Denosumab use reduces risk of rheumatoid arthritis in patients with osteoporosis

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Abstract

Objective

To investigate the protective effect of osteoporosis medications on the risk of developing rheumatoid arthritis (RA) in patients with osteoporosis.

Methods

We conducted a retrospective cohort study from 1 January, 2011 to 31 March, 2023. There was a total of 971901 patients from a hospital-based population in Taiwan. In this cohort, there was a total of 17065 osteoporosis patients with or without pathological fracture. In these patients, 7180 patients were osteoporosis medication users, and 9605 patients were non-osteoporosis medication users, after exclusion of previous RA. The risk of RA in the patients with osteoporosis medications was assessed, and stratified by sex and different medications, including bisphosphonates, denosumab, raloxifene and teriparatide.

Results

Patients with osteoporosis medication use had a reduced risk of RA compared with non-osteoporosis medication users [adjusted hazard ratio (aHR)=0.484, 95%CI: 0.270–0.867, p<0.05), after adjusting for age, comorbidites and medications. Specifically, patients with ever use of bisphosphonates (n=2069) or denosumab (n=4510) had a reduced risk of RA (aHR=0.405, 95%CI: 0.173–0.951, p<0.05, and aHR=0.394, 95%CI: 0.192–0.809, p<0.05, respectively). Notably, patients that only used denosumab (n=2938) had a further reduced risk of RA (aHR=0.32, 95%CI: 0.12–0.83, p<0.05), particularly in female patients (aHR=0.26, 95%CI: 0.09–0.74, p<0.05). Patients taking raloxifene or teriparatide did not have a significantly reduced risk of RA.

Conclusion

Denosumab use reduces the risk of RA in patients with osteoporosis. Receptor activator of nuclear factor kappa B ligand (RANKL) mediated osteoclast joint damage may be involved in the pathogenesis of RA during the preclinical stage.

Key words

rheumatoid arthritis, osteoporosis, denosumab, receptor activator of nuclear factor kappa B ligand, bisphosphonates

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Introduction

The mechanism of osteoporosis medications includes inhibition of bone resorption and induction of bone formation. The main anti-resorptive or anti-catabolic agents are bisphosphonates, selective oestrogen receptor modulators (SERMs) and monoclonal antibody against receptor activator of nuclear factor kappa B ligand (RANKL), which stabilise the skeleton and reduce fracture risk in patients with osteoporosis (1). RANKL is made by osteoblasts which stimulates osteoclast development. Bone forming or anabolic agents are parathyroid hormone and sclerostin inhibitor, which aid in the building up of new bone, increase bone mass and improve bone architecture (2, 3).

Rheumatoid arthritis (RA) is a chronic inflammatory disease affecting the joint and extra-articular organs, resulting in cartilage destruction, bone erosion and disability (4). RA is characterised by altered innate and adaptive immune responses attacking against self-antigens in joint (5). Synovitis, bone erosion, cartilage destruction and periarticular osteoporosis are hallmark of clinical manifestations of RA (4). Focal bone resorption in the arthritic joint occurs due to excessive activity of osteoclasts (6). One study has shown that rituximab delays the development of arthritis in individuals who were positive for both anti-citrullinated peptide antibodies (ACPA) and rheumatoid factor (RF) but without arthritis (7). RANKL is essential for the proliferation, differentiation and survival of osteoclasts. Denosumab is a humanised monoclonal antibody against RANKL, acting as an anti-resorptive osteoporosis medication (8). Several studies have demonstrated that denosumab could inhibit bone erosion and stabilise joint destruction in patients with RA (9~14). To our knowledge, whether osteoporosis medications have the protective effect on the development of RA in patients with osteoporosis has not yet been reported. We aim to investigate the association of osteoporosis medication use with the risk of RA occurrence from a hospital-based population. The study was carried out to assess if the use of specific osteoporosis medication can reduce the risk of developing RA in the osteoporosis patients with or without pathological fracture from the patient database in Taipei Tzuchi Hospital, Taiwan. The osteoporosis medications that were assessed in this study included the anti-resorptive drugs, bisphosphonates, denosumab, raloxifene, and the bone-formation drug, teriparatide.

