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Effects of Risedronate on Osteoarthritis of the Knee

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The purpose of the present study was to discuss the effects of risedronate on osteoarthritis (OA) of the knee by reviewing the existing literature. The literature was searched with PubMed, with respect to prospective, double-blind, randomized placebo-controlled trials (RCTs), using the following search terms: risedronate, knee, and osteoarthritis. Two RCTs met the criteria. A RCT (n = 231) showed that risedronate treatment (15 mg/day) for 1 year improved symptoms. A larger RCT (n = 1,896) showed that risedronate treatment (5 mg/day, 15 mg/day, 35 mg/week, and 50 mg/week) for 2 years did not improve signs or symptoms, nor did it alter radiological progression. However, a subanalysis study (n = 477) revealed that patients with marked cartilage loss preserved the structural integrity of subchondral bone by risedronate treatment (15 mg/day and 50 mg/week). Another subanalysis study (n = 1,885) revealed that C-terminal crosslinking telopeptide of type II collagen (CTX-II) decreased with risedronate treatment in a dose-dependent manner, and levels reached after 6 months were associated with radiological progression at 2 years. The results of these RCTs show that risedronate reduces the marker of cartilage degradation (CTX-II), which could contribute to attenuation of radiological progression of OA by preserving the structural integrity of subchondral bone. The review of the literature suggests that higher doses of risedronate (15 mg/day) strongly reduces the marker of cartilage degradation (CTX-II), which could contribute to attenuation of radiological progression of OA by preserving the structural integrity of subchondral bone.

Key Words: Osteoarthritis, knee, bisphosphonate, subchondral bone

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INTRODUCTION

Osteoarthritis (OA) of the knee is the most common type of arthritis and the major cause of chronic musculoskeletal pain and mobility disability in elderly populations, and therefore represents a significant burden on health care provision. Well established risk factors for OA include aging, obesity, and gender (female).[1] The most recent studies regarding the pathogenesis of OA have shown that the Wnt-β-catenin signal and the related molecules may regulate the development of OA through an endochondral ossification process including chondrocyte mutation and apoptosis.[2]

Optimal management of patients with OA of the knee requires a combination of non-pharmacological and pharmacological modalities of therapy. Recommendations cover the use of 12 non-pharmacological modalities: education and self-management, regular telephone contact, referral to a physical therapist, aerobic, muscle strengthening and water-based exercises, weight reduction, walking aids, knee braces, footwear and insoles, thermal modalities, transcutaneous electrical nerve stimulation, and acupuncture. Eight recommendations cover pharmacological modalities of treatment including acetaminophen, cyclooxygenase-2 (COX-2) non-selective and selective oral non-steroidal anti-inflammatory drugs (NSAIDs), topical NSAIDs and capsaicin, intra-articular injections of corticosteroids and

hyaluronates, glucosamine and/or chondroitin sulphate for symptom relief; glucosamine sulphate, chondroitin sulphate and diacerein for possible structure-modifying effects and the use of opioid analgesics for the treatment of refractory pain.[3] Basically, however, weight loss, physical therapy, and activity are important components of treatment.

Recently, studies using animal models of OA have shown that bisphosphonates are potentially therapeutic agents for disease modification in OA.[4-6] In the Duncan-Hartley guinea pig mode of spontaneous OA (the best-characterized model of primary non-traumatic OA[4]), the bisphosphonate, risedronate was shown to slow disease progression as measured by cartilage lesion size, severity, and osteophyte size, with a maximal effect of disease suppression of 30-40%.[7] There are several prospective, double-blind, randomized placebo-controlled trials (RCTs) reporting on the effects of risedronate on symptoms, function, and progression of OA in patients with OA of the knee.[8-11] Thus, risedronate could be a new candidate for the treatment of OA.[12] The purpose of the present study was to discuss the effect of risedronate on OA of the knee by reviewing the existing literature.

MATERIALS AND METHODS

Approaches for Determining the Effects of Risedronate on Knee OA

Prospective, double-blind RCTs on the effect of risedronate on OA in patients with knee OA were identified through PubMed, using the following search terms: risedronate, knee, and osteoarthritis. The literature search was conducted for English publications on RCTs. The effects of risedronate on symptoms, function, and progression of OA in patients with knee OA were analyzed using the data from RCTs.

