Drug Therapy After Implant

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14.1 Introduction

The most common cause of failure of a hip or knee prosthesis requiring revision is aseptic loosening due to periprosthetic osteolysis, which occurs if the bone supporting the implant is resorbed. Osteolysis in patients with failed orthopedic prosthesis is commonly due to multiple factors, including physical and biological components. The mechanical failure of the prosthesis–host interface arises primarily as the end result of focal periprosthetic inflammatory bone loss occurring at this interface. This proinflammatory microenvironment is driven by particulate wear debris, which is generated primarily at the articular bearing surface and at other nonarticular prosthesis or cement surfaces [1]. The local accumulation of wear particles is associated with specific serum proteins to form a particle–protein complex. This complex interacts with cell surface receptors on macrophages, activating these cells. The smaller particles are subsequently phagocytosed stimulating a cascade of events, resulting in up-regulation of proinflammatory mediators such as cytokines (Il-1, Il-6, TNF-α), activation of the RANK/RANK-L/osteoprotegerin system, and others that through complex cellular interactions are leading to the recruitment and activation of osteoclasts at the bone implant surface which begin degrading the adjacent bone [2, 3]. Stress shielding is also considered as a potent stimulator of bone resorption [4]. In general, high or unusually distributed strains stimulate increases in new bone formation, and thus a more robust structure, whereas low strains, as seen in disuse of redistributions of mechanical load relate to stem design, are associated with bone resorption and a weaker one. The high incidence of fragility fractures in postmenopausal women suggests a failure of this natural regulatory process since continued functional loading is accompanied by loss of bone tissue and an increase in bone fragility. Recently, it has been postulated that the pathogenesis of bone resorption related to stress shielding is due to the activity of osteocytes [5]. As osteocytes can neither form nor resorb bone, it has been hypothesized that they orchestrate mechanically induced bone remodeling by coordinating the actions of cells residing on the bone surface, such as osteoblasts. The recent identification of sclerostin as a molecule preferentially secreted by osteocytes that appears to be regulated by bone's mechanical environment has attracted considerable interest, particularly because this molecule stimulates osteoblasts to produce the receptor activator of nuclear factor-kB ligand (RANK-L), leading to an increase in osteoclastic activity. Therefore, blocking sclerostin action could be promising to prevent bone loss related to stress shielding phenomenon [6].

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Finally, both alteration of bone turnover and intrinsic bone tissue quality in pathologies like osteoporosis could potentially preclude an optimal bone integration [7]. Periprosthetic osteolysis is thus the result of the combined action of an increase in bone resorption, stimulated directly by the particles or through a process of inflammation, associated with reduced bone formation caused by a depression of osteoblastic activity as a result of the toxicity of the debris [8], instability, hydrostatic pressure [9], or poor bone quality [7].

In the past two decades of evolution of arthroplasty, a number of cementing techniques, as well as uncemented arthroplasties and numerous prosthetic design and material changes, have been introduced to improve prosthetic wear resistance and subsequent aseptic loosening, but to date few advances have been made in the medical management of osteolysis. Therefore, efforts to identify patients at risk of revision and develop new pharmacological treatment s to improve implant survival are urgently needed. This chapter briefly describes the major pharmacological intervention used or proposed as potential pharmacological agents, in an attempt to prevent or delay the process of aseptic loosening.

