











# Combination of denosumab and biologic DMARDs in inflammatory muscle-skeletal diseases and connective tissue diseases

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## Abstract

**Objective:** Osteoporosis (OP) can complicate the course of rheumatic musculoskeletal diseases (RMDs) and connective tissue diseases (CTDs). Denosumab, a monoclonal antibody against RANK-L, showed beneficial effect in rheumatoid arthritis in inhibiting radiographic progression and erosive burden. We tested the efficacy, safety, and persistence on the treatment of the combination of biologic disease-modifying antirheumatic drugs (bDMARDs)/denosumab versus bDMARD in patients with RMD and CTD.

**Methods:** This is a retrospective evaluation of a single center, including patients with RMD/CTD (including rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, systemic sclerosis, and overlap syndromes) treatment with bDMARD/denosumab, compared to age, gender, disease, bDMARD, and conventional synthetic disease-modifying antirheumatic drugs-matched controls.

**Results:** Twenty-eight bDMARD/denosumab patients and 49 bDMARD patients were eligible. Despite a statistically significant difference during the first-year efficacy (due to the different baseline time-point), there was no difference in the efficacy profile in the second year of treatment and in the safety profile (including local, systemic, and serious adverse events). Moreover, no statistically significant difference in the persistence of bDMARD treatment over 2 years of evaluation was found. The combination of bDMARD and denosumab was not an independent predictor of disease flare or bDMARD treatment withdrawal.

**Conclusion:** The combination of bDMARD and denosumab does not alter the efficacy and the safety profile of the bDMARD in patients with RMD/CTD. Future studies verifying the radiological disease inhibition could support denosumab use in RMD/CTD other than rheumatoid arthritis, when complicated by OP.

**Keywords:** Osteoporosis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, biologics, denosumab

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## Introduction

In rheumatic diseases, osteoporosis (OP) is a common complication with a 15-25% prevalence in rheumatic musculoskeletal diseases (RMDs), such as rheumatoid arthritis (RA) and spondylarthritis,<sup>1,2</sup> and among connective tissue diseases (CTDs).<sup>2-5</sup> It is well known that cytokines, involved in joint inflammation, have a negative effect on osteoblasts and can, thus, lead to OP. Otherwise, OP can be also fostered by corticosteroids (CCS).<sup>1,2</sup> Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and biologic DMARDs (bDMARDs) represent the cornerstone of the treatment of RMD and CTD,<sup>6-10</sup> and the possible additional effect on the bone was also previously studied. While csDMARDs have not shown a significant effect in preventing OP, bDMARDs, in particular tumor necrosis factor-inhibitors (TNFis), may contribute to maintain bone mineral density (BMD) values.<sup>11,12</sup>

The current treatment of primary and secondary OP relies mainly on bisphosphonates as first-line drugs. In the case of bisphosphonate inefficacy or side effects, the second line treatments are teriparatide or denosumab (a monoclonal antibody against RANK-L).<sup>13</sup> In different cohorts of RMD-OP patients, denosumab has been tested as an anti-OP treatment showing significant beneficial effect in increasing BMD compared to bisphosphonates,<sup>14</sup> regardless previous bisphosphonates exposure,<sup>15</sup> in particular for the treatment of glucocorticoids-induced OP.<sup>16</sup>

Given the role of RANK system in RA pathogenesis, denosumab has also been tested in placebo-controlled randomized clinical trials (RCTs) as a DMARD for the treatment of RA progression. In csDMARD population, different regimens of denosumab (60 mg every 2,<sup>17</sup> 3,<sup>17,18</sup> 6 months,<sup>17-19</sup> and 180 mg every 6 months<sup>19</sup>) showed a significant effect in reducing the erosions burden both on X-ray<sup>17-19</sup> and on MRI.<sup>19</sup> When tested in bDMARD-treated RA patients, data on additional radiographic progression were confirmed for the denosumab treated group.<sup>20</sup>