Reporting findings

Identified RCTs

Two RCTs (four studies) met the criteria regarding the effects of risedronate on OA in patients with knee OA.[8-11] Table 1 shows the details of the identified four studies. The British study of risedronate in structure and symptoms of knee OA (BRISK) tested the efficacy and safety of rise-

Table 1. Studies That Met the Criteria

Investigators (year reported)	Study subjects	Groups	n	Study period	End-points
Spector (2005)[8] (BRISK)	Patients (40 - 80 yrs of age) with mild to moderate medial compartment knee OA	Risedronate (5 mg/day) Risedronate (15 mg/day) Placebo	96 90 98	1 yr	Joint space width, WOMAC OA index, PGA score, use of walking aids, bone and cartilage markers
Bingham (2006)[9] (KOSTAR)	Patients (40 - 80 yrs of age) with medial compartment knee OA and 2 - 4 mm of joint space width	Risedronate (5 mg/day) Risedronate (15 mg/day) Risedronate (35 mg/wk) Risedronate (50 mg/wk) Placebo	628 609 310 314 622	2 yrs	WOMAC OA index, PGA score, radiographic progression of OA
Buckland-Wright (2007)[10]* (KOSTAR)	Patients (40 - 80 yrs of age) with mild to medial compartment knee OA (a part of Bingham's study subjects were used)	Risedronate (5 mg/day) Risedronate (15 mg/day) Risedronate (50 mg/wk) Placebo	310 305 314 313	2 yrs	Subchondral bone structure
Garnero (2008)[11]* (KOSTAR)	Patients (40 - 80 yrs of age) with mild to medial compartment knee OA and 2 - 4 mm of joint space width (A part of Bingham's study subjects were used)	Risedronate (5 mg/day) Risedronate (15 mg/day) Risedronate (35 mg/wk) Risedronate (50 mg/wk) Placebo	In total, 1885 (available for analysis)	2 yrs	Radiographic progression of OA, bone and cartilage markers

OA, osteoarthritis; WOMAC, Western Ontario and McMaster Universities; PGA, patient global assessment; BRISK, The British Study of Risedronate in Structure and Symptoms of Knee OA; KOSTAR, The Knee OA Structural Arthritis.
*Subanalysis of a previous randomized controlled trial (KOSTAR) conducted by Bingham, et al.[9]

dronate in patients with knee OA. The Knee OA Structural Arthritis (KOSTAR) study of North America and the European Union, which is the largest study to date investigating a potential structure-modifying OA drug, tested the efficacy of risedronate in providing symptom relief and slowing disease progression in patients with knee OA. Studies of Backland-Wright, et al.[10] and Garnero, et al.[11] were subanalyses of a previous RCT (KOSTAR) conducted by Bingham, et al.[9] Finally, four studies in two RCTs were identified.

In four studies from two RCTs, the study subjects included patients (40-80 years of age) with mild to medial compartment knee OA. OA was diagnosed according to the clinical and radiological criteria of the American College of Rheumatology.[13] The doses of risedronate were 5 mg/day, 15 mg/day, 35 mg/week, and 50 mg/week. The study periods were 1-2 years. The numbers of study subjects enrolled were 284-2,483, and those analyzed were 231-1,896. The follow-up rates were 37.1-83.3%. The outcomes of RCTs were measured by Western Ontario and McMaster Universities (WOMAC) OA index (total, pain, function, and stiffness),[14] patient global assessment (PGA) scores, use of walking aids, subchondral bone structure, radiographic progression of OA, bone and cartilage markers. WOMAC measurements were collected on a 100-mm visual analog scale (VAS). For assessment of the PGA score, patients answered the following question using a VAS: "Considering all the ways your OA affects you, how have you been in the last 48 hours?" Patients marked values on a scale from 0 to 100 mm.

Effects of risedronate on knee OA

Table 2 summarizes the outcomes of four studies in two RCTs. A RCT (n = 231, study period 1 year) by Spector, et al.[8] showed that risedronate (15 mg/day) reduced urinary levels of C-terminal crosslinking telopeptide of type II collagen (CTX-II) (Fig. 1) and N-terminal crosslinking telopeptide of type I collagen (NTX-I) in a dose-dependent manner, improved PGA scores but not WOMAC scores, reduced the proportion of patients who used walking aids, but did not attenuate joint space narrowing. Thus, risedronate (15 mg/day) reduced markers of cartilage degradation and bone resorption and improved symptoms of OA.