Material and methods

Data source

We conducted a retrospective cohort study using the patient database in a quasi-medical centre, Taipei Tzuchi Hospital, Taiwan. The database contains all records in health care, including patient demographic characteristics, out-patient medical visits, emergency care, hospitalisation, details of disease diagnoses, drug prescriptions and medical procedures from 1 January, 2011 to 31 March, 2023. There was a total of 971901 patients included in the patient database. International Classification of Diseases-9th revision-Clinical Modification (ICD-9-CM) system was used to code the diseases. The patients in the database were encrypted, and patient informed consent was waived. This study was approved by the Institutional Review Board (IRB) of Taipei Tzuchi Hospital, Taiwan (12-XD-039).

Study population and osteoporosis medication use

The study population consisted of patients with newly diagnosed osteoporosis (ICD-9-CM=733.0) or osteoporosis with pathological fracture (ICD-9-CM=733.1) from 2011 to 2023, and age ≧40 years-old. There was a total of 17065 osteoporosis patients with or without pathological fracture.

The osteoporosis patients with or without pathological fracture were divided into two groups with or without osteoporosis medication use. Osteoporosis medications available in our study included bisphosphonates (alendronate, ibandronate, zoledronate), denosumab, raloxifene, and teriparatide. Patients with osteoporosis medication use after diagnosis of osteoporosis with or without pathological fracture were necessary for inclusion as an osteoporosis medication group. Patients without osteoporosis medication

use after diagnosis of osteoporosis with or without pathological fracture were included as a non-osteoporosis medication group. A total of 7344 patients with osteoporosis medications, and a total of 9721 patients without osteoporosis medications were enrolled. To confirm new-onset RA (ICD-9-CM=714.0), we excluded those with previous RA before the diagnosis of osteoporosis with or without pathological fracture. Therefore, a total of 7180 patients with osteoporosis medications, and 9605 patients without osteoporosis medications were included after exclusion of previous patients with diagnosis of RA. The index date was the first date of diagnosis of osteoporosis with or without pathological fracture in both the osteoporosis medication group and the non-osteoporosis medication group. The outcome variable was defined as a diagnosis of RA. Patients were followed up with until the earliest of the occurrence of RA, the date of 31 March, 2023 was reached, or withdrawal from the patient database. The study flow chart to identify these osteoporosis patients with or without osteoporosis medications is shown in Figure 1.

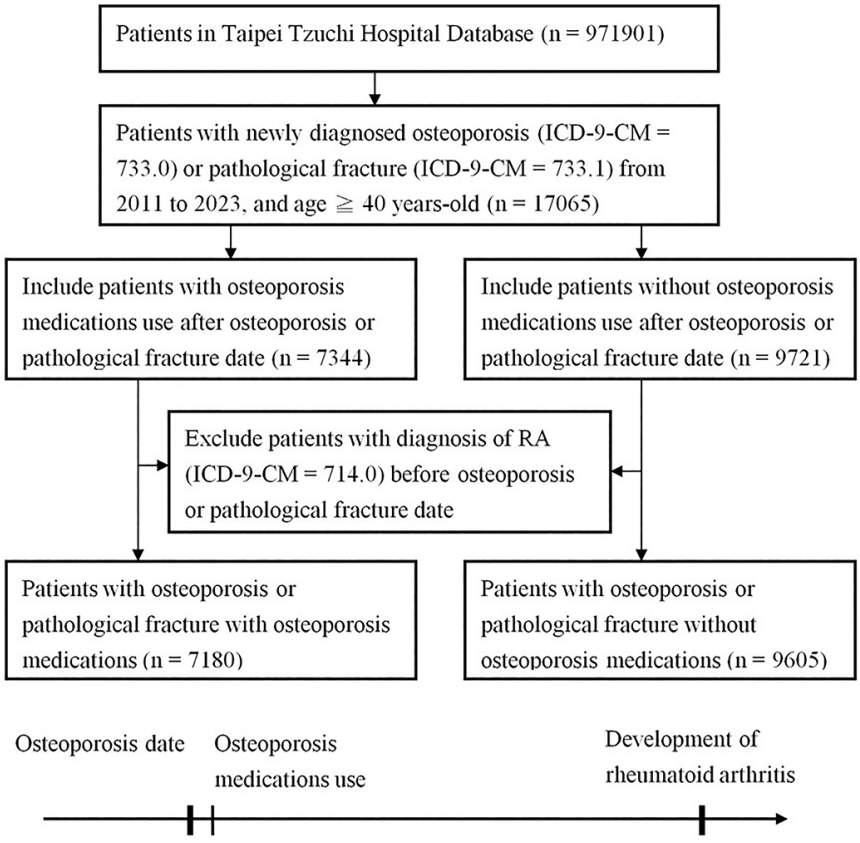

Fig. 1. Study flow chart of the osteoporosis patients using or not using osteoporosis medications.

