

ACTUALIZACIONES / Reviews

USING AGENTS THAT SUPPRESS BONE REMODELING TO TREAT OR PREVENT JOINT DISEASE: QUO VADIS?#

David B. Burr*

Department of Anatomy and Cell Biology, Indiana University School of Medicine and Department of Biomedical Engineering, Indiana University – Purdue University Indianapolis, Indianapolis, IN, USA.

Abstract

Treatment of osteoarthritis (OA) with anti-remodeling agents has had a mixed record of results. It is likely that remodeling suppression is only effective when used in the early phases of OA, before significant progression. Animal and human studies largely bear this out. Treatment of young mice with a RANKL inhibitor suppresses bone resorption and prevents OA progression. Likewise, bisphosphonate treatments in rodents and rabbits with induced injury or inflammatory arthritis, reduced cartilage degeneration when administered pre-emptively, but later administration did not. The increased prevalence of OA in women after the menopause, and presence of estrogen receptors in joint tissues, suggests that treatment with estrogens or Selective Estrogen Receptor Modulators may be effective. However, in clinical trials of knee and hip, results show decreased or increased risk for OA, or no effect. Raloxifene had positive effects in animal models, but no effect in human studies. More recent potential treatments such as strontium

ranelate or cathepsin-K inhibitors may be effective, but may work directly on the cartilage rather than through their well-known effects on bone. The conclusion from these studies is that anti-remodeling agents must be administered pre-emptively or in the very early stages of disease to be effective. This means that better imaging techniques or identification of early structural changes in bone that occur before progressive cartilage destruction must be developed.

Key Words: Osteoarthritis, bisphosphonate, estrogen, cartilage, bone.

Introduction

Treatment of osteoarthritis (OA) with agents that suppress overall bone remodeling that were originally developed for the treatment of postmenopausal osteoporosis has had a mixed record of results. When bone anti-remodeling (or anti-catabolic) treatments have been used to reduce the effects of human OA,

* Dirección postal. Dept. of Anatomy and Cell Biology. Indiana University School of Medicine. 635 Barnhill Dr. Indianapolis, IN 46202. E-mail: dburr@iupui.edu

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the trials have almost universally failed.^{1,2} The idea of anti-catabolic treatment is that suppression of early phase subchondral bone remodeling can prevent or ameliorate vascular invasion to the cartilage, and subsequent effects of cartilage fibrillation and loss. To understand why the results of animal studies and human clinical trials have mixed results, it is important to understand the phases of OA development.³

Historically, OA was thought to be associated with subchondral sclerosis which was considered by some to be causative.⁴⁻⁶ The theory was that dense subchondral bone, being stiffer and less able to absorb joint stresses, caused increased stress in the deep layers of the cartilage,^{7,8} initiating the progressive process of cartilage fibrillation and loss. There was some experimental evidence that this was the case.^{9,10} More recent observations have demonstrated that in early OA, conversely, there is subchondral plate thinning, and cancellous bone loss caused by an increase in remodeling rate (Figure 1).^{11,12} This is followed by reduced remodeling with an imbalance between resorption and formation in favor of formation.¹³ This later phase reduction in remodeling causes the subchondral plate to thicken¹⁴ giving the radiologic appearance of sclerosis, even though the mineralization of the tissue itself may be reduced,¹⁵ and the subchondral cancellous bone beneath it may remain osteopenic.¹⁶

Because subchondral sclerosis is an end-stage product of the disease, it is likely that anti-catabolic treatments can only be effective when used in the early phases of OA development, before significant progression has occurred. Certainly, giving an anti-catabolic treatment when bone density is already greatly increased would make little sense. Animal experiments show that inducing subchondral sclerosis without permitting the prior stage of increased bone remodeling can prevent progressive cartilage fibrillation and loss,¹⁷⁻²⁰ demonstrating that the early phase increased remodeling, together with

the increased vascularity that accompanies it, is a necessary pathogenetic condition for progressive OA to develop.

Even so, clinical studies using anti-catabolic agents provide conflicting and inconsistent results^{2,21} and research into both the safety and the efficacy of these agents continues. The confusion over the potential use of these agents is reflected by the recent position paper from the American College of Rheumatology for use of non-pharmacologic and pharmacologic therapies in OA of the hand, hip and knee,²² which did not recommend any anti-catabolic therapies for the treatment or prevention of OA.

Clinical Studies

Bisphosphonate (BP) treatments for OA

One of the earliest prospective trials using the BP risedronate (RIS) enrolled 284 subjects with mild to moderate OA into a double-blind placebo controlled study.²³ Subjects were treated with 5 or 15 mg/day. Although the study found more subjects with radiographic evidence of joint space narrowing in the untreated group, the numbers were small (placebo n=7; 5 mg RIS n=4; 15 mg RIS n=1) and not statistically significant.

A large multi-center study was initiated RIS at doses of 5, 15 or 35 mg/week in Europe and 50 mg/week in the U.S. Nearly 2,500 patients with established medial compartment knee OA were identified and treated for two years.¹ Progression of OA was identified by an increase of joint space narrowing (JSN) in the knee joint, assessed by radiography, greater than 0.6 mm over the treatment period. Although the treatment appeared to reduce pain (assessed by WOMAC score) and reduced CTX-II, a measure of cartilage catabolism, in both the U.S. and Europe, it had no effect on progression of OA at any dose on either continent (Figure 2). For all treatment groups, about 10-13% of the subject population continued to progress.