A larger RCT (n = 1,896, study period 2 years) by Bingham, et al.[9] showed that risedronate at any doses (5 mg/day, 15 mg/day, 35 mg/week, and 50 mg/week) reduced urinary levels of CTX-II and NTX-I, but did not improve WOMAC scores, PGA scores, average number of days, and number of pills of analgesic medication taken per week, joint space width, and osteophyte development.

Table 2. Effects of Risedronate on Knee OA

Investigators (year reported)	Groups	n (%), who completed the trial	Outcomes
Spector (2005)[8] (BRISK)	Risedronate (5 mg/day) Risedronate (15 mg/day) Placebo	80 (83.3) 71 (78.9) 80 (81.6)	Risedronate (15 mg/day) reduced markers of cartilage degradation and bone resorption and improved symptoms
Bingham (2006)[9] (KOSTAR)	Risedronate (5 mg/day) Risedronate (15 mg/day) Risedronate (35 mg/wk) Risedronate (50 mg/wk) Placebo	493 (78.5) 466 (76.5) 244 (78.7) 218 (69.4) 475 (76.4)	Risedronate did not improve signs or symptoms of OA, nor did it alter progression of OA, although a reduction in the level of a marker of cartilage was observed
Buckland-Wright (2007)[10]* (KOSTAR)	Risedronate (5 mg/day) Risedronate (15 mg/day) Risedronate (50 mg/wk) Placebo	124 (38.3) 115 (37.1) 118 (38.7) 120 (38.2)	Patients with marked cartilage loss (joint space narrowing ≥ 0.6 mm) receiving risedronate (15 mg/day) retained vertical trabecular structure, and those receiving risedronate (50 mg/wk) increased vertical trabecular number, thereby preserving the structural integrity of subchondral bone
Garnero (2008)[11]* (KOSTAR)	Risedronate (5 mg/day) Risedronate (15 mg/day) Risedronate (35 mg/wk) Risedronate (50 mg/wk) Placebo	In total, 1,885 (available for analysis)	CTX-II decreased with risedronate treatment in a dose-dependent manner, and levels reached after 6 months were associated with radiological progression at 2 yrs

OA, osteoarthritis; WOMAC, Western Ontario and McMaster Universities; PGA, patient global assessment; CTX-II: C-terminal cross-linked telopeptide of type II collagen; BRISK, The British Study of Risedronate in Structure and Symptoms of Knee OA; KOSTAR, The Knee OA Structural Arthritis.
*Subanalysis of a previous randomized controlled trial (KOSTAR) conducted by Bingham, et al.[9]

Thus, risedronate did not improve signs or symptoms of OA, nor did it alter progression of OA, although a reduction in the level of a marker of cartilage was observed.

A subanalysis study (the North America arm, n = 477) by Buckland-Wright, et al.[10] used computed method of fractal signature analysis (FSA) to quantify longitudinal changes separately in horizontal and vertical trabeculae in the region of interest (three-fourth width of tibial compartment × 6 mm height) in the medial compartment. It was revealed that patients with marked cartilage loss (joint space narrowing ≥ 0.6 mm) receiving risedronate (15 mg/day) retained vertical trabecular structure, and those receiving risedronate (50 mg/week) increased vertical trabecular numbers, thereby preserving the structural integrity of subchondral bone. Thus, higher doses of risedronate (15 mg/day and 50 mg/week) inhibited trabecular bone loss in the subchondral region of the diseased medial compartment of the tibia.

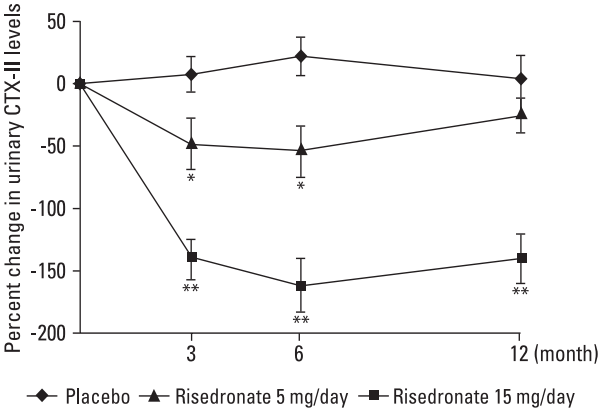

Fig. 1. Changes in urinary CTX-II levels after treatment with placebo or risedronate in patients with Knee OA. OA, osteoarthritis; CTX, C-terminal crosslinking of type II collagen. *$p < 0.05$ vs. placebo, **$p < 0.001$ vs. placebo.