Patients with different sex, and use of specific osteoporosis medication, including bisphosphonates, denosumab, raloxifene and teriparatide were further analysed to determine the risk of developing RA.

The baseline characteristics were age, sex, and common comorbidites, hypertension (HTN) (ICD-9-CM=401), diabetes mellitus (DM) (ICD-9-CM=250), hyperlipidaemia (ICD-9-CM=272.0, 272.1, 272.3, 272.4, 272.9), obesity (ICD-9-CM=278) and renal failure (ICD-9-CM=584, 585, 586, V45.1). Those comorbidites were defined occurring before and within one year of the index date. The medication use of corticosteroids (prednisolone, methylprednisolone), NSAIDs (celecoxib, etoricoxib, meloxicam), lipid lowing agents (statin, triglyceride lowing drugs), and Vitamin D3 after the index date during the study period were included as the covariates.

Statistical analysis

Continuous variables were described as mean ± standard deviation (SD.). Student t-test was used for continuous variables, and Pearson's Chi-squared test was used for categorical variables. Kaplan-Meier analysis was used to estimate the cumulative incidence of RA across the study period, and the log-rank test was used to evaluate the significance. Cox proportional hazard model was used to estimate the hazard ratio (HR) of developing RA in relation to osteoporosis medication use and was adjusted for potential confounding variables. A p-value <0.05 is considered as significant. The statistical analysis was supported by computer programme software (ASUS LUMOS v. 3.3).

Results

Patient characteristics

A total of 7180 patients with osteoporosis medication use and a total of 9605 patients without medication use were included in this cohort study. Age and percentage of female patients were higher in the osteoporosis medication group than the non-osteoporosis medication group (both p<0.001). Percentage of comorbidites with HTN, DM, hyperlipidaemia and renal failure were higher in the osteoporosis medication group than the non-osteoporosis medication group (all p<0.01). The medication use of corticosteroids, NSAIDS, lipid lowing agents and vitamin D3 were higher in the osteoporosis medication group than the non-osteoporosis medication group (all p<0.001). The demographic characteristics of the patients with and without osteoporosis medications are shown in Table I.

Decreased risk of developing RA in patients with osteoporosis medication use, particularly in female patients

HRs for developing RA in patients with osteoporosis medications is shown in Table II. There was a total of 7180 patients with osteoporosis medication use and a total of 9605 patients without osteoporosis medication use. Patients with osteoporosis medications show significantly reduced HR for developing RA when compared with non-osteoporosis medication users (adjusted HR=0.484, 95% CI: 0.270–0.867), after adjusting for age, sex, comorbidities and medi-

Table I. Clinical characteristics of the osteoporosis patients with or without osteoporosis medication use.

Characteristic	Osteoporosis medication users	Osteoporosis medication users (%)	Non-osteoporosis medication users	Non-osteoporosis medication users (%)	*p*-value
Patient count	7180	-	9605	-	NA
Age (mean ± SD)	73 ± 10	-	69 ± 12	-	< 0.001*
Gender (male)	777	10.8	2397	25.0	< 0.001*
Gender (female)	6403	89.2	7208	75.0	< 0.001*
Hypertension	2720	37.9	2838	29.5	< 0.001*
Diabetes mellitus	1273	17.7	1555	16.2	< 0.01*
Hyperlipidaemia	1568	21.8	1867	19.4	< 0.001*
Obesity	60	0.8	130	1.4	< 0.01*
Chronic renal failure	559	7.8	634	6.6	< 0.01*
Corticosteroids	919	12.8	969	10.1	< 0.001*
NSAIDs	3665	51.0	3769	39.2	< 0.001*
Lipid lowing agents	1481	20.6	1651	17.2	< 0.001*
Vitamin D3	2929	40.8	1866	19.4	< 0.001*

