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SYMPOSIUM: ABJS CARL T. BRIGHTON WORKSHOP ON IMPLANT WEAR AND TRIBOCORROSION OF TOTAL JOINT REPLACEMENTS

Are Biologic Treatments a Potential Approach to Wear- and Corrosion-related Problems?

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Abstract

Where Are We Now? Biological treatments, defined as any nonsurgical intervention whose primary mechanism of action is reducing the host response to wear and/or corrosion products, have long been postulated as solutions for osteolysis and aseptic loosening of total joint arthroplasties. Despite extensive research on drugs that target the inflammatory, osteoclastic, and osteogenic responses to wear debris, no biological treatment has emerged as an approved therapy. We review the extensive preclinical research and modest clinical research to date, which has led to the central conclusion that the osteoclast is the primary target. We also allude to the significant changes in health care, unabated safety concerns about chronic immunosuppressive/antiinflammatory therapies, industry's complete lack of interest in developing an intervention for this condition, and the practical issues that have narrowly focused the possibilities for a biologic treatment for wear debris-induced osteolysis.

Where Do We Need to Go? Based on the conclusions from research, and the economic, regulatory, and practical issues that limit the future directions toward the development of a biologic treatment, there are a few rational approaches that warrant investigation. These largely focus on FDA-approved osteoporosis therapies that target the osteoclast (bisphosphonates and anti-RANK ligand) and recombinant parathyroid hormone (teriparatide) prophylactic treatment to increase osseous integration of the prosthesis to overcome high-risk susceptibility to aseptic loosening. The other roadblock that must be overcome if there is to be an approved biologic therapy to prevent the progression of periprosthetic osteolysis and aseptic loosening is the development of radiological measures that can quantify a significant drug effect in a randomized, placebo-controlled clinical trial. We review the progress of volumetric quantification of osteolysis in animal studies and clinical pilots.

How Do We Get There? Accepting the aforementioned rigid boundaries, we describe the emergence of repurposing FDA-approved drugs for new indications and public (National Institutes of Health, FDA, Centers for Disease Control and Prevention) and private (universities and drug and device manufactures) partnerships as the future roadmap for clinical translation. In the case of biologic treatments for wear debris-induced osteolysis, this will

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involve combined federal and industry funding of multicenter clinical trials that will be run by thought leaders at large medical centers.

Introduction

Aseptic loosening secondary to osteolysis induced by wear debris and/or metal ions remains a major limitation of total joint arthroplasty. Although the full impact of ions on implant longevity remains to be clarified, the overall biologic basis for the pathophysiology of wear debris has been studied in detail [33]. Based on in vitro and in vivo studies, there are three distinct cellular pathways that serve as potential targets for biologic therapy: (1) immune cells that mediate the inflammatory response to wear debris; (2) osteoclasts that mediate the bone resorption to wear debris; and (3) osteoblasts and osteocytes whose anabolic function is inhibited by wear debris resulting in uncoupled bone remodeling that leads to osteolysis [51]. Although these pathways are clearly established, the efficacy of currently available treatment modalities needs to be evaluated and compared with possible new interventional approaches that might quell the biologic responses.

For purposes of this review, we defined a biologic treatment as any nonsurgical intervention whose primary mechanism of action is reducing the host response to wear and/or corrosion products, which have long been postulated as solutions for osteolysis and aseptic loosening of total joint arthroplasties (TJAs). Our systematic literature review revealed that biologic treatment for wear and corrosion problems involves not only protein biologics, but also small-molecule chemical agents acting as mediators of biologic processes. As a class, biologics are recombinant proteins that emerged for the most part to treat inflammatory reactions associated with rheumatoid arthritis. The biologics were targeted to act on either immune T and B cells or cytokines having key roles in joint pain, deformity, and destruction [20]. The primary cytokines included tumor necrosis factor (TNF), interleukin (IL)-1, and IL-6. Biologic agents to directly counter inflammation include soluble receptors as competitive decoys, direct receptor antagonists, and monoclonal antibodies to target either cellular receptors and/or other costimulatory integral membrane proteins [41]. Another class of biologics includes the antiinflammatory cytokines [46].