Another subanalysis study by Garnero, et al.[11] (the North America and European Union arms, n = 1,885) revealed that urinary levels of CTX-II and NTX-I decreased with risedronate treatment in a dose-dependent manner (Fig. 2). In particular, higher doses of risedronate (15 mg/day) strongly reduced urinary levels of CTX-II and NTX-I. Patients who had CTX-II levels returned to low levels at 6 months (high/low group in Table 3) had a lower risk of radiographic progression of OA at 24 months than patients whose CTX-II levels were increased both at baseline and 6 months (high/high group in Table 3) (odds ratio 0.57, 95% confidence interval 0.39-0.85) after adjustment for body

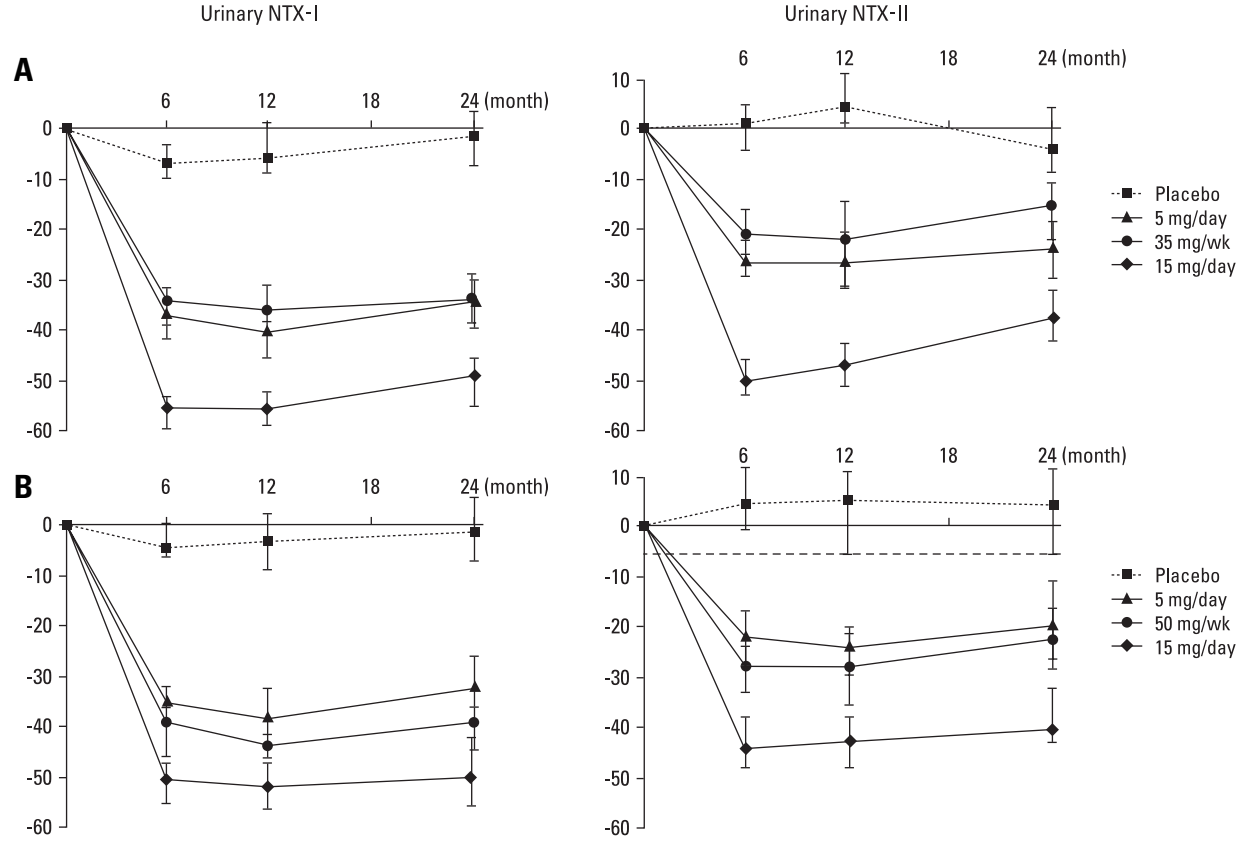

Fig. 2. Changes in urinary NTX-I and CTX-II levels in patients with knee OA treated with placebo or risedronate. The graphs show the median and the confidence interval limits of the percentage change from baseline of NTX-I (left) and CTX-II (right) in the European (A) or North American (B) study. OA, osteoarthritis; NTX, N-terminal crosslinking of type I collagen; CTX, C-terminal crosslinking of type II collagen.