In a recent meta-analysis on RCTs also including RA patients, denosumab was reported to increase the risk of serious but not of non-serious infectious events or infection-related mortality.<sup>21</sup> This was not confirmed in RMD-RCTs, where a similar incidence of adverse events, either the csDMARD/denosumab or csDMARD groups, was found.<sup>17-19</sup> Real-life cohorts data confirmed the same results on bDMARDs patients:<sup>20</sup> bDMARDs/denosumab-treated patients developed similar rates of serious infections in comparison to those treated with bDMARD only<sup>22</sup> and similar rates of infection requiring hospitalization and duration of hospitalization when compared to those treated with bDMARDs/zoledronic acid combination.<sup>23</sup>

Regarding RMD clinical outcomes, rates of RA flares were also comparable between denosumab and placebo in csDMARD-<sup>19</sup> and bDMARD-treated patients. Similarly, no clinically significant change in disease activity was detected in csDMARD-<sup>17,18</sup> and bDMARD<sup>20</sup>-treated RA patient.

Outside RA, no evidence is currently available regarding the impact of bDMARD/denosumab combination for other RMD and CTD.<sup>24</sup> Therefore, our aim was to retrospectively evaluate the safety and the persistence of bDMARD treatment comparing bDMARD/denosumab versus bDMARD only in RMDs patients affected with OP.

## Methods

### Study population

In this retrospective study, we reviewed the charts of RMD and CTD patients followed at the Department of Rheumatology, Careggi University Hospital, Florence, Italy. We included patients who received treatment with a bDMARD for their underlying condition, with concomitant denosumab for the treatment of OP. Patients with concomitant bDMARD/denosumab treatment were identified and labeled as *combination* group. In addition, we selected at least one age ( $\pm 5$  years), gender, underlying RMD/CTD, bDMARD, and concomitant use of csDMARD-matched control case without exposure to denosumab, and named the control population as *monotherapy* group. In the bDMARD group, OP treatment included bisphosphonates and/or calcium and vitamin D supplementations.

Ethics committee approval was received for this study from the Comitato Etico Regionale per la Sperimentazione Clinica della Regione Toscana - Sezione Area Vasta Centro (Approval Date: March 31, 2020; Approval Number: Protocol CEAVC 15659), and patients signed an informed consent.

### Data collection

For both groups, data were collected for the following items: demographics (age, gender, and disease duration), underlying CTD/RMD, ongoing bDMARD, and concomitant RMD/CTD treatments (including CCS, nonsteroidal anti-inflammatory drugs [NSAIDs], analgesics, and csDMARDs); clinical and laboratory evaluations (including erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], tender joint count [TJC], and swollen joint count [SJC]); and safety assessments (serious, systemic, and local adverse events, with particular interest in CTD/RMD clinical relapses and patient perception of disease worsening).

Data collection was performed from baseline (which corresponded to the bDMARD initiation in the *monotherapy* group, and to the time of bDMARD/denosumab overlap in the *combination* group) until latest available follow-up (up to 24 months or treatment withdrawal).

### Statistical analysis

Data were analyzed using SPSS (version 20) (IBM Corp., Armonk, NY, USA) and presented as prevalence (percentage) for categorical variables while mean  $\pm$  standard deviation for continuous variables. Differences between the two groups were tested using chi-square test (for categorical variables) and using Student's t test for paired samples (for continuous variables).

The association between persistence on bDMARD treatment, time to clinical or subjective relapse, and treatment exposure was evaluated using log-rank test and graphically presented with Kaplan–Meier curve. In addition, hazard ratio (HR) and its 95% CI were estimated using Cox model regression, to test the impact of the exposure to denosumab on the development of the above-mentioned outcomes. Statistical significance was set at  $P < .05$ .

## Results

### Study population

We identified 77 RMD/CTD cases treated with denosumab. We excluded 37 for not being exposed to bDMARD and 12 for non-concomitant bDMARD/denosumab treatment.

