Orthopedics This Week

First Peek at Agili-C's Interim Study Results

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Source: Wikimedia Commons and Guido van Nispen

The independent Endpoint Adjudication Committee (EAC) has completed the first Interim Analysis of the landmark, 250 patient, Agili-C clinical study for treatment of broad spectrum of cartilage defects, including mild to moderate osteoarthritis (OA) of the knee, osteochondral defects and focal cartilage lesions.

The Agili-C IDE [investigational device exemption] study is a multi-center, 2:1 randomized, open-label and controlled study. The primary endpoint is change from baseline to 24 months in the average Overall KOOS score (pain, symptoms, QOL, ADL and Sports).

But, as we detail later in this article, this study stands above other clinical knee studies in the way its patient inclusion and exclusion rules model actual clinical experience with osteoarthritic knees.

The EAC is the first independent body to review the study's interim results and announced in December 2019 that, based on the data so far, the predictive probability of trial success with the current sample size was greater than 95% and therefore there's no need to enroll more patients.

The Landmark Agili-C Study

The Agili-C study, sponsored by Israeli-U.S. based CartiHeal Ltd, and funded by Johnson & Johnson, Bioventus, Elron, Accelmed, Access Medical Ventures, aMoon and Peregrine Ventures is one of the most ambitious and promising cartilage repair studies in history.

The table on page 2 is a comparison of cartilage repair studies BEFORE Agili-C and then the first-of-its-kind Agili-C study—FDA sanctioned. The range of defects is large, just like a typical patient population in any orthopedic clinic.

The age range is huge (21-75 years).

The control arm is, effectively, the current common surgical standard of care, microfracture or debridement—not just microfracture.

The number of defects can be as many as three and malalignment is NOT an exclusion (up to 8°).

"The Agili-C trial is very close to real life," said one of the study's lead investigators Antwerp University's Dr. Peter Verdonk. "Randomization is versus current standard of care—either debridement or microfracture. Which is a major advantage of the Agili-C study."

The randomization allocation ratio is 2:1—for every two patients randomized to the implant, one is randomized to control.

It should be noted that as in previous studies, young patients with small, focal defects but no arthritis, are receiving microfracture. Older patients with large lesions and mild to moderate osteoarthritis are randomized against debridement (small focal defects with KL=0 cannot be treated with debridement).

"We are thrilled to be on the leading-edge of orthopaedic sports medicine and joint preservation," said Dr. Seth Sherman, a sports medicine orthopedic surgeon who was one of the first U.S. surgeons to enroll patients in the Agili-C study.

"In the U.S., there are limited options for off-the-shelf cartilage repair technologies that can be used by sports medicine surgeons in a single surgical procedure. Benefits of this technology include its relative low cost, ease of use, no burned bridges, strong basic science and clinical track record."

"Often in studies like this, we enroll a very strict sub-set of young, active patients with

Seth L. Sherman, M.D.
Courtesy of Stanford School of Medicine

	BEFORE Agili-C	Agili-C[1]
Age of Patients	Usually up to 55	Up to 75
Presence of Osteoarthritis	NO	Yes (mild-moderate)
Number of Lesions	1-2	Up to 3
Type of Defects	Cartilage	Cartilage and ostoechondral
Concomitant Procedures	Not allowed	Allowed: meniscectomy and HTO
Total Defect Size	1-4 cm^2 (usually 2 cm^2)	1-7 cm^2
Previous Failed Cartilage Treatment	Not allowed[3]	Allowed
Control/Comparator:	Microfracture[4]	Microfracture and debridement
Malalignment Exclusion?	Yes[5]	No (up to 8°)
Defect Location:	Single condyle only	1 or 2 condyles, condyle & trochlea, 2 condyles & trochlea

[1] https://clinicaltrials.gov/ct2/show/record/NCT03299959?term=cartilage&cond=knee+arthritis&cntry=US&draw=2&rank=48&view=record

[2] https://www.ncbi.nlm.nih.gov/pubmed/22637204?dopt=Abstract

[3] ibid

[4] Crawford DC, DeBerardino TM, Williams RJ 3rd. NeoCart, an autologous cartilage tissue implant, compared with microfracture for treatment of distal femoral cartilage lesions: an FDA phase-II prospective, randomized clinical trial after two years. *J Bone Joint Surg Am*. 2012 Jun 6;94(11):979-89. doi: 10.2106/*JBJS*.K.00533.

