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Risk of infection in postmenopausal women with rheumatoid arthritis and osteoporosis taking denosumab and bDMARDS

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Abstract

Background: There is no clear consensus regarding the potential of denosumab for increasing the risk of infection in patients who concurrently receive biologic disease-modifying anti-rheumatic drugs (bDMARDs). In this study, we compared the rate of infection in postmenopausal women with rheumatoid arthritis who received concurrent bDMARDs and denosumab with those who received bDMARDs alone.

Methods: In a case-control study, postmenopausal patients with a confirmed diagnosis of rheumatoid arthritis who received concurrent bDMARDs and denosumab for at least one year were identified and included as the case group (n=40). A total of 44 age-matched postmenopausal rheumatoid arthritis women who received bDMARDs alone were included as the control group of the study. Using a chi-squared test, the incidence of bacterial or viral infections was extracted from the patients' profiles and compared between the two study groups. Statistical analyses were performed by SPSS for Windows, version 16 (Chicago, Illinois, USA). A p-value of fewer than 0.05 was regarded as significant.

Results: The clinical and demographic characteristics of the patients of the two study groups were not significantly different. In total, four infections were recorded in the present series, two infections in each group. Accordingly, the rate of infection was 4.5% in the bDMARDs alone group and 5% in bDMARDs + denosumab group. This difference was not statistically significant (p=0.655, 95% CI: 0.121-6.742). Three out of four infections were herpes zoster infection. The other one was osteomyelitis of the first metatarsal bone, which occurred in the bDMARDs+denosumab group. None of the infections needed a hospitalization of IV antibiotics.

Conclusion: The risk of infection is comparable between postmenopausal osteoporotic women with rheumatoid arthritis who receive bDMARDS alone and those who receive bDMARDS in combination with denosumab.

Keywords: Rheumatoid arthritis, Postmenopausal osteoporosis, Denosumab, bDMARDs

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↑What is "already known" in this topic:
While denosumab administration in postmenopausal osteoporotic women raised some concerns regarding the increased risk of infection, later investigations revealed the safety of denosumab in this group of patients. Even so, there is still no consensus regarding the potential of denosumab for increasing the risk of infection in postmenopausal osteoporotic women who are concurrently receiving immunosuppressive medications such as biologic disease-modifying anti-rheumatic drugs (bDMARDs).

→What this article adds:
In this study, we compared the risk of infection in postmenopausal osteoporotic women with rheumatoid arthritis who were receiving concurrent bDMARDs and denosumab with the same population who were receiving bDMARDs alone. Based on the results of this study, the rate of infection was not different between the two groups of the study. Therefore, denosumab can be safely used for the treatment of osteoporosis in postmenopausal patients with rheumatoid arthritis who are receiving bDMARDs.

Introduction

The risk of osteoporosis is high in rheumatoid arthritis (RA) patients for several underling reasons including increased production of pro-inflammatory cytokines, hormone mediated mechanisms, physical disability, and cumulative effect of glucocorticoid (1). Accordingly, the prevalence of osteoporosis in RA patients is almost twice in comparison with the general population (2).

Postmenopausal women are also at a high risk of osteoporotic fracture for several reasons, mainly a sharp reduction in estrogen, which protects bone from the resorptive effects of parathyroid hormone (3, 4). According to the Agency for Healthcare Research and Quality (AHRQ) report, approximately 5% of 50-year-old white women, as well as 25% of 80-year-old women have experienced at least one osteoporotic vertebral fracture (5). Considering the health and economic burden of osteoporotic fractures (6), effective treatment of osteoporosis in postmenopausal RA women is of considerable importance.

Denosumab, a human monoclonal antibody to Receptor activator of nuclear factor-kappa-B ligand (RANKL), proved to be highly effective in declining the risk of osteoporotic vertebral, nonvertebral, and hip fractures in postmenopausal females. For these benefits, it received international approval for the treatment of postmenopausal osteoporosis in 2010 (7). Moreover, recent studies provide strong evidence considering the efficacy of denosumab for the treatment of RA, so that its implication inhibited the joint structural damages without increasing adverse events (8, 9).

In spite of the detrimental effects of RANKL on the bone quality of postmenopausal women, RANKL signaling contains several critical roles in the immune system, including its role in development of lymph-nodes, lymphocyte differentiation and tolerance, dendritic cell survival, and T-cell activation (10). These beneficial effects of RANKL raised some concerns regarding the increased risk of infection in patients treated with RANKL inhibitors such as denosumab. Subsequently, several studies aimed to investigate if denosumab administration in postmenopausal osteoporotic women may impose a higher risk of infection on this population. As a result of these investigations, no significant increase was observed in the risk of infection, as well as the risk of cancer, delayed fracture healing, and hypocalcemia (7, 11). However, there is no clear consensus on the potential of denosumab for increasing the risk of infection in patients who are receiving immunosuppressive medications such as biologic disease-modifying anti-rheumatic drugs (bDMARDs) (11).