A total of 28 patients (mean age  $63 \pm 9$  years, 96% women, and 86% concomitant csDMARD) were eligible for the study and populated the *combination* group. Among them, seven patients started the bDMARD while already on denosumab (6-17 months treatment duration), 20 patients started denosumab while on bDMARD (from 8 to 122 months treatment duration), and one patient was prescribed with bDMARD and denosumab on the same visit. The control group was constituted of 49 bDMARD-treated RMD/CTD patients (mean age  $67 \pm 7$  years, 96% women, and 91% concomitant csDMARD).

Almost half of the population was composed of RA patients, with the remaining being psoriatic arthritis (PsA), ankylosing spondylitis (AS), systemic sclerosis, or overlap syndromes patients (see Table 1 for further clinical and serological details). Rheumatoid factor and anticitrullinated cyclic peptide antibodies were positive in more than two-thirds of the RA population, while skin or nail psoriasis was manifested in a similar prevalence of the PsA patients. Both groups presented with increased number of TJC and SJC, as well as raised ESR and CRP, despite the values were significantly lower in the *combination* group.

As per the selection criteria, all patients in the *combination* group were affected by OP, with a third of patients being complicated by fragility fractures and previous teriparatide treatment. In contrast, OP prevalence was in line with the data presented in the literature in the *monotherapy* group.

Regarding the ongoing bDMARD, joint inflammatory involvement was the reason for prescription in all cases. There was a balanced situation between TNFi (mainly etanercept, followed by adalimumab and golimumab)

### Main Points

- Combination of Denosumab and biologic DMARDs is part of current practice.
- Denosumab did not affect the efficacy and safety profile of biologic DMARDs
- Persistence on treatment with biologic DMARDs is not impaired by combination treatment with Denosumab.

**Table 1.** Baseline characteristics of the two groups.

	bDMARD/denosumab group (n = 28)	bDMARD group (n = 49)
Age, years, mean ± SD	63 ± 9	67 ± 7
Underlying RMD/CTD, n (%)	RA: 14 (50) PsA: 7 (25) AS: 1 (3.6) Systemic sclerosis: 3 (10.7) Overlap syndromes: 3 (10.7)	RA: 29 (59.2) PsA: 13 (26.5) AS: 2 (4.1) Systemic sclerosis: 3 (6.1) Overlap syndromes: 2 (4.1)
Anti-CCP antibody positivity, n (%)	10/14 (71.4) RA patients	19/29 (65.5) RA patients
Rheumatoid factor positivity, n (%)	10/14 (71.4) RA patients	17/29 (58.6) RA patients
Skin psoriasis, n (%)	4/7 (57.4) PsA patients	8/13 (61.5) PsA patients
Nail psoriasis, n (%)	1/7 (14.3) PsA patients	2/13 (15.4) PsA patients
HLA-B27 positivity, n (%)	1/1 (100.0%) AS patient	1/2 (50.0) AS patients
TJC, n, mean ± SD	3.6 ± 6.3	6.3 ± 3.5
SJC, n, mean ± SD	3.4 ± 5.7	4.3 ± 4.3
ESR, mm/h, mean ± SD	21 ± 16	30 ± 19
CRP, mg/L, mean ± SD	4.8 ± 8.2	10.8 ± 13.5
bDMARD, n (%)	Abatacept: 4 (14.3) Adalimumab: 3 (10.7) Etanercept: 10 (35.7) Golimumab: 2 (7.1) Rituximab: 4 (14.3) Tocilizumab: 5 (17.9)	Abatacept: 8 (16.3) Adalimumab: 6 (12.2) Etanercept: 18 (36.8) Golimumab: 4 (7.1) Rituximab: 6 (12.2) Tocilizumab: 7 (14.3)
Concomitant RMD medications, n (%)	csDMARDs: 24 (85.7) Methotrexate: 11 (39.3) Leflunomide: 3 (10.7) Sulphasalazine: 0 (0.0) Hydroxychloroquine: 9 (32.1) Other csDMARDs: 1 (3.6) CCs: 15 (53.6) NSAIDs: 6 (21.4) Analgesics: 6 (21.4)	csDMARDs: 45 (91.8) Methotrexate: 17 (34.7) Leflunomide: 8 (16.3) Sulphasalazine: 3 (6.1) Hydroxychloroquine: 11 (22.4) Other csDMARDs: 6 (4.1) CCs: 31 (63.3) NSAIDs: 12 (24.5) Analgesics: 7 (14.3)
Osteoporosis, n (%)	28 (100)	10 (20.4)
Previous bone fracture, n (%)	10 (35.7)	4 (8.1)
Previous treatment with teriparatide, n (%)	11 (39.3)	2 (4.1)