Earlier, Carbone et al.²⁴ had used MRI to

compare knee and patello-femoral pain and bone in women either with or without existing OA who were using anti-catabolic agents (estrogen, raloxifene or RIS) or were treatment naïve. They were unable to identify any

relationship between anti-resorptive use and radiographic evidence that progression of knee OA was slowed by any of the specific anti-remodeling agents for knee OA, or when the treatment groups were pooled. However,

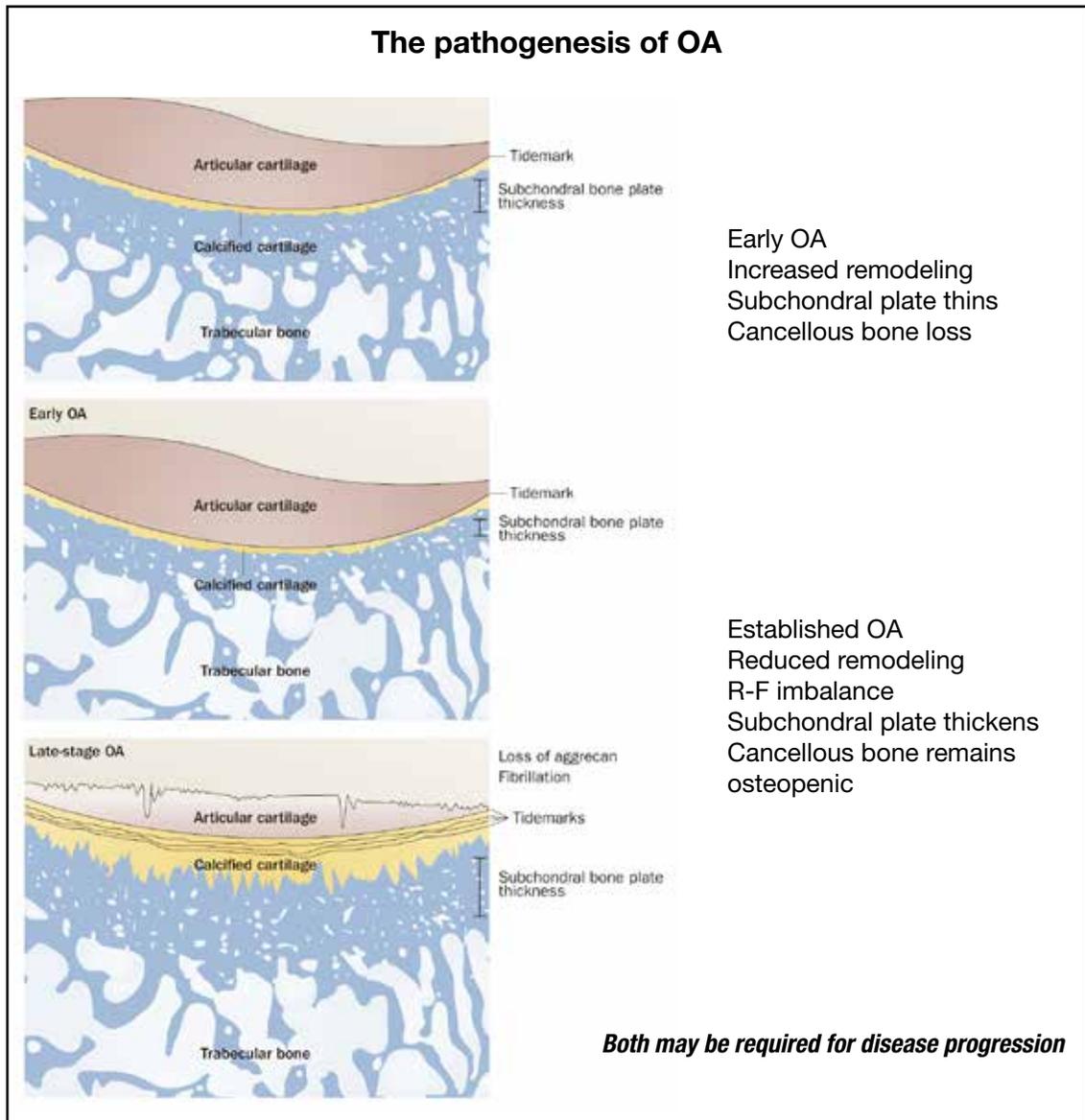


Figure 1. The initiation of osteoarthritis (OA) and the progression of OA are associated with distinctly different processes in the subchondral bone. In early phases of OA, there is an increased rate of bone turnover, leading to a loss of bone volume and thinning of the subchondral plate. In established OA, this process is reversed, with reduced bone remodeling and an imbalance in favor of bone formation. This leads to the subchondral sclerosis that is characteristic of established OA. R-F: resorption-formation (Reproduced with permission from Ref 3).



they did find a reduction in pain and less marrow edema – what we would now call bone marrow lesions (BMLs) – in those who used either estrogen or alendronate (ALN), but a more pronounced reduction in those using ALN, with an 89% reduction in odds ratio after adjusting for co-variables. This is probably not surprising given ALN's potent anti-remodeling effects. However, they were not able to detect any significant change in cartilage lesions, and did not examine changes in joint space width, and so were unable to correlate the prevention of bone changes associated with OA with cartilage loss itself. The duration of the use of the medications was not specified, and likely varied widely among the 214 women who were using anti-remodeling therapies.