Table 3. Urinary CTX-II Levels at Baseline and 6 Months for Predicting 24-Month Radiological Progression

Urinary CTX-II levels (baseline / 6 months*)	Mean ± SE of change in joint space narrowing at 24 months		Radiological progression† at 24 months	
	Absolute change (mm)	% change from baseline	Progressor (%)	Relative risk (95% CI)†
High / High (n = 1,152)	- 0.121 ± 0.015	- 4.2 ± 0.5	15	1.0 (reference)
High / Low (n = 372)	- 0.088 ± 0.023	- 2.9 ± 0.8	11	0.57 (0.39 - 0.85)
Low / High (n = 120)	- 0.108 ± 0.039	- 4.5 ± 1.5	13	0.77 (0.43 - 1.36)
Low / Low (n = 241)	- 0.041 ± 0.024	-1.6 ± 0.9	6	0.36 (0.21 - 0.63)

OA, osteoarthritis; CTX, C-terminal crosslinking of type II collagen; WOMAC, Western Ontario and McMaster Universities; CI, confidence interval.
*Baseline and 6 month cut-off values of CTX-II at 150 nmol/mmol to separate low and high levels.
†Progression was defined as a joint space narrowing ≥ 0.6 mm at any post baseline visit.
†Relative risks were adjusted for body mass index, WOMAC pain, hip OA, knee crepitus at baseline, baseline joint space narrowing and treatment allocation.

mass index, gender, WOMAC pain, hip OA, knee crepitus at baseline, baseline joint space width, and treatment allocation. The lower risk of progression of OA was observed in patients who had low CTX-II levels both at baseline and 6 months (low/low group in Table 3) (odds ratio 0.36, 95% confidence interval 0.21-0.63). Thus, measurements of urinary CTX-II prior to initiating treatment with risedronate and 6 months after the start of therapy provide useful information with respect to the radiological prognosis of patients with knee OA.

The results of these RCTs show that higher dose of risedronate (15 mg/day) strongly reduces the marker of cartilage degradation (CTX-II), which could contribute to attenuation of radiological progression of OA by preserving the structural integrity of subchondral bone. However, the effects of risedronate on symptoms and functions of knee OA were inconsistent.

Adverse events of risedronate

The number of dropouts and withdrawals was similar across groups in two RCTs. Adverse events were categorized using the Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTAT) coding dictionary. The incidence of side effects including upper gastrointestinal adverse events did not differ significantly among subjects treated with risedronate at any doses and placebo. No severe adverse event was observed in any RCTs. All doses of risedronate treatment used in RCTs were well tolerated, and risedronate was confirmed to be safe in patients with knee OA.

DISCUSSION

Treatment of knee OA ought to be conducted in accordance with the principles of evidence-based medicine (EBM). EBM incorporates information derived from the highest-quality investigations with clinical judgment and patient values, to allow optimal clinical management. Available clinical evidence has been classified hierarchically into various levels, with strictly conducted systematic reviews representing the highest level, followed by RCTs or meta-analyses of RCTs, which have long been considered as the "gold standard" in the context of clinical investigations.[15] Thus, the present study was conducted as a review of the literature, especially prospective, double-blind RCTs, to discuss the effects of risedronate on knee OA.

It is known that joint space narrowing, sclerosis of the subchondral bone, and presence of osteophyte are typical structural features of knee OA. Thus, both articular cartilage and subchondral bone were considered to be involved in the pathogenesis of knee OA. However, recent evidence has shown that increased local bone turnover, decreased bone mineral content and stiffness, trabecular bone loss have been observed in the subchondral bone structure of knee OA,[4,16,17] and therefore subchondral bone abnormalities might be a major factor in disease progression. Progressive thickening and flattering of the subchondral cortical plate could produce a "stress shielding" effect, resulting in localized trabecular bone loss as well as increased bone turnover in the subchondral bone.[18-21] Actually, levels of bone turnover markers have been reported to be higher in patients with progressive knee OA similarly to postmenopausal women with osteoporosis.[22] Patients with progressive knee OA may have a higher bone turnover compared with milder knee OA, because urinary levels of CTX-II are correlated with the progression of knee OA.[11] Thus, subchondral bone is an important therapeutic OA target, and could be modified in patients with progressive knee OA by anti-resorptive agents such as bisphosphonates. The main outcomes of four studies in RCTs were not only WOMAC OA index and PGA score, but also radiographic progression of OA, subchondral bone structure, and bone and cartilage markers.