In this study, we aimed to evaluate the potential of denosumab for increasing the risk of infection in RA patients with postmenopausal osteoporosis who were receiving bDMARDs.

Methods

The protocol of this case-control study was approved by the review board of our institute under the code of IR.IUMS.REC.1396.32412 and written informed consent was obtained from the patients to use their medical profile for publication. The medical profiles of postmenopausal patients with a confirmed diagnosis of RA based on the 2010-ACR/EULAR–classification criteria (12) who received bDMARDs and denosumab were reviewed, and eligible patients were included in the study. The inclusion criteria were postmenopausal women, treatment with bDMARDs for the management of RA, treatment with denosumab (60 mg) injections every six months for osteoporosis, current therapeutic regimen for at least one year, absence of any local and systemic infection before the initiation of bDMARDs. Patients who were receiving immunosuppressive therapies for conditions other than RA, such as cancer and organ transplantation, were excluded from the study.

A total of 40 patients who received concurrent bDMARDs and denosumab were identified as eligible for the study. A total of 44 age -matched RA patients who received bDMARDs alone were included as the control group of the study. The type of administered bDMARDs was etanercept (50 mg per week), rituximab (2 gr per six months), or adalimumab (40 mg per two weeks). All patients concurrently received a daily dose of prednisolone (2.5–7.5 mg) plus folic acid and a weekly dose of methotrexate (10 mg per week). The incidence of serious infections (requiring hospitalization or IV antibiotics) was extracted from the patients' profiles. We also called the patients and asked about hospitalization in other centers for serious infection.

Statistical analysis

Statistical analyses were performed by SPSS for Windows, version 16 (Chicago, Illinois, USA). The descriptive data were presented as mean ± standard deviation or number & percentage. A comparison of mean values between the two study groups was performed with an independent t-test or its nonparametric counterpart (Mann–Whitney U test). A comparison of qualitative variables was made using a chi-squared test. A p-value of fewer than 0.05 was regarded as significant.

Results

We compared the risk of infection in RA patients who received either bDMARDs alone (n=40) or concurrent with denosumab (n=44). The mean age of the patients was 62.6±11.7 years in patients who received bDMARDs alone and 63.1±12 years in patients who received concurrent denosumab (p=0.421, 95% CI: -2.270-0.3.351). The mean disease duration was 7.1±1.6 years in patients who received bDMARDs alone and 7.2±1.9 in patients who received concurrent denosumab (p=0.392, 95% CI:-1.301-1.152). The mean duration of biologic use was 15.8±4.6 months in patients who received bDMARDs alone and 15.4±3.2 months in patients who received concurrent denosumab (p=0.284, 95% CI: -4.580-2.607). Type 2 diabetes mellitus was present in five patients (11.4%) who received bDMARDs alone and four (10%) patients who received concurrent denosumab (p=0.515, 95% CI: 0.287-4.635). No significant difference was found between the

clinical and demographic characteristics of the two study groups as well (Table 1).

A number of two infections occurred in each group. Accordingly, the rate of infection was 4.5% in the bDMARDs alone group and 5% in the bDMARDs+denosumab group. This difference was not statistically significant (p=0.655, 95% CI: 0.121-6.742). .

In the bDMARDs alone group, two cases of herpes zoster were recorded in two patients receiving adalimumab. In the bDMARDs+denosumab group, the first one was an osteomyelitis of the first metatarsal bone in a diabetic patient receiving etanercept+denosumab. The duration of denosumab use was 18 months in this patient. The other one was a herpes zoster infection in a patient receiving adalimumab. The duration of denosumab use was 12 months in this patient.

The demographic and clinical characteristics of the patients with an infection are demonstrated in detail in Table 2.

Discussion

In this study, we investigated if the risk of infection is higher in postmenopausal osteoporotic RA patients who received concurrent bDMARDs and denosumab in comparison with those who received bDMARDs alone. According to our results, the risk of infection was 5% in the bDMARDs+ denosumab group and 4.5% in bDMARDs alone group. This difference was not statistically and clinically significant.