14.2 Pharmacological Agents

14.2.1 Bisphosphonates

The bisphosphonates are compound all characterized by P–C–P structure analogs of pyrophosphate that contains an oxygen atom P–O–P instead of carbon. The P–C–P structure allows a great number of possible variations, either by changing the two lateral chains of carbon atom, or by esterifying the phosphate groups. The second- and third-generation bisphosphonates: alendronate, neridronate, ibandronate, pamidronate, risedronate, and zoledronic acid have a nitrogen group and are called nitrogen-containing bisphosphonates in contrast to first-

generation bisphosphonates such as etidronate, clodronate, and tiludronate, which do not. However, each compound has to be considered on its own, with respect to its use, toxicology, and its potency to inhibit bone resorption [10]. Although the detailed mechanism of action of bisphosphonates has not been elucidated, it is clear that at the tissue level, all active bisphosphonates inhibit bone resorption, bone turnover, and therefore bone loss. At the cellular level, there is a general agreement that they act directly and/or indirectly on the osteoclasts recruitment and activity [11]. Despite the myriad of data published so far, the exact mechanisms by which bisphosphonates inhibit bone resorption are still not entirely unraveled. It may be that several mechanisms are operating simultaneously [10]. With regards to wear debris and osteolysis after joint arthroplasties, these drugs seem to have a beneficial effect. It was demonstrated in a canine model that alendronate can inhibit wear debris-mediated osteolysis [12]. In a rat model incorporating a polyethylene (PE) tibial implant and repeated PE particle injections into knee, intraarticular alendronate pumped locally mitigated periprosthetic bone loss [13]. However, instability-induced bone resorption may not be responsive to alendronate [14]. Co-incubation of pamidronate with ultra-high-molecular-weight polyethylene (UHMWPE) particle induced specific macrophages apoptosis. Pre-incubation of macrophages with pamidronate prior to particle stimulation had a more potent effect in the inhibition of TNF-α release. This may suggest that the sequence of events leading to apoptotic cell death were induced by the drug in the absence of particles, thereby making the macrophages less responsive to the stimulatory effects of UHMWPE particles [15]. In a rat calvaria/macrophage co-culture model used to study the effects of various agents upon bone resorption induced by macrophage exposure to bone cement particles, pamidronate was the only agent tested which suppressed the increase in bone resorption. Non-steroidal anti-inflammatory drug, indomethacin, calcitonin, and anti-TNF antibody did not decrease bone resorption using this model [16]. There have

been recent attempts to improve implant fixation by the application of bisphosphonates both systemically [17] and locally by bonding it to hydroxyapatite-coated implants [18]. In an animal experiment, it was shown that pretreating intramedullary implants with hydroxyapatite–zoledronate composite enhances periprosthetic bone quality and bone integration [19].

Bisphosphonates are currently used for the treatment of osteoporosis and other metabolic bone disease, and their clinical effectiveness is well documented. The most extensive studies reported so far have been conducted with alendronate [20–22]. Postmenopausal women treated with alendronate gained significant increases in bone mineral density (BMD) in the spine, hip, and total body, whereas the placebo group lost about 1 % of BMD over the 3 years [20]. Also in the fracture intervention trial (FIT), osteoporotic women who received alendronate gained significantly more BMD than women of the placebo group in multiple skeletal sites [21]. Alendronate has shown its value by effectively preventing fracture [22].

To determine the current understanding of the effect of bisphosphonates on periprosthetic BMD after total joint arthroplasty, a computerized research for randomized controlled trials was conducted, evaluating the use of bisphosphonates in patients treated with primary total joint arthroplasty [17]. In this meta-analysis of six randomized, controlled trials, which included a total of 290 patients, it has been shown that significantly less periprosthetic bone loss had occurred in the treated patients than in the control patients at three months, six months, and twelve months. The larger effect on bone loss was noted following arthroplasties with cement than on bone loss following arthroplasties without cement and on bone loss following total knee arthroplasties (TKA) than on bone loss following total hip arthroplasties (THA), respectively.

In an observational study [23], bisphosphonate use was associated with significantly lower rate of revision surgery of up to about 50 % and a twofold greater median implant survival time after primary total arthroplasty of the lower limb

in patients without a previous fracture. In the same study, bisphosphonate use was also associated with an almost twofold increase in implant survival time. However, a recent case–control study [24] reported an insignificant association between the long-term use of bisphosphonate and a reduced risk of revision, but an increased risk of revision due to deep infections among bisphosphonate users. Regarding the effect of bisphosphonate on periprosthetic bone loss, a recently published systematic review [25] and a meta-analysis [26] have also provided conflicting results.