AS, ankylosing spondylitis; bDMARD, biologic disease modifying antirheumatic drug; CCP, citrullinated cyclic peptide; CCs, corticosteroids; CRP, C-reactive protein; csDMARD, conventional synthetic disease modifying antirheumatic drug; CTD, connective tissue disease; ESR, erythrocyte sedimentation rate; NSAIDs, nonsteroidal anti-inflammatory drugs; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RMD, rheumatic musculoskeletal disease; SJC, swollen joint count; TJC, tender joint count.

and non-TNFi (tocilizumab, abatacept, and rituximab in similar proportions) treatments. The two groups were not statistically different in terms of underlying RMD/CTD condition, ongoing bDMARD, and concomitant medications at baseline.

#### Efficacy

All the efficacy measures assessed (TJC, SJC, ESR, and CRP) showed a statistically significant decline after 12 and 24 months when compared to the baseline visit in the *monotherapy*

group (Table 2). In the *combination* group, all values declined numerically, but no statistically significant change was observed. When comparing the changes in the four parameters, as expected, there was a statistically significant greater decline of ESR and CRP between baseline and 12 months evaluations in the *monotherapy* compared with the *combination* group. All variations between baseline and month 24, as well as between month 12 and month 24 were not statistically different between the two groups (Table 2).

#### Safety

Our data showed safety being comparable in the two groups: four (9.8%) patients in the *monotherapy* and one (4.8%) patient in the *combination* groups reported an injection site reaction ( $P = .654$ ). Systemic adverse events were reported by 21 (77.8%) patients in the *combination* and 41 (83.7%) patients in the *monotherapy* group during the study course, with no statistically significant difference ( $P = .549$ ). There was a similar distribution of the type of adverse reactions

**Table 2.** Clinical and laboratory evaluations at baseline, 12, and 24 months and their changes in time.

	bDMARD/denosumab group (n = 28)				bDMARD group (n = 49)				Comparison between groups		
	Baseline	12 months	24 months	P value*	Baseline	12 months	24 months	P value*	Change at 12 months vs baseline	Change at 24 months vs baseline	Change at 24 months vs 12 months
TJC, n, mean ± SD	3.6 ± 6.3	1.5 ± 2.6	0.2 ± 0.4	NS	6.3 ± 3.5	2.6 ± 4.3	1.3 ± 1.2	†,‡	0.666	0.909	0.499
SJC, n, mean ± SD	3.4 ± 5.7	1.3 ± 1.8	0.4 ± 0.8	NS	4.3 ± 4.3	1.7 ± 2.4	1.1 ± 1.4	†,‡	0.126	0.667	0.973
ESR, mm/h, mean ± SD	21 ± 16	22 ± 18	2 ± 12	NS	30 ± 19	19 ± 15	19 ± 19	†,‡	0.017#	0.240	0.121
CRP, mg/L, mean ± SD	4.8 ± 8.2	4.5 ± 8.2	3.6 ± 5.7	NS	10.8 ± 13.5	3.6 ± 5.1	3.2 ± 0.4	†,‡	0.028#	0.345	0.583

\*Statistically significant  $P < .05$ .

†Statistically significant difference between baseline and 12 months, within the group.

‡Statistically significant difference between baseline and 24 months, within the group.

#Using Student's t test between the two groups, favoring bDMARD over bDMARD/denosumab group.

bDMARD, biologic disease modifying antirheumatic drug; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SJC, swollen joint count; TJC, tender joint count.