Values are shown as Mean ± standard deviation or patient number (%).
Student t-test was used for continuous variables and, and Pearson's Chi-squared test was used for categorical variables. *Significance.

cation use. Further analysis was performed, and the HRs for developing RA between patients with and without osteoporosis medications, stratified by sex is shown in Table II. In the female subgroup, there was a total of 6403 patients with osteoporosis medication use and a total of 7208 patients without osteoporosis medication use. Female patients with osteoporosis medication use had reduced HR for developing RA when compared with non-osteoporosis medication users (adjusted HR=0.471, 95% CI: 0.259–0.856). In the male subgroup, there were a total of 777 patients with osteoporosis medication use and a total of 2397 patients without osteoporosis medication use. Osteoporosis medication use in male patients did not have significant association with developing RA when compared with non-osteoporosis medication users (adjusted HR=0.788, 95% CI: 0.077–8.094).

HRs for developing RA in patients with osteoporosis using different osteoporosis medications was further investigated.

Decreased risk of developing RA in patients with ever use of bisphosphonates or denosumab, particularly in female patients

HRs for developing RA in the patients with ever use of specific osteoporosis medication were further assessed, including bisphosphonates, denosumab, raloxifene and teriparatide (Table III). There was a total of 2069 patients with ever use of bisphosphonates and a total of 9605 patients without osteoporosis medication use. Patients with ever use of bisphosphonates had significant reduction of HR for developing RA when compared with non-osteoporosis medication users (adjusted HR=0.405, 95% CI: 0.173–0.951), after adjusting for age, comorbidities and medication use. In the female subgroup, patients with ever use of bisphosphonates had significant reduction of HR for developing RA when compared with non-osteoporosis medication users (adjusted HR=0.422, 95% CI: 0.178–0.997).

There was a total of 4510 patients with ever use of denosumab and a total of 9605 patients without osteoporosis medication use. Patients with ever use of denosumab had significant reduction of HR for developing RA when compared with non-osteoporosis medication users (adjusted HR=0.394, 95% CI: 0.192–0.809), after adjusting for age, comorbidities and medication use. In the female subgroup, patients with ever use of denosumab had significant reduction of HR for developing RA when compared with non-osteoporosis medication users (adjusted HR=0.360, 95% CI: 0.170–0.761).

Ever use of raloxifene or teriparatide in the patients with osteoporosis did

Table II. HRs of developing RA in osteoporosis patients using osteoporosis medications compared to non-osteoporosis medication users, and stratified by sex.

	Number of patients	n. of events	Observed person-years	Incidence rate (per 1000) person-years)	Crude HR	95% C.I. (Lower)	95% C.I. (Upper)	*p*-value	Adjusted HR+	95% C.I. (Lower)	95% C.I. (Upper)	*p*-value
Osteoporosis patients												
Non-medications	9605	36	27397.19	1.314	1	-	-		1	-	-	
Medication use	7180	21	26973.49	0.779	0.607	0.354	1.040	0.07	0.484	0.270	0.867	< 0.05*
Female patients												
Non-medications	7208	33	20479.54	1.611	1	-	-		1	-	-	
Medication use	6403	20	24666.6	0.811	0.519	0.298	0.905	< 0.05*	0.471	0.259	0.856	< 0.05*
Male patients												
Non-medications	2397	3	6917.65	0.434	1	-	-		1	-	-	
Medication use	777	1	2306.89	0.433	1.055	0.110	10.162	0.96	0.788	0.077	8.094	0.84

Osteoporosis medication use include: bisphosphonates, raloxifene, denosumab and teriparatide.
+Adjusted for age, HTN, DM, hyperlipidaemia, obesity, renal failure, corticosteroids, NSAIDs, lipid lowing agents, Vitamin D3.
*Significance; HR: Hazard ratio.

Table III. HRs of developing RA in the osteoporosis patients with ever use one specific osteoporosis medication compared to non-osteoporosis medication users, and stratified by sex.