14.2.2 Denosumab

The accumulation of macrophages in the prosthetic implant bed is believed to be important in aseptic periprosthetic bone loss. Many studies have shown that macrophages phagocytose the prosthetic particles, which in turn causes the release of the mediators of bone resorption [27, 28]. There is also evidence that precursors of osteoclasts reside in the granulomatous tissues adjacent to areas of periprosthetic bone loss, since cells isolated from this tissue can develop into functional osteoclasts under appropriate conditions in vitro [29]. In addition, it was found that the formation of osteoclasts from these tissues is associated with the expression of the osteoclastogenic molecules RANKL and RANK [30]. The understanding of the role of these factors in periprosthetic bone loss may help to identify targets for therapy in this pathology.

Denosumab is a novel biological agent for the treatment of osteoporosis in postmenopausal women with increased risk of fractures [31] and reduces the risk of new vertebral, nonvertebral, and hip fractures [32]. This compound is the first approved RANK ligand inhibitor and a fully human monoclonal antibody [33]. It exerts its anti-resorptive effects by inhibiting the formation, function, and survival of osteoclasts. Subcutaneous administration of denosumab once in every six months leads to a rapid and marked reduction in bone resorption. In a comparative study on murine model, it was reported that

denosumab and alendronate treatments increased strength and stiffness of the fractured bones [34]. Currently, a clinical trial using subcutaneous denosumab for nonsurgical treatment of periprosthetic bone osteolysis is ongoing, but the results are not yet available. If successful, this study will lead to further studies to develop the use of denosumab to prevent aseptic loosening.

14.2.3 Strontium Ranelate

Strontium ranelate is a pharmaceutical agent composed of an organic moiety (ranelic acid) binding two stable strontium atoms that acts via a dual mode of action with both bone-forming and bone-resorbing properties [35], leading to an improvement in bone quality, strength, and microarchitecture. Clinical trials have demonstrated the efficacy of strontium ranelate to reduce fracture risk [36]. This agent is approved for the prevention of vertebral and hip fractures in postmenopausal osteoporosis. Strontium ranelate is the only osteoporosis treatment that dissociates the processes of bone resorption and bone formation [35]. Strontium ranelate acts on osteoblast by increasing mRNA and protein levels of osteoprotegerin (OPG) and suppressing those of RANKL. Strontium ranelate also stimulates osteoblast replication and differentiation and prolongs the lifespan of osteoblasts. Knocking down calcium-sensing receptor (CaSR) suppresses strontium ranelate-induced stimulation of OPG mRNA, reductioning RANKL mRNA, and increasing replication, indicating the involvement of CaSR in these responses. These results demonstrate that osteoblasts play a key role in the mechanism of action of the anti-fracture agent, by mediating both its anabolic and anti-resorptive actions, at least in part, via activation of CaSR [37, 38]. At the same time, strontium ranelate inhibits osteoclastic activity, as shown by a reduction in expression of functional osteoclast markers and disruption of the cytoskeleton essential for resorption [39, 40]. There is also evidence of the benefits of strontium ranelate on bone microarchitecture in different animal models. The 2D and 3D histomorphometric analyses have demonstrated prevention in the deterioration of bone microarchitecture with strontium ranelate in ovariectomized rats, leading to prevention of bone strength decrease [41]. The beneficial effects of the strontium ranelate regarding the improvement of bone integration of implants have been reported in various animal models. Li et al. [42], in a study designed to evaluate the effect of systemic strontium ranelate treatment on fixation of hydroxyapatite (HA)-coated titanium screws in ovariectomized rats that received unilateral implants in the proximal tibiae, suggest that this treatment can dose-dependently improve the fixation and facilitate the stability of the implant in the osteoporotic bone. Moreover, in another rat model study, strontium ranelate was found to improve implant bone integration with a positive effect on both bone biomaterial microarchitecture and bone biomaterial properties in the vicinity of a titanium implant versus untreated animals [43]. All these data strongly suggest that strontium would have the potential to improve peri-implant bone structure. Furthermore, in a midterm evaluation of strontium-containing hydroxyapatite bone cement in a goat, revision hip hemi-arthroplasty model ranelate was superior to polymethylmethacrylate (PMMA) bone cement in terms of bone-bonding strength [44].

