Emerging Ideas

Can Erythromycin Reduce the Risk of Aseptic Loosening?

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Abstract

Background Persistent inflammatory reaction to wear debris causes periprosthetic osteolysis and loosening. Some authors have advocated pharmaceutical approaches to reduce the inflammatory reaction. Erythromycin has anti-inflammatory effects independent of its antimicrobial properties. Although oral erythromycin reportedly inhibits periprosthetic tissue inflammation in patients with aseptic loosening, long-term systematic erythromycin treatment is not recommended owing to its side effects. Therefore, it would be advantageous to restrict erythromycin delivery to the inflammatory periprosthetic tissue without causing side effects.

Questions/hypotheses Erythromycin eluted from hydroxyapatite-coated titanium (Ti) pins inhibits periprosthetic tissue inflammation and osteolysis.

Method of study We propose restricting erythromycin delivery to the inflammatory periprosthetic site. A previously described rat model of ultrahigh molecular weight polyethylene (UHMWPE) particle-induced periprosthetic

tissue inflammation and osteolysis will be used to test the effect of local delivery of erythromycin via Peri-Apatite™-coated Ti implants. The outcome measures will include bone ingrowth (μ CT), implant stability (pullout test), and histologic analysis of periprosthetic tissues.

Significance Pharmacologic intervention aimed at slowing, preventing, or reversing the aseptic loosening process would represent an advance in the management of joint replacement. Erythromycin may be appropriate for prophylactically treating patients who have repeated revision surgery and/or show early signs of progressive osteolysis after arthroplasty.

Questions/Hypotheses

Erythromycin eluted from PA-coated titanium pins inhibits periprosthetic tissue inflammation and osteolysis in a rat model of revision arthroplasty.

Background

Aseptic loosening of joint implants occurs for many reasons [40]. There is compelling evidence that the most important factor in late periprosthetic osteolysis is a persistent inflammatory reaction to wear debris [47]. Inhibiting periprosthetic inflammation through pharmaceutical intervention is one approach to limiting osteolysis [5, 27, 35]. There are numerous commercially available antiinflammatory drugs, such as NSAIDs, cyclooxygenase (COX) inhibitors [11, 20, 24, 43, 46], antagonists of TNF and IL-1 (eg, etanercept, infliximab, and anakinra) [5, 34, 36], and RANKL inhibitor [6, 39]. However, for long-term use, all of these drugs have major side effects, most notably

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the antianabolic effects of NSAIDs and COX-2 inhibitors, and the immunosuppressive effects of all of these antiinflammatory drugs.

Bisphosphonates are currently the most important and effective class of antiresorptive drugs by induction of osteoclast apoptosis [33]. Several clinical trials [19, 45, 49] document the ineffectiveness of bisphosphonates for treating rheumatoid arthritis, an autoimmune disease associated with inflammatory bone loss. Despite broad off-label use of bisphosphonates in patients with periprosthetic osteolysis, successful treatment has yet to be reported. This lack of efficacy in conditions of inflammatory bone loss has been ascribed to the antiapoptotic inflammatory signals that render osteoclasts insensitive to bisphosphonate-induced apoptosis [49].

Erythromycin has antiinflammatory effects in addition to those as an antibiotic [3, 10]. Two studies reported successful treatment of diffuse panbronchiolitis with erythromycin (DPB) [16, 17]. There are reasons to believe erythromycin might be used to limit periprosthetic inflammatory reactions from wear debris. First, erythromycin reportedly inhibits wear debris-induced osteoclastogenesis by inhibition of NF- κ B activity in a RAW264.7 macrophage cell line and mouse bone marrow progenitor cells [30]. Second, erythromycin inhibits wear debris-induced inflammatory osteolysis in a murine osteolysis model [31]. Third, oral erythromycin (600 mg/day) reportedly reduced periprosthetic tissue inflammation in a group of 32 patients with aseptic loosening who were candidates for surgical revision [29].

However, long-term systemic use of erythromycin raises concerns about various side effects, including bacterial resistance, hepatotoxicity, and gastrointestinal discomfort. Local delivery systems might provide adequate doses to reduce inflammation without such side effects.

Proposed Program

We propose restricting erythromycin delivery to the inflammatory periprosthetic site using a rat model of revision orthopaedic implantation [32]. Animal models for studies of aseptic loosening typically involve the use of large animals such as dogs, sheep, and rabbits [4, 8, 9, 12, 26]. Although these models have the advantages of large bone/joint size and the ability to use a realistic prosthetic implant, the cost and ethical issues prevent broad use of large animals. Therefore, we have developed a rat model of revision orthopaedic implantation based on previous models [2, 21]. This rat model represents a long-term prosthesis failure model. It has an orthotropic weight-bearing implant and realistic wear debris for at least 2 months. Considering the normal rat lifespan of 2 to

3 years, 2 months may be equivalent to approximately 5 years of human life, comparable to the clinical long-term progress of aseptic loosening.