	Number of Patients	n. of events	Observed person-years	Incidence rate (per 1000 person-years)	Crude HR	95% C.I. (Lower)	95% C.I. (Upper)	*p*-value	Adjusted HR+	95% C.I. (Lower)	95% C.I. (Upper)	*p*-value
Bisphosphonates												
Non-medications	9605	36	27397.19	1.314	1	-	-		1	-	-	
Ever use	2069	7	10529.03	0.665	0.563	0.250	1.27	0.17	0.405	0.173	0.951	< 0.05*
Female												
Non-medications	7208	33	20479.54	1.611	1	-	-		1	-	-	
Ever use	1788	7	9392.98	0.745	0.527	0.232	1.197	0.13	0.422	0.178	0.997	< 0.05*
Male												
Non-medications	2397	3	6917.65	0.434	1	-	-		1	-	-	
Ever use	281	0	1136.05	0	2.93E-07	-	infinity	1	9.18E-09	-	infinity	1
Denosumab												
Non-medications	9605	36	27397.19	1.314	1	-	-		1	-	-	
Ever use	4510	11	16068.4	0.685	0.524	0.267	1.029	0.06	0.394	0.192	0.809	< 0.05*
Female												
Non-medications	7208	33	20479.54	1.611	1	-	-		1	-	-	
Ever use	4010	10	14737.78	0.679	0.425	0.209	0.8629	< 0.05*	0.360	0.170	0.761	< 0.01*
Male												
Non-medications	2397	3	6917.65	0.434	1	-	-		1	-	-	
Ever use	348	0	917.18	0	3.19E-07	-	infinity	1	3.62E-08	-	infinity	1
Raloxifene												
Non-medications	9605	36	27397.19	1.314	1	-	-		1	-	-	
Ever use	1510	8	7453.08	1.073	0.873	0.404	1.883	0.73	0.580	0.255	1.323	0.2
Female												
Non-medications	7208	33	20479.54	1.611	1	-	-		1	-	-	
Ever use	1509	8	7442.08	1.075	0.722	0.332	1.567	0.41	0.584	0.255	1.337	0.2
Male												
Non-medications	2397	3	6917.65	0.434	1	-	-		1	-	-	
Ever use	1	0	11	0	2.04E-05	-	infinity	1	0.021	-	infinity	1
Teriparatide												
Non-medications	9605	36	27397.19	1.314	1	-	-		1	-	-	
Ever use	845	4	3332.93	1.200	0.915	0.326	2.571	0.87	0.574	0.187	1.767	0.33
Female												
Non-medications	7208	33	20479.54	1.611	1	-	-		1	-	-	
Ever use	753	4	3058.73	1.308	0.822	0.291	2.322	0.71	0.593	0.192	1.838	0.37
Male												
Non-medications	2397	3	6917.65	0.434	1	-	-		1	-	-	
Ever use	92	0	274.2	0	9.61E-07	-	infinity	1	3.8E-08	-	infinity	1

Non-medications: not use of bisphosphonates, raloxifene, denosumab and teriparatide.
+Adjusted for age, HTN, DM, hyperlipidaemia, obesity, renal failure, corticosteroids, NSAIDs, lipid lowing agents, Vitamin D3.
*Significance; HR: Hazard ratio.

not show significant association with developing RA when compared with those with non-osteoporosis medications, after adjusting for age, comorbidities and medication use.

Decreased risk of developing RA in patients with only use of denosumab, particularly in female patients

HRs for developing RA in patients with only use of specific osteoporosis medication was assessed, including bisphosphonates, denosumab, raloxifene and teriparatide (Table IV). After excluding ever use of bisphosphonates, raloxifene and teriparatide in the patients with ever use of denosumab, there was a total of 3428 patients with only use of denosumab. Patients with only denosumab use had significant reduction of HR for developing RA when compared with non- osteoporosis medication users (adjusted H =0.32, 95% CI: 0.12–0.83), after adjusting for age, comorbidities and medication use. In the female subgroup, patients with only denosumab use had significant reduction of HR for developing RA when compared with non-osteoporosis medication users (adjusted HR=0.26, 95% CI: 0.09–0.74). Only use of bisphosphonates, raloxifene and teriparatide in the patients with osteoporosis did not show significant association with developing RA when compared with non-osteoporosis medication users.