A more recent study compared patients with early stage radiographic knee OA who were classified as either BP users (ALN or RIS) or BP-naïve.²⁵ This study showed significantly fewer patients with OA progression in

those taking BPs after three years of observation ($p=0.041$), although this significance was lost in year four ($p=0.057$). Further, a trend towards reduced joint space narrowing by year three was also observed ($p=0.083$ in year 3, and 0.057 in year 4) (Figure 3). This suggests that the duration of treatment may be important to identifying the efficacy of BPs for OA progression, which makes logical sense given the long period required for OA to develop.

Estrogen and Selective Estrogen Receptor Modulators (SERMs)

The increased prevalence of OA in women after the menopause,²⁶ and presence of estrogen receptors in joint tissues,²⁷⁻²⁹ suggests that treatment with estrogens or SERMs may be an effective treatment for OA progression with direct effects on both bone and cartilage or synovial tissues. However, in clinical trials of both knee and hip, results of hormone replacement therapy have been mixed,

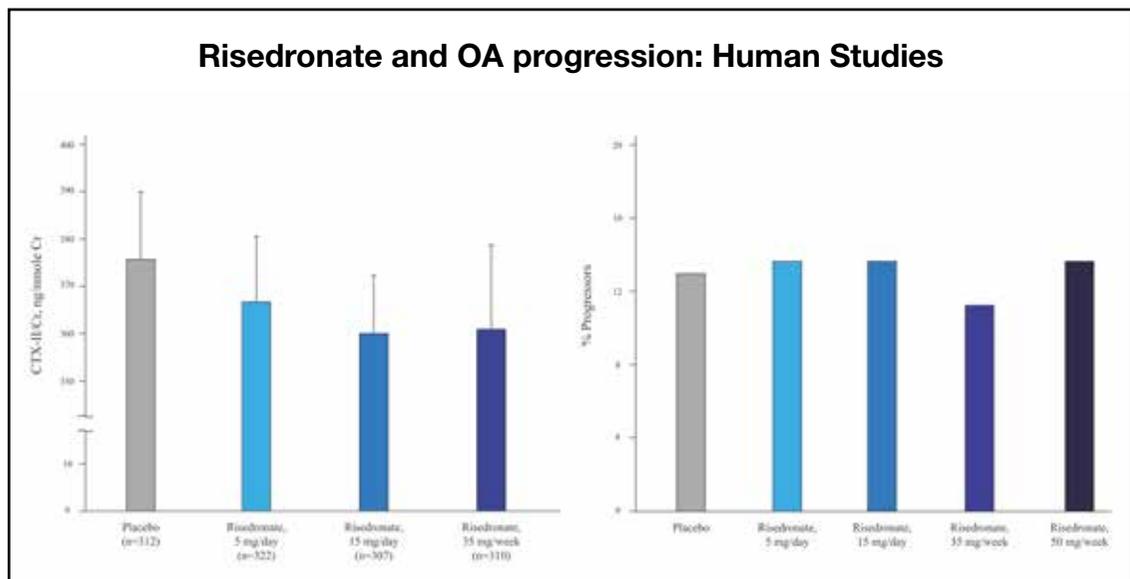


Figure 2. An early clinical study showed that treatment with the bisphosphonate risedronate led to a non-significant reduction in Type II collagen (CTXII) degradation in cartilage, but had no effect on progression of OA even at higher doses (Data from Ref 1).

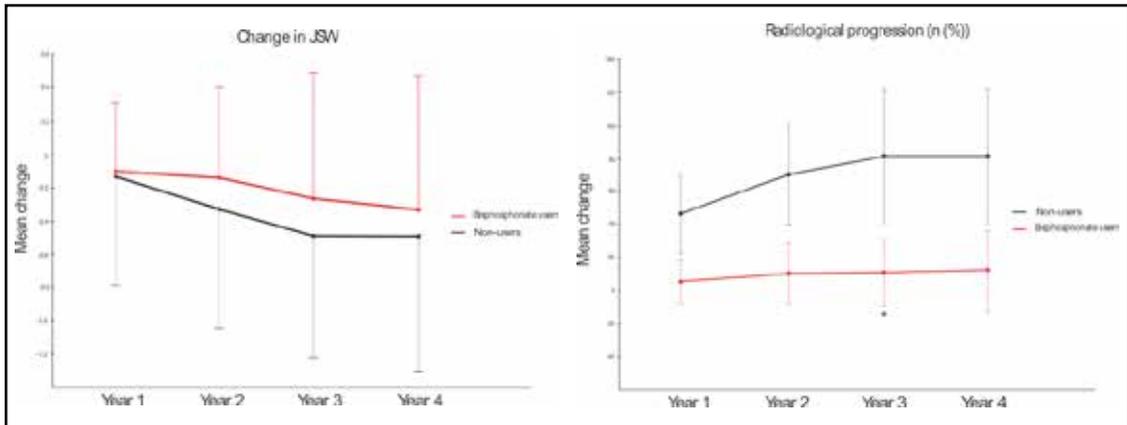


Figure 3. Patients with early stage OA who were had been BP showed no significant change in joint space width (JSW) on average after a 3 year observation period. However, there was some evidence that BP slowed progression of OA. This difference reached statistical significance in year 3, but significance was lost in year 4, probably due to the large variation in the patient population. It is worth noting, however, that OA tended to progress in only about 10% of BP users, compared with nearly 80% of those not taking BPs (Data from Ref 25).