The rationale underlying this review is that in the intervening 6 years since this topic was carefully considered in the context of an international symposium [38], important changes have been implemented with respect to TJA. These changes include improved biomaterial processing, implant design, surgical techniques, patient expectations, and a basic knowledge of pathogenic mechanisms that impact periprosthetic loosening and the surrounding dense connective tissues and bone. However, despite better outcomes accompanying these engineering and biological advances, osteolysis secondary to wear and corrosion continues to be a limitation to overall perfect success. Therefore, in this review, we sought to examine what features of biological treatment might yet deserve future attention to ultimately achieve this goal in arthroplasty. To this end, we performed a literature review to assess the potential of biologic treatments to resolve wear- and corrosion-related problems, focusing in particular on the current state of biological treatments of wear products and metal ions in arthroplasty, the preclinical evidence in support of these treatments, and promising therapeutic avenues that may emerge in the next decade.

Search Strategy and Criteria

We built a search strategy based on an exploration of the history of various therapeutic interventions as they have been developed and applied for inflammatory reactions associated with osteolysis induced by wear and corrosion products (Appendix 1 [Supplemental materials are available with the online version of CORR®.]). The initial part of the search included a review of the Cochrane Library using the keywords biologic treatment. The search yielded 152 records selected from 8106 records. Further restricting the search to TNF antibody led to a comprehensive report on adverse effects associated with FDA-approved biologics used in treating inflammatory disorders [49]. A second search focused on PubMed publications related to bone loss, particles, corrosion, and periprosthetic inflammation. This search yielded 120 papers for further review and selection. The results of this search prompted a third search of chemical agents such as the bisphosphonates. This search yielded a total of 48 papers for review with restrictions to arthroplasty and particle-induced osteolysis. A fourth search was added to determine recent reports of biologic interventions in animal models of osteolysis, which returned 384 records. Restricting this search to particle-induced osteolysis yielded 35 papers for evaluation with respect to strength of data, experimental design, and efficacy of treatment. Finally, a search of clinicaltrials.gov showed a total of seven relevant studies, three active and one enrolling patients. In addressing our questions, the literature search revealed a spectrum of medicines, classified as biologics, chemicals, hormones, vitamins, vaccines, and toxins, that might selectively reduce wear debris-mediated bone loss.

Where Are We Now?

Currently, emerging information about the risk for adverse events raises a question regarding the attractiveness of biologics for treating wear and corrosion product-dependent inflammation. Unlike other inflammatory conditions, the benefits may not outweigh potentially harmful effects. To this end, a recent review presenting risk estimates associated with selected biologic agents has been published as a network meta-analysis and Cochrane overview [43]. The Cochrane overview characterized data regarding nine biologics including TNF inhibitors, an IL antagonist, IL-6 antagonists, and anti-CD28 and anti-B cell therapy. The methods included reviews of randomized controlled trials, controlled clinical trials, and any open-label extension study in which any one of the biologics was applied in patients for any disease condition except HIV. The TNF inhibitors included adalimumab, certolizumab, etanercept, golimumab, and infliximab. Other antagonists included anakinra, tocilizumab, abatacept, and rituximab. The results of the overview confirmed that this group of biologics exhibited an increase in total adverse effects and in treatment withdrawals resulting from adverse events. In addition, the biologics were associated with higher rates of serious opportunistic and bacterial infections, including reactivation of tuberculosis.