Discussion

Our study compared 7180 patients with osteoporosis medications and 9605 patients without osteoporosis medications in the patient database from a single hospital centre between 2011 and 2023. The patients with osteoporosis medication use had a 51.6% reduction in the risk of developing RA, and 52.9% reduction in female patients. The patients with ever use of bisphosphonates had a

Table IV. HRs of developing RA in the osteoporosis patients with only use one specific osteoporosis medication compared to non-osteoporosis medication users, and stratified by sex.

	Number of Patients	n. of events	Observed person-years	Incidence rate (per 1000 person-years)	Crude HR	95% C.I. (Lower)	95% C.I. (Upper)	*p*-value	Adjusted HR+	95% C.I. (Lower)	95% C.I. (Upper)	*p*-value
Bisphosphonates												
Non-medications	9605	36	27397.19	1.31	1	-	-		1	-	-	
Only use	1284	3	5438.27	0.55	0.45	0.14	1.46	0.18	0.39	0.12	1.28	0.12
Female												
Non-medications	7208	33	20479.54	1.61	1	-	-		1	-	-	
Only use	1064	3	4609.42	0.65	0.44	0.13	1.44	0.17	0.41	0.12	1.38	0.15
Male												
Non-medications	2397	3	6917.65	0.43	1	-	-		1	-	-	
Only use	220	0	828.85	0	3.13E-07	-	infinity	1	9.78E-09	-	infinity	1
Denosumab												
Non-medications	9605	36	27397.19	1.31	1	-	-		1	-	-	
Only use	3428	5	9825.8	0.51	0.37	0.15	0.94	< 0.05*	0.32	0.12	0.83	< 0.05*
Female												
Non-medications	7208	33	20479.54	1.61	1	-	-		1	-	-	
Only use	3007	4	8847.75	0.45	0.27	0.09	0.75	< 0.05*	0.26	0.09	0.74	< 0.05*
Male												
Non-medications	2397	3	6917.65	0.43	1	-	-		1	-	-	
Only use	421	1	978.05	1.02	2.72	0.28	26.45	0.39	2.69	0.25	28.72	0.41
Raloxifene												
Non-medications	9605	36	27397.19	1.31	1	-	-		1	-	-	
Only use	708	4	2679.18	1.49	1.16	0.41	3.27	0.77	0.88	0.31	2.55	0.82
Female												
Non-medications	7208	33	20479.54	1.61	1	-	-		1	-	-	
Only use	708	4	2679.18	1.49	0.95	0.34	2.70	0.93	0.90	0.31	2.59	0.84
Male												
Non-medications	2397	3	6917.65	0.43	1	-	-		1	-	-	
Only use	0	0	0	0	NA	NA	NA	NA	NA	NA	NA	NA
Teriparatide												
Non-medications	9605	36	27397.19	1.31	1	-	-		1	-	-	
Only use	273	1	588.29	1.70	1.18	0.16	8.60	0.87	1.08	0.14	8.14	0.94
Female												
Non-medications	7208	33	20479.54	1.61	1	-	-		1	-	-	
Only use	231	1	511.28	1.96	1.09	0.15	8.00	0.93	1.15	0.15	8.73	0.89
Male												
Non-medications	2397	3	6917.65	0.43	1	-	-		1	-	-	
Only use	42	0	77.01	0	7.42E-06	-	infinity	1	4.06E-07	-	infinity	1

Non-medications: not use of bisphosphonates, raloxifene, denosumab and teriparatide.
+Adjusted for age, HTN, DM, hyperlipidaemia, obesity, renal failure, corticosteroids, NSAIDs, lipid lowing agents, Vitamin D3.
*Significance; HR: Hazard ratio.

59.5% reduction in the risk of developing RA. The patients with ever use of denosumab had a 60.6% reduction in the risk of developing RA. The patients with only use of denosumab had a 68% reduction in the risk of developing RA, and 74.0% reduction in female patients. Denosumab demonstrated the preventive effect on the developing of RA in osteoporosis patients with or without pathological fracture. It implies the pathogenetic role of RANKL induced joint osteoclastogensis may be involved in the earliest, prearthritis stage of RA.