with reports of decreased prevalence of OA [the Chingford study for radiologic OA of the knee;^{30,31} the SOF study with a longer duration of treatment for hip OA^{32,33}]; increased risk for OA [for radiologic OA of the knee;^{34,35} and the Rancho Bernardo study for clinical OA of the hip³⁶]; or of no effect of treatment on radiologic^{37,38} or clinical^{24,39,40} OA of the knee or hip. The inconsistent results may in part reflect a dose-response effect as higher doses of estrogens are known to have catabolic effects, whereas lower doses have been shown to be chondroprotective in some instances.⁴¹⁻⁴³ In the Framingham study, although the odds ratio for a protective effect of HRT on OA was not significant, there appeared to be a duration effect with use of > 5 years associated with a lower risk of knee OA than shorter-term use.⁴⁴ This is consistent with a separate study which showed that women taking HRT for more than 5 years had greater tibial cartilage volume, measured by a T1-weighted fat-suppressed MRI image and adjusted for covariates, than women who had never taken

estrogen therapy.⁴⁵ In the following two years of observation, average tibial cartilage volume decreased by 2.4% per year compared to 3.2% annually in non-users, but the difference was not statistically significant.⁴⁶ This may be due to the small cohort size, inability to accurately measure cartilage volume, or disease that was only slowly or not progressing.

It is probably not worthwhile to review these studies here in detail, given that many of them are older studies performed when estrogen-replacement therapy was more common before the Women's Health Initiative identified side effects that reduced patients' and physicians' confidence about its safety. However, an excellent review of this literature can be found in de Klerk et al.,⁴⁷ who concludes that the preponderance of evidence suggests no effect of "exogenous hormone use" for the treatment of hand, hip or knee OA.

SERMS, on the other hand, appear to prevent cartilage degradation, at least when measured against changes in biochemical markers such as CTX-II. Both Levormeloxi-



fene⁴⁸ and raloxifene²⁴ reduced CTX-II following 12 months of treatment, although no effect was evident on cartilage structure by MRI.^{24,49} Once treatment was stopped, CTX-II reverted to pre-treatment levels, suggesting that the effect was short-term. However, raloxifene had no effect in human studies of postmenopausal women.⁴⁹

What does this tell us?

There are several reasons that differences between treatment groups may not have been detected in many of these studies. First, OA is a condition that progresses very slowly, and it is possible that a two year treatment period is insufficient. Second, the patient populations were ones in which medial compartment OA was already well established. An anti-resorptive treatment may only be beneficial in controlling the initial stages of the disease at a time when vascular invasion from the subchondral bone is active. The study by Laslett et al.²⁵ is instructive in showing that longer treatment periods are needed to demonstrate an effect, and that even in this case it is necessary to start with a population in which the disease has not progressed to a moderate or severe level. Third, radiographic measurements are insensitive to small changes in joint space width; changes over a short period of time are unlikely to be detectable.

It is possible, however, that BPs or estrogens have a direct effect on cartilage constituents. BPs have been suggested to stimulate both collagen synthesis and aggrecan formation.⁵⁰ BPs at high doses also have been shown to block metalloproteinases (MMP-9 and MMP-13) which are known to cleave type II collagen, and BPs may act directly on cartilage as a chondroprotective agent.⁵¹ Unlike their effects in bone which tend to be sustained after treatment withdrawal, effects of ALN on CTX-II levels return to baseline relatively quickly,⁵² suggesting independent effects on bone and cartilage.

Likewise, IGF-1 has been associated with

radiographic OA in the Rotterdam study,⁵³ and synovial IGF-1 and -2 levels are increased when estrogen is given unopposed by progesterone.⁵⁴ Further, estradiol has an effect on IL-6 production by chondrocytes,⁵⁵ although it is not clear whether this affects the catabolic activity of the chondrocytes. Moreover, estrogens may decrease the catabolic activity of MMP 1,⁵⁶ protecting the cartilage from degradation. Their role in proteoglycan synthesis is less clear, with reports that proteoglycan synthesis is either increased⁵⁷ or decreased.^{58,59} These differences are likely the result of different doses and treatment of different chondrocytic cell lines. For in vivo studies, whether estrogens increase or decrease proteoglycan synthesis is likely dependent on whether the treatment is effective at reducing cartilage loss, which in turn is partially dependent on when the treatment is initiated.

Still, as Goldring and Berenbaum⁶⁰ point out in a recent review, agents that directly attack enzymes that degrade cartilage are not completely effective, or have significant side effects, causing their use to be discontinued. They suggest that prevention of disease progression may be a more effective strategy, although it is necessary to identify the disease process early in order to manage this.

Pre-clinical models using BPs to prevent OA

BPs and RANKL inhibitors

These human trials provide no evidence that BPs will be effective treatment modalities, although the studies were limited by duration of treatment and by insufficient methods of imaging and quantifying progressive cartilage loss in vivo. Animal models in which timing and dose of treatments can be more easily manipulated, and in which histological changes can be assessed instead of relying on imprecise imaging techniques, can shed light the importance of these variables in assessing the efficacy of treatment.