In contrast to protein-based biologics, organic compounds, known as small-molecule drugs, were identified by review of current clinical trials as agents to intercede in common pathways for bone loss or formation [8, 52]. The most prominent agents include the two forms of bisphosphonates, either nitrogen-containing or simple [37]. The simple bisphosphonates, tiludronate, chlodronate, and etidronate, intercede by deposition within the mineralized matrix making it less susceptible to resorption. Candidate nitrogen-containing molecules are also deposited in the matrix but act through an enzymatic action. The nitrogen-containing bisphosphonates currently approved by the FDA for prevention and/or treatment of osteoporosis include alendronate, ibandronate, residronate, and zoledronic acid.

Alendronate was the first of the nitrogen-containing bisphosphonate drugs to gain FDA approval [56]. Because of widespread use, followup data from greater than 10 years substantiate the efficacy of multiple bisphosphonates in decreasing bone resorption. In 2003, a study documented that administration of alendronate together with calcium supplementation reduced periprosthetic bone loss around cemented hip implants at 2 years' followup [53]. The study in patients was carried out based on in vitro studies documenting that alendronate had an inhibiting effect on particle-induced osteolysis and a single in vivo study demonstrating prevention of bone loss for noncemented THA. Between 2002 and 2004, multiple studies were published supporting efficacy of alendronate in preventing loss of bone mineral density in both the knee and hip. In 2005, Bhandari et al. [6] published a meta-analysis examining five complete papers and one abstract representing a total of 290 patients. Their results showed that less periprosthetic bone loss occurred in bisphosphonate-treated patients when compared with control patients at 3, 6, and 12 months. Without data showing important effects on clinical outcome, a potential beneficial effect of bisphosphonates on periprosthetic bone after TJA was viewed with reservation [45]. From 2006 to the present, multiple studies established efficacy of oral alendronate on bone mineral density around the knee and the hip [1, 15, 18, 32, 47]. These studies generally related to loss of bone resulting from mechanics and not osteolysis.

In 2010, a study showed that administration of alendronate with calcium daily for 6 months decreased bone loss in the proximal part of the femur [49]. However, at the same time, a study showed that, in patients with previously established aseptic osteolysis, administration of alendronate at a dose of 70 mg once weekly for 8 weeks had no effect on inflammatory cytokine proteins and mRNA in the pseudomembrane. Effects of bisphosphonates on bone density after TJA have been extended to other antiresorptive molecules such as risedronate and zoledronic acid. Risedronate, taken weekly for 6 months after TJA, reduced periprosthetic bone resorption around an uncemented femoral stem up to 1 year after surgery [44]. A randomized double-blind controlled trial testing the effect of a single infusion of zoledronic acid on early implant migration after THA showed that bisphosphonate treatment minimized migration of acetabular cups in both the transverse and vertical directions [40]. With respect to clinical outcomes in this study, the Harris hip score increased over time in both the treatment and control groups, but the improved score was more pronounced in the group treated with zoledronic acid than in the control group. The current appraisal of bisphosphonates to prevent loosening remains under study and different modes of administration are being studied in three ongoing clinical trials, as documented by FDA-approved clinical trials [23, 48].

With respect to animal models, the addition of particles to rats and rabbits represented studies that examine biologic effects on cortical bone challenged with different types of particles [52]. In the rat model, osteolysis was induced when titanium pins were implanted in the femoral canal with UHMWPE particles. After 2 months, the animals were treated with erythromycin, and after a treatment period, the percent bone volume was higher and osteolysis was decreased [36]. In a similar study, addition of lipopolysaccharide-coated polyethylene particles and addition of an antibody to sclerostin, an osteocyte-secreted molecule that interacts with LRP5/6 at the cell membrane, suppresses

the Wnt signaling pathway [23]. Recent studies of osteolysis in the rabbit, a model that permits addition of particles into the medullary canal and analysis of cortical bone resorption, show that diverse treatment modalities inhibit bone turnover [30, 34, 61, 62].