We will coat a Ti pin (diameter, 1 mm; length, 10 mm; with a flat head) with 30 to 50 μ m hydroxyapatite (Peri-Apatite™, (PA); Stryker Orthopaedics, Mahwah, NJ, USA). PA is a pH-controlled solution precipitated hydroxyapatite coating that enhances bone ingrowth and bony apposition [50, 51]. In previous studies the intra-articular injections of UHMWPE particles appeared to simulate implant wear and initiated the process of periprosthetic tissue inflammation and osteolysis [2, 32] similar to that seen around loose implants in the clinical setting [1, 14, 23]. Revision surgeries will be performed 2 months after the index surgery (local inflammatory osteolysis developed after UHMWPE stimulation). The previously implanted pins will be removed and replaced with new PA-coated Ti pins with and without erythromycin loading. A group of rats treated with zoledronate will be included for comparison [37, 41]. MicroCT (μ CT) scans will be performed immediately after the revision surgery to provide baseline information regarding periprosthetic bone volume. Rats will be sacrificed 6 weeks after revision surgery. The drug efficacy will be evaluated by bone ingrowth (μ CT), implant stability (pullout test), and histologic and molecular profiles of periprosthetic tissues.

We expect the PA-erythromycin composite, at current drug-loading capacity and drug-release kinetics [32], will reduce the growth of the inflammatory interface membrane and inhibit osteoclastogenesis and osteolysis. Studies suggest local bisphosphonate (such as zoledronate) delivery improves implant fixation [25, 37, 42]. Our proposed study will compare the drug efficacy of erythromycin (antiinflammatory) with that of zoledronate (induction of osteoclast apoptosis), given their distinctive action mechanisms. It is our expectation that erythromycin is superior to zoledronate in improving UHMWPE particle-induced tissue inflammation and enhancing implant fixation.

Limitations

The rat model of revision arthroplasty provides a reliable and long-term system in which to study drug effects on wear debris-induced periprosthetic tissue inflammation and bone loss [32]. Considering the normal rat life span of 2 to 3 years, 2 months may be equivalent to approximately 5 years of human life, comparable to the clinical long-term progress of aseptic loosening. However, the limitations of the lack of Haversian systems and small bone size of rats should be considered [44]. Another major concern is that the erythromycin efficacy may not last through the entire designed study period (6 weeks) because of the burst drug

Fig. 1A–B Structure comparisons of (A) erythromycin and (B) ABT-229 are shown. Compared with erythromycin, ABT-229 contains an (1) enol configuration and (2) lacks hydroxyls on the 14-member lactone ring, and (3) on the cladinose [4''] sugar. In addition (4), a methyl of the N-dimethyl amino group of the desosamine sugar has been replaced by an ethyl.

release, occurring during the initial hours of the PA-coated prosthesis [32, 38, 50, 51]. More efforts are needed to fabricate a PA coating surface that will allow us to deliver erythromycin or other antiinflammatory drugs to the periprosthetic tissue in a sustained and controllable manner.

Next Steps

More efforts are needed to address several practical issues before the erythromycin treatment can be used to halt or even reverse the progress of aseptic loosening before development of extensive osteolysis. To avoid erythromycin-induced side effects, one alternative approach is to develop structural analog(s) of erythromycin that preserve the biologic activities of erythromycin but lose its antimicrobial activity. ABT-229 (8,9-anhydro-40-deoxy-39-*N*-desmethyl-39-*N*-ethylerythromycin B-6,9-hemiacetal) is a synthetic derivative of erythromycin that is completely devoid of antimicrobial activities [7] (Fig. 1). Additional efforts are needed to determine whether ABT229 is a safer and more specific osteoclast antagonist for treatment of pathologic bone loss, including aseptic loosening.

We need to develop reliable and quantifiable outcome measure(s) for evaluation of erythromycin effects on periprosthetic tissue inflammation. A macrophage-specific PK11195 (isoquinoline carboxamide) positron emission tomography (PET) technology has been established [18]. PK11195 is a synthetic compound that binds to the peripheral benzodiazepine receptor (PBR), which is abundantly present in macrophages [22, 48]. PK 11195 has been labeled with ^{11}C for PET and successfully used in humans to monitor macrophage accumulation in the brain [13, 15, 28, 48]. Our proposed study will determine whether repeated ^{11}C -PK11195 PET scans provide a quantitative outcome measure of PA-erythromycin composite efficacy by real time observation of periprosthetic membrane macrophage kinetics in a rat model of revision orthopaedic implantation.

Vision of the Future

Pharmacologic intervention aimed at slowing, preventing, or reversing the aseptic loosening process would provide another important tool for treating arthroplasty. Local delivery of erythromycin might provide one approach for patients who might need repeat revision surgery, and/or show early signs of progressive osteolysis after arthroplasty, because of its clinical value, effectiveness, simplicity, and good compliance. Such an approach might not only improve the quality of life for patients with aseptic loosening, but also reduce costs.

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