[5] ibid

a single isolated cartilage defect," continued Dr. Sherman. "In reality, that's not the typical patient we see every day in clinic."

"This study and this implant are different because they are both indicated for a wide range of situations including patients with multiple cartilage defects and even those with mild-moderate osteoarthritis. We can use Agili-C in study patients who are in their 20s or those who are in their 60s. This versatility allows us to consider more patients who may benefit from this procedure."

The Agili-C study is a prospective, multicenter, open-label, randomized, and controlled, with adaptive sample size. Its primary endpoint is to show superiority of the Agili-C implant over the current Surgical Standard of Care: microfracture and debridement in the treatment of wide range of joint surface lesions.

Enrollees are evaluated at 2 weeks after treatment, then again at 3, 6, 12, 18 and 24 months.

Investigators are using KOOS, IKDC Knee Examination Form 2000, IKDC Subjective Knee Evaluation, SF-12 Health Survey, Tegner Activity Score, Anterior-Posterior (A/P) and Lateral knee X-rays and MRI's to conduct their evaluations.

If the final results will indeed show clear superiority over microfracture and debridement for the treatment of joint surface knee lesions it will truly be a landmark event.

Why This Study Is so Important

A 1994 article in the *New England Journal of Medicine* ("Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation" by Brittberg M, Lindahl A, Nilsson A, Ohlsson C, Isaksson O, Peterson L.) effectively launched cartilage repair in the United States.

One year later Boston-based Genzyme Corporation took the autologous chondrocyte transplantation (ACI) technology described in the *NEJM* article and created a cartilage repair product and process named Carticel.

Two years ***after that***, the FDA granted Genzyme a license for Carticel. It was the first time the FDA had licensed/approved or cleared a living cell technology for commercial sale.

Jump ahead 25 years, and after more than 1 million annual cartilage treatment procedures in the U.S., including 430,000 debridement procedures and 220,000 microfracture surgeries (source: *SmartTRAK.net - Cartilage Replacement – U.S.*, January 3, 2019), cartilage repair remains more a hope than a standard of care.

Carticel along with another ACI treatment, MACI (autologous cultured chondrocytes on porcine collagen membrane), are the most popular cartilage repair technologies in the United States. Those treatments (along with a related technology for wound repair—Epicel) generate about $40-45 million in annual product sales.

Other cartilage repair products that were also developed include Zimmer's DeNovo-NT, plug-type scaffolds for arthroscopic delivery like Dunlop Corp's carbon fiber plug or Smith & Nephew's True-Fit plug, Tigenex's Chondromimetic implant and Histogenic's NeoCart (collagen scaffold with autologous living cells).

Even so, within the overall market to treat deteriorating knees, cartilage repair product sales barely register.

In terms of dollars ($7 billion), knee replacement surgery is the principal treatment modality for patients suffering from end-stage osteoarthritis. Hospitals, physicians, suppliers and payers understand that that is the bread and butter of the industry.

A quick perusal of American Academy of Orthopaedic Surgeons' (AAOS) clinical practice guidelines for osteoarthritis of the knee finds a whole range of pre-knee replacement therapies including NSAIDs, cortisone shots, platelet rich plasma injections and osteotomies.

But no technologies for cartilage repair or regeneration.

What Is Agili-C and How Is It Implanted?

The Agili-C is a biocompatible and biodegradable tapered-shaped solid implant. It is manufactured from aragonite (calcium-carbonate), derived from sea coral. When implanted into a pre-prepared osteochondral hole it acts as a 3D scaffold that potentially supports and promotes the regeneration of the articular cartilage and its underlying subchondral bone.

In previously published animal studies, Agili-C demonstrated the ability to regenerate hyaline cartilage—as confirmed by the presence of Type II collagen and proteoglycans, and the absence of Type I collagen—without relying on growth factors, or external stem cells.

One of the key attributes of Agili-C's 3D scaffold is its interconnected porosity which maximizes cell contact and promotes matrix deposition.

The implant looks like this:

"Basically, what CartiHeal designed with the Agili-C is an implant with ideal porosity that enables simultaneous regeneration of the articular cartilage and remodeling of the subchondral bone," explained Prof. Verdonk.

Implanting Agili-C, says Prof. Verdonk, is surprisingly simple. "The procedure to implant Agili-C is very close to what the orthopedic surgeon is used to, i.e., drill the hole, place the implant and push it in. Very user-friendly procedure. Only few minutes per implantation."

Stay tuned, for sure. ♦

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