Our study showed that patients with osteoporosis medications had a significant reduced risk of developing RA when compared with non-osteoporosis medication users, particularly in female patients, after adjusting for age, comorbidities and medication use. Osteoporosis medication use in male patients did not have a significant association with development of RA. The possible preventive effect of osteoporosis medications on developing RA was found in patients with osteoporosis. Specific osteoporosis medication might be involved in preventing development of RA in patients with osteoporosis.

Interestingly, the patients with ever use of bisphosphonates and denosumab, particular in female patients, had a significant reduced risk of developing RA when compared with non-osteoporosis medication users. Furthermore, the patients with only use of denosumab, also particular in female patients, had a further reduced risk of developing RA when compared with non-osteoporosis medication users. The osteoporosis patients with only use of denosumab had a greater reduction in the risk of developing RA as compared to those with ever use of denosumab. Patients with use of

raloxifene or teriparatide did not have significantly reduced risk of developing RA when compared with non-osteoporosis medication users. Denosumab has the unique advantage of preventing development of RA in patients with osteoporosis. Denosumab, a potent anti-resorptive drug for osteoporosis, might has the potential benefit for reducing risk of RA development.

The inhibition of osteoclast through RANKL pathway may possibly prevent or slow down the emergence of RA. Bone-resorpting osteoclasts are critically involved in the joint bone destruction in RA (4, 15). Erosion of periarticular cortical bone results from excessive local bone resorption and inadequate bone formation (15). The binding of RANKL to RANK and the subsequently inducing osteoclastogenesis are essential for osteoclasts development, activation and survival (16). RANKL is mainly produced by osteoblasts in normal physiological conditions, but in RA, Th17 cells, macrophages, dendritic cells, activated B cells and fibroblast-like synoviocytes are the main production source of RANKL (17~19). Denosumab is a fully human monoclonal IgG2 antibody that binds RANKL and inhibits its activity.

Denosumab is used for osteoporosis treatment, because it inhibits osteoclast maturation and suppresses bone resorption to preserve bone mass (20, 21). Patients with RA receiving denosumab had increased bone mineral density (BMD) in lumbar spine (12). Denosumab has the advantage of preserving BMD in the femoral neck, total hip and lumbar spine, and preventing vertebral and non-vertebral fractures in patients with RA (10, 12, 20, 22, 23).

Osteoprotegerin, a decoy receptor for RANKL reduces osteoclast numbers and prevents bone erosion in collagen-induced arthritis, but has no impact on joint inflammation (24). Denosumab could inhibit the progression of bone erosion in patients with RA by suppressing osteoclast differentiation and activation in several clinical studies (11, 23). The increase in the MRI erosion score was lower in patients with RA with 180-mg denosumab at 6 months than in placebo (14). Denosumab inhibited the progression of modified Sharp erosion score in patients with RA at 12 months (13, 25). Denosumab treatment reduced worsening of modified total Sharp score and bone erosion score at 12 months, but no effect on joint space narrowing score in patients with RA (9, 10, 12). In a systemic review and pooled analysis, denosumab decreased the changes in modified total Sharp score and modified Sharp erosion score in patients with RA (22). In another systematic review and meta-analysis, the changes in the modified total sharp scores, erosion scores and joint space narrowing scores at 12 months after denosumab treatment were all smaller than placebo (23).

Denosumab could preserve bone mass loss and block bone erosion, but not inhibit progression of joint space narrowing and reduce inflammation in patients with RA (10, 21, 26). Denosumab did not have beneficial effect on cartilage destruction and synovitis activity in RA (10, 21). Denosumab reduces joint destruction in RA especially with positivity for ACPA (9). Early treatment of denosumab could better maintain the inhibition of joint bone erosion in RA (11). Denosumab suppressed the joint destruction in a dose dependent manner, the higher dosage and frequency had better effect on bone erosion (9, 11, 12, 14, 25). Disease-modifying anti-rheumatic drugs (DMARDs) predominantly interfere with inflammation process, but not bone erosion and osteoporosis in the joint (27). Denosumab combining together with DMARDs could be a useful strategy for RA therapy both in structure integrity and disease activity (6, 26, 27).

