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CORR Insights®: Hyaluronic Acid-based Hydrogel Coating Does Not Affect Bone Apposition at the Implant Surface in a Rabbit Model

Ryan McLemore PhD

Where Are We Now?

The National Hospital Discharge Survey documented more than 1 million primary and revision hip and knee procedures in 2009 [5] and those numbers are projected to grow over the next decade [6]. Approximately 1% to 2% of primary arthroplasties develop a surgical site infection (SSI) [1, 2], and the risk of infection is much higher in patients who undergo revision arthroplasty due

to trauma. The prevention and treatment of deep/organ space infections around prosthetic joints remains an area of concern among orthopaedic surgeons.

While a variety of approaches involving premade antibiotic-containing spacers, beads, and synthetic materials are used to treat patients with prosthetic joint infections, these approaches must be used in concert with intravenous antibiotics to achieve clinical effectiveness. The Minimum Biofilm Eradication Concentration can be 100 to 1000 times the Minimum Inhibitory Concentration necessary to control planktonic bacteria with antimicrobials, and requires exposure times on the order of 24 to 48 hours at those concentrations.

One strategy for preventing infection is to protect the surface of implants so that bacteria cannot attach. There have been “race to the surface” paradigms, where low-dose antimicrobial cement is thought to protect the surrounding implant from bacterial colonization. A number of other techniques have also been tried, or are in development, including chemically bonding antimicrobials to the surface of the implant (vancomycin-bone) [10], silver and gold nanoparticles to create antibacterial microcurrent, and poly(lactic-co-glycolic acid) coatings [4] (among others). Most of these approaches require considerable modification to the implant-manufacturing process, are damaged by scratches or rough handling, and would add substantial cost and difficulty to the use of devices in orthopaedic surgery. Several groups, including my own, [7, 8] have advanced the idea of hydrogel-based, high-dose delivery for antimicrobials. These hydrogels are intended to be space filling, provide different amounts of chemical release, and

This CORR Insights® is a commentary on the article “Hyaluronic Acid-based Hydrogel Coating Does Not Affect Bone Apposition at the Implant Surface in a Rabbit Model” by Boot and colleagues available at: DOI: 10.1007/s11999-017-5310-0.

The author (RM) has stock ownership in Sonoran Biosciences (Scottsdale, AZ, USA). All ICMJE Conflict of Interest Forms for authors and *Clinical Orthopaedics and Related Research*® editors and board members are on file with the publication and can be viewed on request.

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This *CORR Insights*® comment refers to the article available at DOI: 10.1007/s11999-017-5310-0.

R. McLemore PhD (✉)
Leidos Inc, 5202 Presidents Court,
Frederick, MD 21703, USA
e-mail: ryan.mclemore@gmail.com

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degrade or dissolve once their payload has been delivered. Ideally, the gels would be compatible with any implant design and procedure, and could be widely used in orthopaedic surgery, plastic surgery, and other disciplines to prevent SSIs.

Where Do We Need to Go?

To my knowledge, no similar products currently have FDA approval, and the development of a hydrogel-delivery system will require extensive safety and efficacy trials. These trials should treat active infections in order to have an infection rate high enough to demonstrate statistical significance for efficacy. Since the underlying risk of infection in most elective orthopaedic procedures is relatively low, the trials will likely require multiple referral and treatment centers. What this all adds up to is a major cost for investors in this technology, and no guarantee that the investment will turn a profit. A first step towards decreasing investor risk and attracting financial supporters involves showing that the degradation of the material does not interfere with the normal healing of bone. Such evidence is critical if the technology is to be seen as a viable application alongside plates, screws, intramedullary nails, or press-fit hip and knee components. The hydrogels are likely to be

regulated as drugs rather than devices, and each formulation will, initially, have to be individually FDA approved. The current work shows that the gel does not impair healing chemically, nor evaluates the gel in an environment where the implant is providing structural support; (ie, there is no potential for instability with implant slippage or failure, and minimal mechanical loading on the implant). Eventually, the technologies should be demonstrated in small-animal infection and bone-healing models, which do not incorporate instability, followed by large animal bone-healing studies that incorporate instability, similar to a true human knee or hip replacement. Successful completion of these animal studies will provide data that could potentially increase investment in the development of these technologies and may also provide preliminary data for large grants to funding agencies to help offset the costs of pivotal clinical trials necessary for technology approval.

How Do We Get There?

The current study represents an effort to embark on the animal data necessary to attract investment and begin to organize pivotal drug trials. Emerging technologies will need to team either with venture capital sources,

established corporations, or other players in the field to finance long-term studies of these technologies before they reach the clinic. The current study was performed in the Netherlands, and cited work on the Disposable Antibacterial Coating, which appears to be proceeding through the European novel drug approval process. This work should help to make the field more aware of the topic, and may help with building referral networks and recruiting eventual clinical champions for development trials. Showing infection management in a large animal surgical model with instability will help to catalyze investment in this and similar technologies so that one or more can make their way to the market and begin helping patients. If these technologies are as effective as their originators think they will be, they have the potential to considerably reduce the cost and burden associated with SSIs, and majorly reduce the resultant patient mortality and morbidity. The next key and critical step is finding a funding partner that believes in this technology enough to propel it through the long regulatory pathway ahead.

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