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CORR Insights®: Local Gentamicin Delivery From Resorbable Viscous Hydrogels Is Therapeutically Effective

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Where Are We Now?

Orthopaedic infection can be a devastating consequence of traumatic injuries and surgical interventions, including prosthetic joint replacements and revisions [9]. The risk of persistent, recurrent, or

new infection in revision total joint arthroplasty may be as high as 20% when the indication for revision is infection [4]. Attachment of bacteria or fungi to implants to form biofilm presents a tremendous challenge to clinical treatment, particularly when polymicrobial contamination is present [8]. Due to the senescent phenotypic state of biofilm microorganisms, as well as to the secretion of protective mucopolysaccharide matrices, biofilm microorganisms evade common microbicidal strategies. These are only eradicated by antibiotic concentrations 100 to 1000 times the minimum inhibitory concentration for planktonic microorganisms [7], and because of this, at present, most of these infections are treated by removal of the infected implant followed by aggressive débridement of necrotic tissue. In most cases, systemic antibiotic

delivery to poorly vascularized orthopaedic injuries cannot achieve concentrations high enough to treat biofilm infection, so local drug delivery strategies have become essential in the treatment of these challenging infections. Commonly used clinically local delivery strategies vary from antibiotic-loaded bone cement [10], antibiotic-loaded calcium-based beads [6], resorbable polymer delivery systems [5], to simply sprinkling powdered antibiotics into the surgical site [3]. There are no ideal local delivery systems for antibiotics, as many of these common clinical delivery systems have inadequate or uncharacterized release patterns, poor degradation profile, or biocompatibility issues.

Where Do We Need To Go?

Local delivery systems for antibiotics must be improved in order to increase clinical success. In the current study, Overstreet and colleagues conducted preliminary evaluations of an injectable, temperature-sensitive gel loaded

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with antibiotics. The gentamicin-loaded drug delivery system is designed to overcome the limitations of previously mentioned antibiotic delivery systems of poor release and inadequate wound coverage. This liquid delivery system forms a viscous gel that is retained at the injection site to release antibiotic through the course of 3 days to 5 days, and then is completely resorbed as hydrolysis occurs through 4 weeks. This approach offers advantages of defect site coverage that bead or powder based systems cannot provide. Additionally, the complete resorption of the viscous hydrogels prevents the delivery vehicle itself from becoming a nidus for infection. In this study, the aminoglycoside gentamicin was chosen as the antimicrobial for delivery, since it has broad-spectrum activity as well as demonstrated efficacy in combating biofilm when released locally in contaminated tissue. The preliminary release and toxicity studies demonstrate that gentamicin levels are released at high enough concentrations to eradicate biofilm infections with transient indicators of toxicity evident only when high volumes of antibiotic-loaded hydrogels, and thus high total doses of gentamicin, are delivered to the tissue. In large tissue defects, the volume of delivery vehicle required for complete coverage of contaminated tissue may be high.

Total dose may need to be controlled to minimize the risk of systemic levels of antibiotic reaching toxic levels.

How Do We Get There?

After proving efficacy in this small animal model of implant-associated biofilm infection, demonstration of clinical efficacy and biocompatibility in Phase I clinical trials should follow. While loading the antibiotic gentamicin singly into this novel hydrogel system provided a reliable antibiofilm effect, as well as a regulatory pathway for initial clinical translation, future modifications could improve biofilm targeting while minimizing toxicity. Newly approved and next generation antibiotics under development, such as ceftaroline, have broad-spectrum activity and may also be effective when released locally from this type of vehicle [1]. Additionally, local delivery of a combination of antibiotics with other antimicrobials or with molecules that specifically target biofilm could provide synergism against pathogenic polymicrobial biofilm [2]. This hydrogel platform may allow for adaptation to accommodate different antimicrobials at the clinician's discretion to meet individual patient needs.

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