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Editorial

Does denosumab not only prevent fractures, but also bone erosions in rheumatoid arthritis?

This editorial refers to 'Therapeutic efficacy of denosumab for rheumatoid arthritis: a systematic review and meta-analysis', by Yagita *et al.* [1]

Osteoporosis occurs predominantly in postmenopausal women, in whom bone turnover is upregulated and the risk of low bone mineral density (BMD) and vertebral and non-vertebral fractures is elevated [2, 3]. The majority of osteoporotic patients are treated with antiresorptive drugs: alendronate, risedronate, ibandronate, zoledronic acid, raloxifene and denosumab. For all these antiresorptive drugs, a reduction in bone resorption, an increase in BMD of the lumbar spine and hips and a reduction in (vertebral) fractures has been described in postmenopausal women. Meta-analyses of oral bisphosphonates report a 30–45% reduction of vertebral fractures compared with placebo and an even larger risk reduction $\leq$70% for zoledronic acid and denosumab [4].

However, denosumab has a different mode of action from bisphosphonates. Modern (nitrogen-containing) bisphosphonates act primarily on the mevalonate pathway to inhibit osteoclastic bone resorption. Denosumab is a monoclonal anti-RANKL antibody, which inhibits osteoclastic formation by binding to RANKL on the osteoblast. The question is whether denosumab has a favourable effect on both generalized bone loss (measured by BMD) and local bone loss (erosions) in patients with RA, a chronic inflammatory disorder in which bone resorption can be upregulated [5].

The systematic review and meta-analysis by Yagita *et al.* [1] is therefore very welcome. The study is based on a thorough selection process that is well conducted and includes 12 cohort studies and six randomized controlled trials, including almost 1700 RA patients and 1200 controls. More than two-thirds of included patients were postmenopausal women. Treatment with denosumab during 1 year compared with placebo leads to a significant increase in BMD at the lumbar spine, total hip and femoral neck of 5.27% (95% CI 4.37, 6.18), 2.82% (2.46, 3.18) and 3.07% (2.66 to 3.48), respectively. Although no effect was found on fractures, the clinically most relevant endpoint, it is plausible that the increase in BMD during denosumab treatment is associated with an increase in bone strength and that the number of patients was too low to expect a difference in fracture rate.

Of even more interest is the suggested inhibitory effect of denosumab on bone erosions, observed in all five studies included in the meta-analyses, emphasizing the consistency of data. The mean difference in modified total Sharp score and erosion score after 1 year between denosumab- or placebo-treated patients was −0.49% (−0.92 to −0.07) and −0.70% (−0.96 to −0.45), respectively.

In contrast to the effect of denosumab on BMD and on bone erosions in RA, there seems to be some uncertainty on the effect on cartilage. Yagita *et al.* [1] observed in five studies a small but significant difference in joint space narrowing between denosumab- and placebo-treated patients [−0.07% (−0.10 to −0.04)], but this finding should be interpreted with caution because the main effect is based on a single study [6], and no direct effect of denosumab on chondrocytes has been determined in previous studies. In line with that, Cohen *et al.* [7] performed a high-quality randomized, double-blind, placebo-controlled study in RA, and they found an increase in BMD, a decrease in erosion score, but no effect on cartilage and on joint space narrowing. Therefore, although all antiresorptive drugs are effective anti-osteoporotic drugs in postmenopausal women and reduce (vertebral) fractures, the crucial question is whether antiresorptive drugs other than denosumab also reduce the formation of bone erosions in RA.

We performed a literature search on the effects of antiresorptive drugs on bone erosions in RA (see Table 1). In total, six studies investigated the use of different bisphosphonates in RA patients, of which four studies showed no favourable statistically significant effect on erosions. One study with zoledronic acid by Jarrett *et al.* using MRI showed a reduction in the number of hand and wrist bones with erosions *vs* placebo [8]. Another study by Maccagno *et al.* showed significantly fewer bone erosions reported after 1 year of treatment with high-dose pamidronate (1000 mg/day) [9]. In a study by Eggelmeijer *et al.* with 300 mg/day pamidronate, with 3 years of observation, no effect on radiological joint damage was found [10].

