Bisphosphonates: A threat or an option?

Prof. Per Aspenberg, Sweden

ONJ is indeed a problem. However, it's less a problem than a problem. Local bone — bisphosphonates reduce the resorptive response to trauma without impairing the bone formation response, therefore having a net anabolic effect. This explains why both local and systemic bisphosphonates have been shown to improve the early fixation of knee and hip replacements in randomised blinded clinical trials.4

Bisphosphonates are often regarded negatively, owing to the small risk of ONJ. Most dentists will be familiar with bisphosphonates mainly as a cause of osteonecrosis of the jaw (ONJ). ONJ is a complication of systemic treatment. In contrast, locally applied bisphosphonates have been proven efficacious for improving the fixation of dental implants. Theoretical reasoning, experimental data, and small clinical trials suggest that local application of bisphosphonates is safe and effective in periodontology and implant surgery.

Bisphosphonates have positive effects on many conditions in bone and few and rare side-effects. Their efficacy in osteoporosis is well known, and there is evidence for improved implant fixation in an increasing number of applications. In dentistry, however, bisphosphonates are often regarded negatively, owing to the small risk of ONJ.

ONJ is a complication of systemic bisphosphonate treatment. In dentistry, however, bisphosphonates are associated with ONJ too. Bisphosphonate coating improved implant fixation without complications in randomised blinded clinical trials in periodontology and dental implant surgery. How can this be? Here is an explanation.

Bisphosphonates either bind to bone mineral or are quickly excreted. Normally, they do not enter cells and are therefore not toxic. Only osteoclasts can resorb bone, and when they do so, the dissolved bone material passes through the cell. Therefore, bisphosphonates can reach the intracellular space of osteoclasts. Once inside the osteoclast, they will inactivate the cell and thus reduce bone resorption.

When bone is infected, the bone surrounding the infection will be quickly resorbed. The infected bone will therefore become surrounded by richly vascularised soft tissue that demarcates the infected area. Thus, a good resorption capability is important for preventing the spread of bone infection. This protection mechanism can be impaired if resorption is reduced by any potent anti-resorptive, leading to the spread of infection and established osteomyelitis. In dentistry, this kind of osteomyelitis is called osteonecrosis. Thus, from a pathological perspective, ONJ is a somewhat misleading term. The already well-known anti-osteoclastic effects of bisphosphonates are sufficient to explain ONJ without suppositions about other, less known, mechanisms. Moreover, the theory fits with the observation that non-bisphosphonate anti-resorptives are associated with ONJ too.

When implants are inserted into bone, numerous studies have shown that — especially in cancellous bone — bisphosphonates reduce the resorptive response to the trauma without impairing the bone formation response, therefore having a net anabolic effect. This explains why both local and systemic bisphosphonates have been shown to improve the early fixation of knee and hip replacements in randomised blinded clinical trials.4

Because bisphosphonates bind strongly to bone, local treatment will stay there more or less forever, and thus not impair the resistance to infection anywhere else. In an animal model of dental implants (at sites compromised by local wounding), the author’s group showed that systemic bisphosphonate treatment induced osteomyelitis (ONJ), whereas implants with a bisphosphonate coating improved implant fixation without problems in spite of the compromised insertion site.4 Moreover, if an implant site in humans were infected, only the bone about one millimetre away from the implant surface would contain bisphosphonate and could be removed if necessary.

In a randomised blinded controlled trial of dental implants coated with a protein layer loaded with bisphosphonates, improved fixation was demonstrated. The resonance frequency was 6.9 ISQ units higher for the coated implants compared with the controls (p = 0.0001, Cohen’s d = 1.3). Radiographs showed less marginal resorption both at two months (p = 0.012) and at six months (p = 0.012). The patients were followed for five years without complications.

To conclude, systemic anti-resorptives may impair protection against osteomyelitis, thereby increasing the risk of ONJ in patients with other risk factors. Local bisphosphonates seem not to confer this risk, and improve implant fixation by their net anabolic effect.

Local bisphosphonate treatment could become an important tool in dentistry and maxillofacial surgery.