Hayami et al.⁶¹ showed a significant reduction in cartilage damage 10 weeks following

ACL transection in Sprague-Dawley rats with ALN administered at two different doses starting immediately after injury. They were further able to show an association with vascular invasion of calcified cartilage, which was significantly reduced especially with the higher dose (240 µg/kg s.c./week). Pamidronate treatment reduces cartilage degeneration that occurs within 6 weeks following complete or partial medial meniscectomy in ovariectomized (OVX) C57BL/6 (C57) mice and in mice genetically modified to overexpress Runx2 that have rapid bone turnover,^{62,63} but not in C57 mice crossed with Balb/c mice (B6CF strain). The reduction in cartilage degeneration may be caused by reduced cleavage of the proteoglycans as markers of cartilage catabolism (ADAMTS-4 and 5) are also reduced.⁶² Although pamidronate prevented cartilage destruction in the Runx2 over-expressing mice, there was no initial difference in cartilage deterioration between the wild-type B6CF mice and the over-expressers following partial meniscectomy, suggesting that the rapid bone turnover was not an underlying factor in the cartilage deterioration. In this study, it could be that pamidronate had direct effects on cartilage, and that the reduced bone turnover was not the cause of the improvement.

Likewise, ALN partially protects rabbits from cartilage deterioration following ACL transection (ACLT).⁶⁴ More potent BPs such as zoledronate (ZOL) completely prevented progression of cartilage damage in rabbits with ACLT when started immediately after injury.⁶⁵ This may indicate that there is a dose effect required for prevention. Other studies show similar effects with BPs following injury-induced OA in rabbits⁶⁶ and dogs,⁶⁷ although the effect on morphometric lesions is inconsistent.⁶⁸ Not surprisingly, in all cases the chondroprotective effects of BPs are accompanied by reduced subchondral resorption, leading some to imply a causative association,⁶⁶ but causation cannot be clearly demonstrated by these studies. Nevertheless, these studies are compelling in suggesting that BP treatment started soon after injury is effective in preventing

subsequent progressive cartilage disease.

Fewer studies have been done with other potent anti-catabolic treatments such as RANKL inhibitors. Treatment of young mice with osteoprotegerin (OPG), a decoy receptor for RANKL, potently suppresses bone resorption and has been shown to prevent the progression of OA in mice [Kadri et al., 2008]. Following medial meniscectomy, 10 week old C57 mice were treated 2x/week with OPG or an interleukin receptor antagonist (IL-1RA). Cartilage in the OPG-treated group was maintained with almost no degradation, significantly healthier than cartilage in the IL-1RA treated or saline-treated groups. ADAMTS-4 and -5 positive cells were significantly fewer in OPG-treated mice, and of course there were fewer osteoclasts and greater subchondral bone volume. Again, this suggests that an agent that suppresses early remodeling following joint injury can prevent subsequent progressive cartilage degradation.

First generation BPs (clodronate and YM175) also have been shown to be effective in rat models of inflammatory arthritis induced either by collagen or by adjuvant.⁶⁹⁻⁷¹ This set the stage for investigating the efficacy of more potent recent generation BPs such as ZOL, which has been shown to be effective at reducing cartilage loss and pain in chymopapain-induced OA in rabbits,⁷² and mono-iodoacetate (MIA)-induced OA in rats.^{19,73}

These studies suggest the benefits of BPs as chondroprotective agents, but the timing of treatment initiation may be critical to the effectiveness of the treatment. Yu et al.¹⁸ showed that both the timing of treatment and the dose used are significant factors in effectiveness. They induced medial meniscus tears in adult Sprague-Dawley rats and observed changes over a 12 week experimental period. They treated the rats with 100 µg/kg s.c. of ZOL twice a week starting either immediately following the injury, or 4 or 8 weeks after injury. This model showed progressive cartilage change over the 12 week period, but initiating ZOL treatment either immediately or within 4 weeks of injury caused significantly



less cartilage destruction than when ZOL was started 8 weeks after injury. A separate experiment using a low dose (10 µg/kg s.c.) or the higher dose (100 µg/kg s.c.) administered starting immediately after injury showed both doses of ZOL to be effective in significantly reducing cartilage damage by the end of 4 weeks, but with a clear dose response. This provides convincing evidence that pre-emptive administration of a potent anti-catabolic agent may be effective at preventing subsequent progressive disease.

Early administration may be effective even when using less potent BPs.²⁰ ALN was used to prevent OVX-induced loss of cartilage over an 18 week period and was administered either immediately after OVX, or 8 weeks after OVX. ALN administered immediately completely prevented cartilage erosion following 10 weeks of treatment, but ALN initiated 8 weeks following OVX was not effective in reducing cartilage lesions with 10 weeks of treatment, even though it prevented subchondral bone loss. This suggests that the timing of initiation of treatment is critical to efficacy. This study also implies that rescue of subchondral bone is insufficient to prevent the changes of OA, but the prevention of early bone loss (and the vascularity that accompanies it) is associated with prevention of progressive cartilage disease. Whether this is because the bone changes were prevented, or that ALN acted directly on the cartilage during the early phases of disease cannot be determined. In this case, MMP-9 and MMP-13 levels were reduced^{20,64} as were some other cartilage catabolic agents such as vascular endothelial growth factor, VEGF, which can have an effect on both vascular invasion to the deep cartilage layers but is also produced by chondrocytes superficially.⁶⁴

Other studies are suggestive, but have significant problems with experimental design. Pre-emptive treatment was recently shown to be important in treatment of MIA-induced inflammatory arthritis in rat knees.¹⁹ In this case, treatment with ALN (15 µg/kg s.c. 2x/week)

was started pre-emptively (0-2 weeks after induction), early (2-6 weeks after induction) or late (6-10 weeks after induction). Pre-emptive treatment partially prevented cartilage degeneration, whereas early or delayed treatment had no effect. The modest effect of ALN, even when given pre-emptively, may in part be due to its less potent activity than ZOL. However, the study was flawed because animals treated pre-emptively were sacrificed after 2 weeks, whereas those treated early or later were sacrificed at 6 and 12 weeks respectively. Nevertheless, this implies that pre-emptive treatment may be effective for inflammatory arthritides as well as for OA.

