abound. Incubators for culturing cells lie next to cyropreservation freezers that chill to -150C.

Centeno's process is also unique. For the same-day procedure (Regenexx-SD), his clinic staff isolates the mesenchymal stem cells from a sample of the patient's bone marrow. These cells are then injected back into the patient's treatment area that same day and are combined with the growth factors found in the patient's blood platelets. The goal is to deliver much greater numbers of stem cells to the injured area than the patient's own body could manage.

Among the points of differentiation, the Regenexx procedure doesn't use an automatic bedside centrifuge to prepare cells but uses sophisticated lab procedures that are part of a lab in a medical practice. Second, while some practices add platelet rich plasma to their stem cell concentrate, Centeno's clinic uses a proprietary "super platelet" mix. By mixing highly concentrated lab prepared PRP (platelet rich plasma— slow release growth factors) and platelet lysate (immediately available growth factors), Centeno's lab data shows that the adult stem cells grow many times more than just PRP alone.

184 Patient Follow-up Using Registry Data

Among Dr. Centeno's passions is data. While treating patients with their own cells and growth factor proteins, Centeno is also collecting data. . He employs a full-time clinical research staff and has created proprietary software to help keep track of massive numbers of patients in a registry.

As of mid-March, he and his staff at his Broomfield, Colorado clinic have treated and are tracking approximately 4,300 orthopedic procedures with the Regenexx family of autologous biologic solutions.

On the website for the Centeno/Shultz clinic, Centeno has posted several of his published studies and podium presentations. One such study, which was derived from his clinic's registry is regarding the Regenexx-SD procedure, provides data for 184 patients (73% male, 27% female, average age 50, 25.5 BMI [body mass index]) who've been treated with Regenexx-SD. According to Centeno, the patients who had their moderate to severe knee arthritis treated with Regenexx-SD experienced a mean improvement at 18 months of 56%. Patients who had the most severe arthritis (Kellgren grade 3-4) reported a 29% rate of improvement. More than 90% of patients reported some improve from baseline. Patients with moderately severe arthritis reported the best rate of improvement. How long did the pain relief endure? According to his data, patients at the 18-month period reported greater levels of pain relief than the patients at 3-4 weeks.

Super Concentrated Platelets

One of Centeno's other autologous procedures is a method of super concentrating platelets. Branded Regenexx-SCP, it is a mixture obtained from whole blood that is similar to

platelet rich plasma (PRP) but it is low in red and white blood cells. Centeno claims that his process produces platelet rich plasma that is capable of stimulating more local stem cell growth than that produced by bed side PRP machines. "Most bedside machines that make PRP can concentrate platelets up to five times normal concentrations. However, our data shows that better stem cell growth can be obtained with 10, 20, 30, or even 40x concentrations," said Dr. Centeno. And Regenexx's procedure, according to Centeno, delivers those higher levels.

147 Patient Registry Follow-Up With Regenexx PL-Disc

Regenexx PL-Disc is a procedure that removes the concentrated growth factor proteins from the patient's own platelets and makes them immediately available for injection into the patient. Centeno tested his Regenexx PL-Disc against steroid epidural injections for spine disc treatment. In his study, Centeno injected 147 patients with Regenexx PL-Disc and compared the results with 85 patients who'd been treated with steroid epidural injections.

The average Regenexx PL-Disc patient received an average of 1.25 injections and the average steroid epidural patient received 1.44 injections. Eleven of the steroid epidural patients crossed over to receive the Regenexx PL-Disc treatment. None of the Regenexx patients crossed over to the steroid epidural arm of the study.

According to Centeno's registry, patients who'd received their own growth factors via the Regenexx PL-Disc process reported a significant Functional Rating Index (FRI) score improvement. The FRI index measures the patient's self-reported experience of pain as well as the ability to walk, sit, lift, bend, etc. The 60 patients treated with Regenexx PL-Disc reported substantially better FRI scores (about 4x better) at three months than epidural steroid injections. The pain and function relief remained significant at the six-month level for Regenexx PL-Disc patients.

Centeno and the FDA

Approximately four and a half years ago, the FDA notified Centeno that the autologous cell material he was creating using his Regenexx C (cultured) procedure in his medical practice constituted the manufacturing of a drug. The FDA argued that because one of the solutions used in the process of expanding the patient's cells was shipped via interstate commerce it made his process a "drug" under federal regulations. On that thin reed of an argument, the FDA said in court that Regenexx must only be performed pursuant to a New Drug Application and under the drug factory regulations known as current Good Manufacturing Practices (GMP).

On July 23, 2012, U.S. Federal District Court Judge Rosemary Collyer, in an admittedly close call, sided with the FDA. Regrettably for orthopedists and other doctors, Collyer's decision to side with FDA means that the agency has the ability to apply drug production guidelines meant to apply to the likes of Pfizer and Merck to a physician's practice. For example, as Centeno states, "Applying cGMP manufacturing guidelines to an OR would cost millions per year per operating room and not measurably improve anything".

Practice of Medicine Is an FDA Jurisdiction?

"The interesting thing is that this is the first time FDA has concerned itself in a 'one-off' therapy. The only existing model to compare this to is a five-day blastocyst procedure being performed as part of IVF fertility treatments. IVF fertility treatments are practice of medicine and do not require FDA approval and don't follow drug mass manufacture guidelines and drug approvals; instead it uses guidelines designed for this purpose that were promulgated by the College of American Pathologists. In addition, when asked if this position of applying drug standards to cultured autologous cells made any medical or public health common sense, every big player in the late 1990s said no. . This included everyone from the American Red Cross to multiple big physician organizations," said Dr. Centeno.

This is not the first time this issue was triggered by an FDA action.

Fifteen years ago, in 1997, the FDA proposed a set of regulations (the same ones that Centeno has dealt with) that would classify stem cell transplant procedures as prescription drugs or devices. In August 1998 ASCO (American Society of Clinical Oncology) filed its vehement opposition saying:

> "ASCO objects in the strongest terms to FDA's proposed regulation of stem cell transplants. This misguided proposal is unnecessary, would jeopardize the proper treatment of cancer patients and impede the development of new therapies, would substantially increase the cost of stem cell transplants, and exceeds FDA's legal authority.
>
> Stem cell transplants are medical procedures. Their use is the practice of medicine, not the manufacturing of biologi-

> cal products as FDA asserts. Transplantation procedures and their associated stem cells do not in any way resemble the products that FDA is chartered to regulate."

The Society pointed to bone marrow transplants that have been performed since 1971 and have been standard therapy for certain conditions since the late 1970s.

Centeno has appealed the District Court's ruling. As Lee Buckler, a noted biotechnology industry consultant said recently in his blog about the ruling, "This is a case that was always destined for the appellate courts regardless of which way the initial court ruled." and "This is just the beginning of what will be a long and interesting battle. The ruling was nothing more than the granting of an injunction in response to the government's motion for summary judgment."

Regenexx Network?

Approximately 20 affiliated clinics around the United States are now offering versions of Centeno's Regenexx autologous therapies. One clinic in the Cayman Islands still offers the cultured Regenexx-C procedure.

Centeno's goal is to continue spending on his registry infrastructure and allow the outcome data being collected to do the talking. His Colorado clean room lab is humming with multiple scientists hired by generous private grants. Here mesenchymal stem cells are as rare as water out of the faucet. Their focus is greatly pursuing autologous biologic therapies – one patient at a time. ♦

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