To date, the largest number of studies evaluating biologic and other agents that show efficacy in an animal model of osteolysis have used a mouse calvaria model [21, 24]. These studies can be divided into two classes based on systemic treatment or locally applied treatment. Systemic agents applied to intercede in particle-dependent bone resorption include a spectrum of different agents targeting multiple cellular pathways that alter macrophage, osteoblast, and osteoclast metabolism [16, 58]. These agents include estrogen receptor antagonist to block TNF production and luteolin to inhibit TNF, both agents reducing osteolysis [29, 42]. Intraperitoneal application of the antibiotic tetracycline as an inhibitor of matrix metalloproteinase-9 decreased RANKL production [10]. Application of the p38 mitogen-activated protein (MAP) kinase inhibitor SB203580 decreased osteolysis [9]. An agonist for the adenosine A2A receptor decreased osteolysis [28]. The protease inhibitor bortezomib decreased osteolysis and importantly decreased formation of vascularized granulomatous tissue [25, 26]. Addition of other agents, including berberine, captropril, dynastat, and N-acetyl-L-cysteine, decreased particle-dependent inflammation and associated osteolysis [14, 16, 60, 61]. In studies taking advantage of knockout mutations, protein replacement of calcitonin and IL-6 increased bone and decreased inflammation, respectively, in calcitonin-negative and IL-6-negative animals [11, 19]. The mouse model of osteolysis also allowed agents to be tested locally at the site of the applied particles. Two agents, an antisense oligonucleotide and micro-RNA, were tested for effects on TNF and vascular endothelial growth factor gene expression, respectively, and a third agent, a short interfering RNA, was tested to prevent BMPR1b expression [13, 54, 59]. Other locally applied agents included erythromycin and inhibitors of the MAP kinase and the NFATc1 pathways [27, 57]. One local treatment tested effects of adding an antioxidant into the UHMWPE to decrease the reactivity of the particles and prevent osteolysis [17]. Two approaches applied the antiinflammatory cytokine IL-4 alone or in combination with IL-13 to the site of particle addition [55]. Addition of IL-4 at the time of addition of particles in a subcutaneous model showed that bone thickness was improved and that TNF and RANKL expression was decreased [35]. In addition, the type of macrophage localized at the site of particle deposition was shifted to an M2 profile from an M1 profile.

Where Do We Need to Go?

The remarkable advances in drug development for the treatment of joint inflammation and bone erosion that occur in patients with rheumatoid arthritis suggest that they have potential as interventions in wear- and corrosion-related problems as well. However, when considering the well-established side effects of biologics that target the adaptive and innate immune response (ie, opportunistic infections and cancer) [43] and the high costs of these treatments (~USD 15,000/year for anti-TNF therapy) [4], we do not see how the potential benefits can be justified. We used two criteria to define therapies that have a realistic potential to become established biologic therapies. The first criteria were restrictive for drugs whose mechanism of action has been formally established to specifically target the increased bone resorption and decrease bone formation responsible for periprosthetic osteolysis in rigorous preclinical and clinical studies. The rationale for this restriction is based on high efficacy requirements. The second criteria were restrictive to FDA-approved drugs for osteoporosis therapy whose effects on the progression of periprosthetic osteolysis can be evaluated in on-label observational clinical studies of patients with wear problems that are also being treated for their high risk of osteoporotic fracture as indicated by the product label. The requirement for this second criteria is addressing the reality that there are no economic models to posit a return of investment over the "Valley of Death" costs in time (~12 years) and money (~USD 800 million) necessary to obtain an FDA-approved indication for periprosthetic osteolysis and the absence of any progress to this end after the publication of the first prospective, double-blind, placebo-controlled clinical pilot of a biologic therapy [39]. Finally, we defined the leading drug candidates for three different patient populations: (1) patients with osteoporosis undergoing primary TJA who are at elevated risk of wear problems as a result of limited osseous integration of the implant and would benefit from prophylactic anabolic therapy; (2) patients who start osteoporosis therapy, have radiographic evidence of early wear and periprosthetic osteolysis, and would benefit from potent antiresorptive therapy; and (3) patients with osteoporosis with signs and/or symptom of metal corrosion problems who are contraindicated for revision surgery and would benefit from combination anabolic and anticatabolic therapy.