In a retrospective study, Hasegawa et al. aimed to compare RA patients treated with denosumab (60 mg injections every six months) plus bDMARDs (n=40) to those treated with bDMARDs alone (n=40). The types of bDMARDs in their study included infliximab, adalimumab, etanercept, abatacept, and tocilizumab. Based on their report, rates of adverse events, including infection, were comparable between the two study groups (9). Similarly, we found a comparable rate of infection between the bDMARDs+ denosumab group and the denosumab alone group. Though, the types of administered bDMARDs were different in two studies.

Lau et al. investigated the risk of serious infection in RA patients treated with bDMARDs plus denosumab in comparison with those who received bDMARDs alone. In total, 308 patients (102 in the concurrent group and 206 in bDMARDs alone group) met the eligibility criteria to include in the study. Three serious infections occurred in the bDMARDs+ denosumab group, which all were cases of pneumonia. Four serious infections occurred in the bDMARDs-alone group, which included three cases of pneumonia, and one case of upper respiratory tract infection. Moreover, one case of opportunistic infection occurred in the bDMARDs -alone group. Based on the results of this study, the risk of serious infection following the concurrent use of bDMARDs denosumab group was negligible and comparable with bDMARDs -alone group (13).

Bray et al. aimed to identify the rate of infection among patients with RA and psoriatic arthritis who concurrently received denosumab. In total, 96 patients (90 RA patients and 6 psoriatic arthritis patients) met the eligibility criteria for this study. Based on their results, the infection rate seemed to be low among patients who receive concurrent denosumab and bDMARDs (3 cases, 3.1%). However, prednisone administration found to be associated with an increased rate of infection (14).

Curtis et al. aimed to investigate whether the rate of hospitalized infection in patients with RA who concurrently receive bDMARDs and denosumab (n=1354) is higher than those who concurrently receive bDMARDs and

Table 1. Comparison of the demographic and clinical characteristics of the two study groups

Variable	bDMARDs alone (n=44)	bDMARDs ± denosumab (n=40)	p
Age (year)	62.6±11.7	63.1±12	0.421
BMI (kg/m^2)	26.9±4.5	27.1±4.8	0.643
Type 2 Diabetes	5 (11.4)	4 (10)	0.515
Mean disease duration (year)	7.1±1.6	7.2±1.9	0.392
Mean duration of bDMARDs use (month)	15.8±4.6	15.4±3.2	0.284
Type of bDMARDS			
• Etanercept	28 (63.6)	29 (72.5)	
• Rituximab	7 (15.9)	4 (10)	0.263
• Adalimumab	9 (20.5)	7 (17.5)	

BMI: body mass index; bDMARDs: Biologic disease-modifying anti-rheumatic drugs.
Data are show as mean± standard deviation or number (%). A p value of <0.05 is considered significant.

Table 2. The demographic and clinical characteristics of patients who were presented with a serious infection

Variable	bDMARDs alone		bDMARDs ± denosumab	
	Patient 1	Patient 2	Patient 1	Patient 2
Type of infection	Herpes zoster	Herpes zoster	Osteomyelitis	Herpes zoster
Age (Year)	59	64	65	62
Sex	Female	Female	Female	Female
BMI (kg/m^2)	26.8	25.9	27	25.5
Disease duration (year)	6	8	7	5
Duration of bDMARDs use (month)	17	12	16	22
Type of bDMARDs	Adalimumab	Adalimumab	Etanercept	Adalimumab
History of Diabetes	No	No	yes	No

BMI: body mass index; bDMARDs: Biologic disease-modifying anti-rheumatic drugs.

zoledronic acid (n=4460). According to their results, the crude rate of hospitalized infections for bDMARDs + denosumab was comparable to that for ZA (14.9/100 person-years versus 13.9/100 person-years) (15).

According to our findings, joint with the results of earlier investigations, concurrent use of bDMARDs, and denosumab in postmenopausal patients with RA does not increase the rate of infection in these patients. Therefore, denosumab can be used for the treatment of osteoporosis in postmenopausal RA patients, with no concern.

The limitations of our study were the retrospective identity of research, as well as small patients' numbers, which did not allow the subgroup analysis, such as evaluating the risk of infection with different types of bDMARDs. Small number of patients might have also affected the power of statistical tests. Therefore, future complementary studies are warranted to confirm the results of present study.

Conclusion

According to the results of this study, the risk of infection in postmenopausal osteoporotic RA patients was not significantly different between the denosumab and bDMARDs concurrent therapy compared with the bDMARDs alone. This finding suggests that denosumab could be used as a safe medication in the treatment of osteoporosis in RA patients receiving bDMARDs.

Conflict of Interests

The authors declare that they have no competing interests.

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