Another fact to consider is that the treatment with this drug is not associated with osteonecrosis of the jaw (ONJ). This represents a distinct advantage compared to bisphosphonates and denosumab as, despite the poor evidence, many dentists or oral surgeons are reluctant to administer due to the possibility of ONJ development. Lastly, it is also relevant to emphasize that BMD continues to increase after strontium saturation is reached in bone and even after stopping the drug [45]. However, these current results need to be confirmed by clinical studies and longer-term follow-up investigation to support the effect of strontium ranelate on a potential role in osteolysis.

14.2.4 Parathyroid Hormone

Bone anabolic therapy with the recombinant human parathyroid hormone (PTH) analogue, teriparatide (PTH-1-34), or full-length PTH-1-84 has been an option in the treatment of osteoporosis. Both drugs have been shown to have an anabolic effect on bone when administered intermittently. Mechanisms of action by which PTH induces bone anabolic effects include increase in osteoblast number and activity, leading to increases in trabecular bone mass and strength [46–48] and increase in cortical bone [49]. The positive effect on bone remodeling has been confirmed in human fracture prevention studies [50, 51]. However, recently, it was reported that in terms of anti-fracture efficacy, treatment with PTH is not superior to treatment with potent anti-resorptive agents. However, while the process by which osteoporosis emerges is arrested in response to anti-resorptives, PTH acts as a bone anabolic with reversal of the process. Although this mechanism of action seems favorable, the use of PTH is limited by a much higher cost than that of anti-resorptive agents. As long as a superior anti-fracture efficacy has not been proven, PTH should be confined to patients with severe spinal osteoporosis, including patients in whom treatment with an anti-resorptive has failed [52]. Some studies have investigated the effect of PTH on various types of implant fixation. These comprise rodent models with insertion in pathological bone [53–55] or transcortical implantation in normal bone [56, 57]. The general finding in these interference-fit rodent models is improved incorporation in bone. In ovariectomized rats, administering PTH [1–34] daily increased osseointegration, bone volume, stiffness, and toughness of conical titanium screws [54] that prevent resorption of newly generated trabeculae around the implant [55] and increase new bone formation on the surface of hydroxyapatite-coated implants [55]. Transcortical implantation in normal bone of rats also indicates that intermittent treatment with PTH may enhance the early fixation of orthopedic implants [56, 57]. Finally, in a canine model, intermittent treatment with PTH [1–34] improved histological bone integration of a prosthesis-inserted press-fit at surgery in cancellous bone, with no additional improvement of the initial mechanical fixation at this time point [58]. However, despite these experimental studies bring back positive results in terms of bone integration, the possible role of PTH administration in preventing osteolysis in humans after joint implants remains to be shown with controlled clinical trials and long-term evaluation of the results.

14.3   Conclusions

Different studies suggested that bisphosphonates and other pharmacological agents mainly used for the treatment of osteoporosis and prevention of fragility fractures might have a beneficial effect with regard to maintaining more periprosthetic BMD than that in controls. However, the limitations of the available studies and the lack of analyses of clinically relevant outcomes (functional outcomes, revision rates, and quality of life) necessitate the planning and conduct of a sufficiently sized, methodologically sound study with clinically relevant end points. Until this has been done, the current evidence regarding the beneficial effects of pharmaceutical compound on periprosthetic bone after total joint arthroplasty should be interpreted with caution.

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