All of these studies suggest that early administration of an anti-catabolic agent reduced cartilage degeneration, but later administration did not. This indicates that timing of treatment with an anti-remodeling agent is critical to prevent the progression of early cartilage fibrillation to frank OA.

Estrogen and SERMS

Similar to human studies, the effects of estrogen treatment on OA in animals is unclear. Only half of the 22 animal studies reviewed by Sniekers et al.¹¹ showed protective effects of estrogen treatment in mice, rats, rabbits and sheep. More than 25% of the studies reviewed showed estrogen actually to be detrimental to cartilage health. Delayed administration of estrogen in OVX rats was less effective than immediate administration,⁷⁴ again suggesting that even in the event that estrogen has benefits for cartilage health, treatment of established OA with estrogens will be ineffective. Timing is key, as estrogen – or any hormonal or pharmaceutical treatment – might be able to downregulate the catabolic functions of chondrocytes, and prevent vascular invasion from bone, but cannot restore cartilage matrix once it is damaged. No known agent can stimulate chondrocytes to functionally repair cartilage that has already become fibrillated.

Studies with larger animal models, and

those closer taxonomically to humans may be better indicators of whether treatment will work in humans. Three years of estrogen treatment of cynomolgus monkeys begun immediately following OVX was associated with less severe OA than in controls, when adjusted for age and weight.⁷⁵ Either increased proteoglycan production by chondrocytes shown in the monkey study,⁷⁶ or possibly reduced proteoglycan degradation as shown in sheep treated with estradiol pellets⁷⁷ may account for the chondroprotective effects in these studies. A subsequent study in nonhuman primates, however, found neither changes in proteoglycans or any effect on cartilage degradation.⁷⁸

Changes in proteoglycan content may account for a positive mechanical outcome even in cases when there is no apparent effect on cartilage structure. Treatment of OVX sheep with estradiol implants, similar to the subsequent Richmond study, was associated with restoration of articular cartilage modulus (stiffness) to sham values, significantly greater than the modulus of untreated OVX sheep.⁷⁹

In contrast, most studies using SERMs to reduce cartilage degradation have shown positive results. In collagen-induced arthritis in mice with a mutated *ncf1* gene, either estrogen or a raloxifene analogue reduced cartilage deterioration,⁸⁰ as did levormeloxifene in rats,⁴⁸ and tamoxifen in meniscectomized rabbits.⁸¹⁻⁸³ Interestingly, in the mouse model of collagen-induced inflammatory arthritis, the raloxifene analogue and estrogen both were demonstrated to have positive effects on established arthritis, with fewer animals presenting evidence of arthritic changes and with significantly less cartilage degradation.⁸⁰ The precise mechanism for this effect is unclear, but various signaling pathways have been implicated in the beneficial effects of SERMS. One suggestion is that, because both raloxifene and tamoxifen are known to be GPER1 agonists, both affect PI3K/Akt and PKC/MAPK pathways.

Potential new therapies

More recent potential treatments such as strontium ranelate (SrRan) or cathepsin-K inhibitors (CatK) may be more effective than existing anti-catabolic treatments,^{84,85} but may act directly on cartilage rather than through their well-known effects on bone. Interestingly, SrRan has been shown to reduce gene expression for CatK in a canine OA model,⁸⁶ and in vivo studies using CatK in the canine model also demonstrated some beneficial effect.^{87,88}

SrRan

Several human trials using SrRan for the treatment of OA have shown encouraging results. An early study (TROPOS) demonstrated that SrRan decreased CTX-II regardless of whether the patient had OA.⁸⁹ This provided encouragement for larger and more extensive trials focused on OA. The SEKOIA trial was an international, multi-center randomized double-blind placebo-controlled phase 3 trial of knee OA in patients with primary knee OA.^{85,86} MRIs were used at baseline and 1, 2 and 3 years following treatment to evaluate cartilage volume and bone marrow lesions (BMLs). Treatment with SrRan at the higher dose (2 g/day, which is the osteoporosis dose) was associated with significantly less cartilage loss and both doses were associated with less joint space narrowing than in placebo controls. BMLs were reduced following three years of treatment, a significant finding given that BMLs have been shown to be an early indicator of progressive OA.⁹⁰

A study in the ACL transection model in dogs, in which cartilage could be evaluated histologically rather than with imaging techniques, supports the conclusions that SrRan may reduce cartilage lesions and preserve the collagen network, assessed by picrosirius red staining. The dosages used in this study (25, 50 and 75 mg/kg/day) span the range used for human osteoporosis (2 g/day or about ~25-40 mg/kg/day), but the greatest



effects were found for the higher dosages (50 and 75 mg/kg/day) suggesting that any beneficial effect of SrRan in OA may require doses higher than those used for postmenopausal osteoporosis. This could create negative side effects as high doses of Sr are known to suppress mineralization, but it is not clear whether the doses used in this study are sufficiently high to cause this. Interestingly, however, the thickness of the subchondral plate was reduced at all doses of SrRan compared to placebo treated dogs, an interesting finding for an agent that is used in postmenopausal osteoporosis to retain bone.