The science of implant fixation is a mature field in which many biologic adjutants to improve osseous integration have been investigated. Although several of these biologic treatments have demonstrated improvements in the osseous integration of implants, recombinant parathyroid hormone (teriparatide) is the only one that is FDA-approved for osteoporosis therapy. Thus, teriparatide is

considered to be the most realistic prophylactic therapy to prevent wear and corrosion problems based on efficacy demonstrate in both small [22] and large [12] animal models and clinical studies that have demonstrated effects of this hormone on fractures [2, 3] and alveolar bone defects and osseous wound healing in the oral cavity [5] after 6 to 8 weeks of therapy.

As stated, there are several effective FDA-approved antiresorptive therapies for osteoporosis that fulfill our selection criteria for realistic interventions for wear debris-induced osteolysis. However, our identification of anti-RANKL (denosumab) as the most realistic is based on its known mechanism of action as the final effector molecule in osteoclastogenesis, for which there is no redundancy in vivo [7], and its demonstrated superiority over all the other drugs for this indication, including the most potent bisphosphonates (ie, zoledronic acid), as a result of its ability to induce osteoclast apoptosis in the setting of inflammatory bone loss [50]. In some patients, a combination therapy to stimulate anabolic osteoblastic bone formation and to inhibit osteoclastic resorption may be needed. The emergence of the importance of the osteocyte and the sclerostin-Wnt pathway as the central regulator of bone homeostasis in adults provides the potential that a single agent could be developed as a combination therapy for these patients. This therapy, antisclerostin (romosozumab), is currently in Phase 3 registration clinical trials for an indication as an osteoporosis therapy [31].

How Do We Get There?

Although biomedical research has produced many potential biologic approaches to treat wear- and corrosion-related problems, the apparently insurmountable practical issues (such as formulations, safety concerns, and costs) that must be overcome render the vast majority unrealistic. By bringing these reality issues to the forefront within selection criteria, the potential of several approaches must be disregarded for this indication. This deduction is also the case for drug development in general, in which the high risks of product development, combined with major changes in healthcare reimbursement that eliminate potential reward, has spawned the new era of Public-Private Partnerships (PPP) that are narrowly focus on existing molecules that have been deemed to be safe for human use by the FDA. Of note is that in addition to FDA-approved drugs, these PPP also include a large array of drugs that were proven to be safe and well tolerated in FDA registration trials but failed to meet their prospective efficacy endpoints for the intended indication. These PPP posit that three independent entities synergize to dramatically reduce the costs and development time of new biologic therapies. The first is the pharmaceutical company who has already developed a drug for human use and will provide it for free for preclinical research and clinical trials in a new indication. The second is the public partner (ie, National Institutes of Health, Department of Defense), who will fund a significant portion of the preclinical studies and clinical trials through a competitive granting mechanism. The third is the large medical center (primarily university-affiliated) that has the investigators and patient populations to compete for peer-reviewed grants and resources to complete these studies. This highly innovative thinking came to fruition in the unprecedented National Institutes of Health-industry Roundtable in April of 2011 and resulted in the "Limited Competition for NIH-industry Pilot Program: Discovering New Therapeutic Uses for Existing Molecules (UH2/UH3)" that was first announced in September of 2012. Based on the remarkable success of this program, the National Institutes of Health has reissued this mechanism of funding this year, which will be focused on pediatric therapies. Thus, if we are to develop a biologic therapy for wear debris-induced osteolysis and aseptic loosening in the foreseeable future, we need to establish a PPP that will provide the osteoporosis drug, fund the research and clinical trials, and establish academic consortia that will compete for the funding and complete the necessary work.

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