It has not been elucidated fully whether the reported lack of effect of bisphosphonates in reducing radiological joint damage in RA is attributable to shortcomings in study design or a lack of effectiveness, but there is a striking contrast with the data of denosumab, as demonstrated in the study by Yagita *et al.* [1]. The observed reduction in the number of bone erosions, in contrast to the above presented data of bisphosphonates, could be related to the higher number of patients in the denosumab meta-analyses [1], but it could also be related to a higher potency of denosumab. In a study in postmenopausal women, the decreases in serum CTX (C-telopeptide of type 1 collagen, a marker of bone resorption) after 3 months of treatment was much larger for denosumab than for alendronate: −89% *vs* −66% [14]. Another possibility is that it is related to the different mode of

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Table 1 Literature search on the effects of bisphosphonates on bone erosions in RA

Author	Design	Drugs	Follow-up	Findings
Maccagno *et al*. [9]	RCT	Pamidronate 1000 mg daily ($n = 14$) *vs* placebo ($n = 13$)	1 year	Significantly less erosions in pamidronate group
Eggelmeijer *et al*. [10]	RCT, DMARD-treated RA patients	Pamidronate 300 mg daily ($n = 54$) *vs* placebo ($n = 51$)	3 years	No difference in radiographic progression
Valleala *et al*. [11]	RCT, DMARD-treated RA patients	Etidronate ($n = 19$) *vs* control ($n = 20$)	2 years	No difference in radiographic progression
Jarrett *et al*. [8]	RCT, MTX-treated RA patients	Zoledronic acid week 0 and 13 ($n = 18$) *vs* placebo ($n = 21$)	26 weeks	No difference in number of erosions in hands/wrists on MRI/X-ray
Valleala *et al*. [12]	RCT, DMARD-treated RA patients	Clodronate 1600 mg daily ($n = 30$) *vs* control ($n = 30$)	2 years	No difference in radiographic progression
Ebina *et al*. [13]	Retrospective case–control study in biologic naïve female RA patients	Continuing bisphosphonate ($n = 30$) *vs* switch to denosumab ($n = 30$) *vs* switch to teriparatide ($n = 30$)	1 year	mSES significantly lower only in denosumab group

mSES: modified sharp erosion score; RCT: randomized controlled trial.

action of denosumab *vs* bisphosphonates and its specific effect on RANKL. Data from this meta-analysis regarding safety show no increased risk of upper respiratory infection in patients treated with denosumab.

In conclusion, denosumab is a good option for the prevention of vertebral and non-vertebral fractures in postmenopausal osteoporotic women with RA [15]. Although all anti-resorptive drugs reduce vertebral fractures, denosumab seems to have the unique advantage of a beneficial effect on joint preservation by inhibition of development of bone erosions in RA, already after 1 year of treatment. For rheumatologists and their postmenopausal RA patients, the advantage of denosumab in reducing both generalized bone loss leading to fractures and local bone loss associated with bone erosions is attractive. Of course, these positive factors have to be outweighed against the risk of vertebral fractures after stopping denosumab and drug costs [15].

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Data availability statement

No new data were generated or analysed in support of this research.

Anneke F. Marsman[1], Sjoerd C. Heslinga[1] and Willem F. Lems[1,2]

[1]Department of Rheumatology, Amsterdam University Medical Center, location VUmc, [2]Department of Rheumatology, Amsterdam Rheumatology and Immunology Center, location Reade, Amsterdam, The Netherlands

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Correspondence to: Anneke F. Marsman, Department of Rheumatology, Amsterdam University Medical Center, location VUmc, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands. E-mail: a.marsman1@amsterdamumc.nl

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