The mechanism for the beneficial effect of SrRan on cartilage is not entirely clear, but several possibilities exist. Early observations showed that SrRan helped to promote the aggregation of proteoglycans with the hyaluronic backbone to form the large aggrecan molecules that give cartilage its compressive stiffness.⁹¹ There is also some evidence in vitro that Sr may enhance the effects of IGF-1.⁹² Recent evidence in a canine model shows that SrRan downregulates metalloproteinases (MMP-1, 3 and 13), and ADAMTS5 in cartilage, as well as IL-1 β in synovium.⁸⁶ Downregulation of IL-1 β was also shown in vitro in chondrocytes.⁹² Both in vitro and in vivo studies suggest that SrRan may somehow re-balance an imbalance between chondrocyte-mediated cartilage catabolic and anabolic functions. The observation that higher doses of SrRan cause less loss of cartilage volume both at 1 and 3 years of treatment also could reflect a retention of water rather than, or in addition to, a retention of the organic and protein matrix.

*Cathepsin-K inhibitors***

Interestingly, one of the effects of SrRan is a significant reduction in CatK at high doses (75 mg/kg/day).⁸⁶ This raises the possibility that CatK inhibitors, which have mild anti-resorptive effects on bone, could be effective chondro-protective agents (Figure 4). This could counter the effect in human osteoarthritic cartilage of increased intracellular CatK activity⁹³ that occurs primarily in the superficial regions of cartilage which are most likely to become fibrillated,^{94,95} and in OA synovium.⁹⁶ CatK is known to be able to cleave collagen at sites that are different from those cleaved by MMPs^{93,97} and can degrade aggrecan.⁹⁶ Preclinical studies using transgenic mouse models show overexpression of CatK in a model that develops OA,⁹⁸ and a delay⁹⁹ or prevention⁸⁸ of cartilage loss in CatK knockout mice subjected to joint instability. In the latter studies, two different knockout models were used (Ctsk^{-/-} and CatK^{-/-} respectively) and two different models of joint instability (partial medial meniscectomy with transection of both MCL and ACL, vs. only an ACL transection, respectively), reinforcing the idea that the prevention of OA progression in these models was the result of the absence of CatK. Whether CatK expression is a cause or an effect of cartilage deterioration is not clear, but given its catabolic effects on type II collagen, its overexpression in association with cartilage deterioration at least suggests that it may be involved in the process of progressive cartilage loss. These roles for CatK do not preclude that inhibition of this cysteine protease may also prevent subchondral bone remodeling and vascular invasion to cartilage, and CatK may be a dual-acting treatment that can affect both cartilage and bone catabolism.

** The Editorial Committee of **Actualizaciones en Osteología** recognizes that the studies performed using the cathepsin K inhibitor odanacatib in the osteoarthritis model contribute to our understanding of the mechanism of action of the drug in this pathology. However, it should be noted that the company that developed odanacatib decided not to continue filing for FDA approval or any further development of the drug, due to the increased risk of stroke in post-menopausal women during the Phase 3 trial.

A short-term, 28 day experiment in partially-menisectomized female beagles treated with a CatK inhibitor (GlaxoSmithKline) also suggests some effect of this treatment, especially on the medial side of the weight bearing area of the tibial plateau,⁸⁷ in the area of the pre-existing meniscus. A >75% reduction in urinary CTX-II was also observed within one week following meniscectomy and in animals treated with the inhibitor, suggesting that this may prevent cleavage of Type II collagen and be chondroprotective.

Head to head studies comparing another CatK inhibitor (Merck and Co.) to ALN in an ACLT model in rabbits suggest that CatK inhibition at the higher dose (50 mg/kg/day, p.o., 5x higher than the dose used to retain bone in

OVX rats) was as effective as ALN (200 µg/kg, 3x/week, s.c., 3 times higher than the OVX dose) eight weeks after surgery.⁸⁸ As the CatK inhibitor at low dose resulted in greater retention of bone volume than ALN, but was not as effective at preventing cartilage changes, the effect of CatK inhibitors may be directly on the cartilage matrix itself, rather than through suppression of subchondral bone remodeling. Both doses of CatK inhibitor reduced urinary CTX-II, although the higher dose was more effective, and consistent with the reduction in CTX-II with ALN treatment. Therefore, the effect of CatK inhibitor in this case is likely through an inhibition of type II collagen degradation.