In patients with RA, denosumab increases hand BMD at 6 and 12 months (13). Denosumab increases bone mass in hand, femoral neck, total hip and lumbar spine in patients with RA. Denosumab could prevent bone loss and provided protection against bone erosion in hand. Zoledronic acid prevents bone destruction, reducing eroded surface, osteoclast surface and osteoclast numbers in collagen-induced arthritis (28). In patients with early RA, the number of hand and wrist bones erosions was significantly lower for zoledronic acid treatment compared with placebo. MRI of hand and wrist erosions were lower for zoledronic acid treatment compared with placebo, but did not show statistical significance (29). One-year teriparatide treatment does not reduce joint erosion in patients with RA (30). Denosumab was superior to bisphosphonates and teriparatide for the protection of joint destruction in patients with RA (22). The beneficial effect of denosumab on reducing bone erosion and increase bone mass in the joint, might contribute to prevent the development of RA in patients with osteoporosis.

Denosumab could not only prevent fractures, but also inhibit joint bone erosions in RA. Bone erosion occurs early in the course of RA. The protect effect of denosumab on early joint erosion may possibly slow the progression of preclinical stage of RA to clinical disease onset, thus reducing the risk of development of RA. RA is characterised by infiltration of the synovial membrane with T cells, B cells and monocytes (31). The joint inflammation in RA is initiated and maintained by a complex interplay between dendritic cell, macrophages, neutrophils, T cells, B cells, fibroblasts and osteoclasts (32). Previous study showed that a single infusion of 1000 mg rituximab delays the development of arthritis in individuals who were positive for both ACPA and RF but without arthritis (7). The presence of a bone loss in ACPA positive individuals without arthritis suggests the effect of ACPA on bone destruction starts in early stage (33). Development of osteoclasts from precursor cells occurs locally in the synovial tissue as a result of expression of osteoclastogenic mediators, such as macrophage colony-stimulating factor 1 and RANKL (34). ACPA were demonstrated to enhance osteoclasts differentiation through a PAD dependent IL-8 mediated autocrine loop (35). ACPA together with RANKL mediated osteoclastogenesis may be involved in bone loss and joint damage in preclinical stage of RA (5).

RA develops in genetically predisposed individuals with risk factors, includes musculoskeletal symptoms, smoking, obesity, periodontitis and infections (16, 36). Preclinical stage of RA can be

identified by circulating autoantibody in the absence of clinically inflammatory arthritis (37). The major auto-antibodies shown in preclinical RA are RF and ACPA (38). The risk of developing arthritis within 2 years in individuals positive for both ACPA and IgM-RF is approximate 40% (7). In the metacarpophalangeal joints of ACPA positive healthy individuals, BMD and cortical thickness were reduced as compared with control. Structural bone damage starts before the clinical onset of arthritis in individuals with ACPA (39, 40).

Denosumab is an antiresorptive drug used for postmenopausal osteoporosis, osteoporosis in men, glucocorticoid-induced osteoporosis and high-risk patients for fracture (20). Denosumab may possibly inhibit early osteoclasts differentiation and maturation in preclinical stage of RA, preventing the transition from ACPA and IgM-RF-positive healthy individuals to patients with inflammatory arthritis. Up to 10 years use of denosumab demonstrates a favourable safety and efficacy profile in patients with osteoporosis (20). The rate of osteonecrosis of jaw and atypical femoral fracture are rare in patients with denosumab therapy (8).

Our study has some limitations; first, our cohort is from a single hospital, thus our results cannot be extrapolated to patients from a general population. Second, the treatment of denosumab did not include the cumulative dosage, and duration of usage, the dosage effect of denosumab on RA development could not be demonstrated in this study. Third, this is a retrospective cohort analysis, a further prospective cohort study is needed to investigate the protective effect of denosumab on RA development, and evaluate the balance between the benefits and cost of side effects.

In conclusion, denosumab use greatly reduces the risk of developing RA in osteoporosis patients with or without pathological fracture, but the protective effect is not shown in other class of osteoporosis medications. RANKL mediated osteoclast articular bone damage may be involved in the pathogenesis of RA during the preclinical stage. Denosumab could be the choice of drug in the osteoporosis patients with ACPA and IgM-RF positivity. Further prospective investigation on using denosumab for prevention of RA in the non-osteoporosis individuals at high risk for imminent RA is recommended.

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