Modulating subchcondral bone turnover by bisphosphonates has become an attractive approach as a potential structure modifying anti-OA drug target. Bisphosphonates are anti-resorptive compounds that regulate bone turnover

through suppression of osteoclastic activity. The effect of risedronate on bone turnover helps to preserve the trabcular architecture and thus improve bone strength in humans.[23] The results of the present review of the literature show that higher doses of risedronate (15 mg/day) strongly reduce the marker of cartilage degradation (CTX-II), which could contribute to attenuation of radiological progression of OA by preserving the structural integrity of subchondral bone. However, clinical relevance of suppression of bone turnover and preservation of the structural integrity of subchondral bone by risedronate treatment remains uncertain.

Both RCTs showed risedronate treatment reduced urinary levels of CTX-II and NTX-I,[8,9] and a subanalysis study of the RCT (KOSTAR) by Garnero, et al.[11] revealed that urinary levels of CTX-II, but not NTX-I, reached after 6 months of risedronate treatment were associated with radiological progression of knee OA at 24 months. CTX-II is a marker of cartilage degradation, while radiological progression of knee OA might be associated with subchondral bone structure. The association of urinary CTX-II and progression of knee OA could be explained by the studies suggesting that CTX-II is not only released from the surface of the cartilage, but also from the bone to cartilage interface region within the calcified region.[24,25] The rapid reduction in urinary levels of CTX-II might be attributable to decreases in subchondral bone turnover and articular and/or calcified cartilage degradation.[11]

The effects of risedronate on symptoms and functions of knee OA were inconsistent when WOMAC OA index and PGA scores were used as end-points. In a subanalysis study of the RCT (BRISK) by Buckland-Wright, et al.,[10] there was a beneficial effect of higher doses of risedronate (15 mg/day and 50 mg/week) on subchondral bone structure, but this was not correlated with a concomitant treatment effect for signs and symptoms of knee OA. The radiological severity of knee OA is not always correlated with signs and symptoms, because clinically, various factors including quadriceps muscle weakness could contribute to signs and symptoms. Thus, additional treatments to risedronate may be needed to improve WOMAC OA index and PGA scores in terms of symptoms and functions in patients with knee OA.

Like risedronate, other bisphosphonates such as alendronate, zoledronate, and neridronate may have the potential to be efficacious for radiological progression of knee OA,[26] although there are no reports of RCTs in patients with knee OA. Recently, Neogi, et al.[27] conducted a secondary analysis of patients randomly selected from the Fracture Intervention Trial (FIT), and demonstrated a small reduction in spinal osteophyte progression in those patients randomized to receive alendronate compared with placebo. Bruyere, et al.[28] also conducted a post-hoc analysis of pooled data from the Spinal Osteoporosis Therapeutic Intervention (SOTI) and TReatment Of Peripheral OSteoporosis (TROPOS) trials, and showed that strontium ranelate could reduce the progression of the radiographic features of spinal OA and back pain in women with osteoporosis and prevalent spinal OA. Thus, alendronate and strontium ranelate could be a potential interest in OA. However, further studies are required to establish the effect of those bisphosphonates and strontium ranelate on knee OA.

There are critical limitations in the present review study. First, the number of RCTs was so small that meta-analysis or systematic review was not possible. Second, the proportion of patients included in RCTs who had significant progression of joint space narrowing was so small that a longer-period of observation or subjects with more risk factors for disease progression might be needed to determine the effect of risedronate on the progression of knee OA. Meta-analysis or systematic review studies analyzing RCTs with longer period of observation in patients with more risk factors for disease progression including further RCTs are needed to establish the efficacy of risedronate for symptom, function, and progression of knee OA.

In conclusion, the review of the literature suggests that higher doses of risedronate (15 mg/day) strongly reduces the marker of cartilage degradation (CTX-II), which could contribute to attenuation of radiological progression of OA by preserving the structural integrity of subchondral bone. However, meta-analysis or systematic review studies analyzing RCTs including further RCTs are required to establish the efficacy of risedronate for symptoms, function, and progression of knee OA.

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