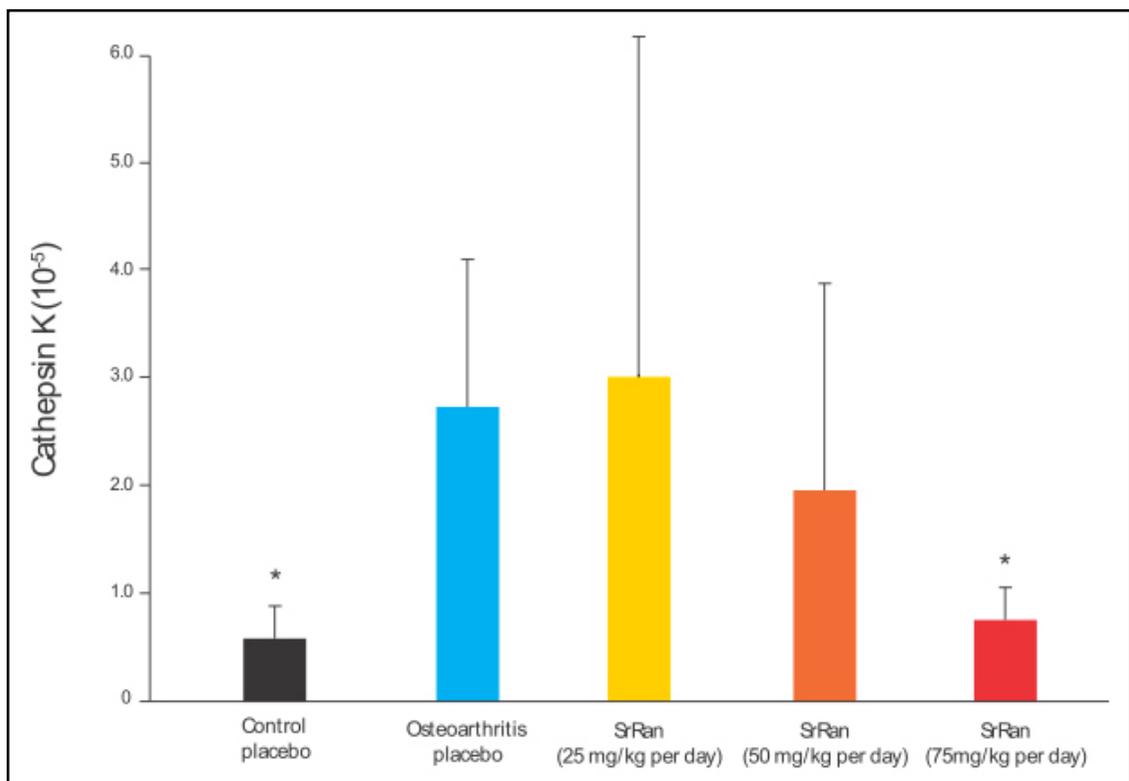


Figure 4. CatK is upregulated in articular cartilage chondrocytes in the early phases of OA, and the digestion of type II collagen by CatK may be associated with cartilage fibrillation. SrRan suppresses the production of CatK significantly, especially at high doses, and may protect the cartilage from deterioration (Data from Ref 86).



Conclusion

The conclusion from many of these studies is that anti-resorptive agents must be administered pre-emptively or in the very early stages of disease to be effective. This has several important implications. First, it suggests that remodeling suppressive treatments for OA will be most effective in cases of post-traumatic injury, when the timing of the occurrence of injury is well known. It will probably not be a terribly useful therapy in age-related joint degeneration, which develops over a long period of time and in which the timing of events initiating the cartilage loss cannot be determined. Second, better and earlier detection methods for joint disease would be useful, with an emphasis on biochemical or structural markers for early cartilage changes.¹⁰⁰ Imaging techniques that can be used to identify early structural changes in bone that pre-sage the progressive development of cartilage destruction must be developed. Recent evidence⁹⁰ suggests this may be on the near horizon. This study showed that progression of OA could be detected and predicted as long as two years before the appearance of radiographic OA by identifying synovitis (hazard ratio (HR) = 1.76-1.81) or damage to the medial meniscus (HR = 1.83). Bone marrow lesions apparent one year before the radiologic appearance of OA were an even stronger indicator (HR = 6.50). As BPs have been shown to have an effect on BMLs,²⁴ using BMLs as an indicator to begin treatment with an anti-catabolic agent may have some merit. However, it may not be possible in the near future to predict progression of cartilage disease with sufficient precision or sufficient lead time to make the use of bone anti-remodeling treatments aimed to prevent vascular invasion feasible. Therefore, in the near future, we should concentrate on those situations in which the onset of progressive cartilage changes is known, and progressive OA changes are predictable. Thus, for now, these treatments may be more beneficial in cases of ligament tears (e.g. ACL disruption) or

post-traumatic osteoarthritis (PTOA). However, it will still be necessary to determine in these cases whether the treatment is actually effective, and when treatment should be initiated.

Newer treatments that are incidentally anti-catabolic on bone, such as SrRan and CatK inhibitors, may also have direct effects on cartilage that are not dependent on bone. The mechanism of action of these agents is important to know and understand as well. Performing experiments that are time-sensitive in relation to the development of OA may also contribute to our understanding of the mode of action of the various different anti-remodeling agents. If some or all of them are effective, are they effective because of their action on bone, because of direct effects on cartilage catabolism/anabolism, or through a combination of these effects that may entail some feedback or cross talk between the bone and cartilage?

What do we need to do experimentally?

To fully evaluate the utility of bone anti-remodeling treatments in preventing the onset or progression of cartilage deterioration that eventually leads to OA, temporal changes in cartilage degradation should be evaluated using an animal model of OA exposed at different times (and perhaps for different durations) to remodeling-suppressive therapies. Because the beneficial effects of such therapies seem to depend on preventing the early phases of disease that involve vascular invasion of the deep layers of cartilage, an acute model of OA, such as the ACL transection model or a model of post-traumatic OA, should be used. Treatment with an anti-catabolic agent at three different time points could elucidate the value of the anti-remodeling therapy at different phases of OA progression. Treatment at three timepoints could be suggested:

- 1) Prior to evidence of aggrecan loss or cartilage clefting/fibrillation.
- 2) Following superficial clefting and loss of aggrecan in the superficial layers of the articular cartilage.

3) Following frank subchondral sclerosis Such a study could identify the appropriate timing for treatment in these common human conditions that are known to lead, over time, to progressive cartilage deterioration, and which have the advantage of a clear initiating time point at which treatment could be most effectively begun – a clinically valuable outcome. And, as pointed out above, such a study might help to further expose the target tissues and mechanism of action of the various compounds used for chondroprotection – a mechanistically-valuable outcome.

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