**Table 3.** Adverse events in the study course, comparing bDMARD/denosumab and bDMARD groups.

	bDMARD/denosumab group (n = 28)	bDMARD group (n = 49)	Comparison between groups; P value
AE, n (%)	21 (77.8)	41 (83.7)	.549
Serious AE	3 (14.3)	6 (14.6)	>.999
Injection site reactions	1 (4.8)	4 (9.8)	.654
Systemic AE	19 (95.2)	38 (92.7)	>.999
Infectious AE	12 (57.1)	30 (73.2)	.255
Laboratory tests AE	7 (33.3)	9 (22.9)	.369
Constitutional AE	2 (9.5)	9 (22.0)	.305
Cardiovascular AE	2 (9.5)	2 (9.8)	>.999
Osteonecrosis of the jaw	2 (9.5)	1 (2.4)	.211
Disease clinical flare	9 (32.1)	10 (20.4)	.281
Other AE	3 (14.3)	1 (2.4)	.148

AE, adverse events; bDMARD, biologic disease modifying antirheumatic drug.

between the two groups, with infections, reduced cell blood count or increased liver enzymes, and constitutional symptoms as the most common events. In particular, the rate of mandibular osteonecrosis was not statistically different in the two groups (further details in Table 3).

During a mean follow-up of 19.6 ± 5.1 months, clinical relapses were detected by the treating physician in 19 (24.7%) patients: nine (32.1%) belonged to the *combination* and 10 (20.4%) to the *monotherapy* group, without statistically significant difference ( $P = .281$ ). The cotreatment with denosumab was not

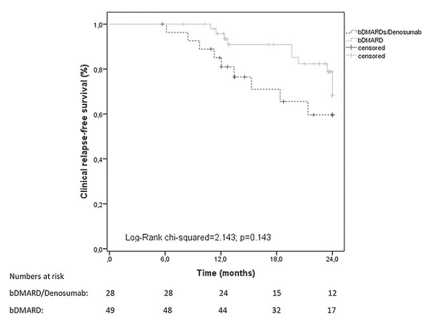
an independent predictor of clinical disease flare (HR: 1.936, 95% CI: 0.784-4.782,  $P = .152$ ), and there was no significant difference in the time to the development of clinical relapse among the two groups (Kaplan–Meier analysis graph is reported in Figure 1).

Similarly, patient perception of disease worsening was reported by 19 patients (24.7%), with higher prevalence in the *combination* group (n = 8, 28.6%) over the *monotherapy* group (n = 11, 22.4%). Again, there was no difference in the time to the development of patient perception of disease worsening between the two groups (Kaplan–Meier anal-

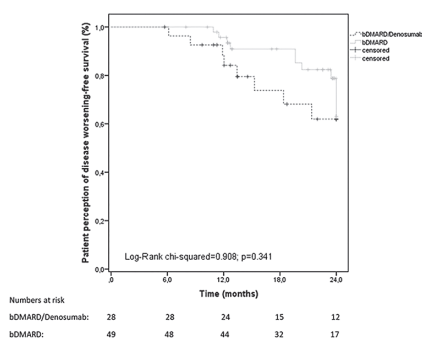
ysis graph is presented in Figure 2), and denosumab was not an independent predictor of its onset over time (HR: 1.549, 95% CI: 0.621-3.864,  $P = .349$ ).

**Persistence on treatment**

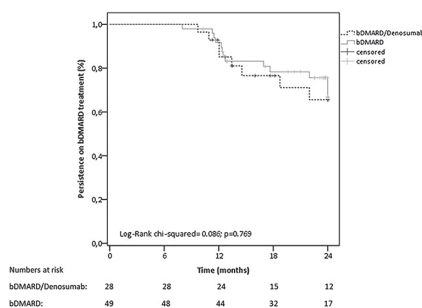
During the study observation, a total of 21 (27.3%) patients interrupted their bDMARD treatment, with similar distribution between the *combination* (n = 8, 28.6%) and the *monotherapy* (n = 13, 26.5%) groups. The bDMARD treatment persistence over time was comparable between the two groups, with 67.3% patients in the bDMARD and 71.4% in the bDMARD/denosumab groups continu-



**Figure 1.** Kaplan–Meier curve for clinical relapse-free survival for the bDMARD/denosumab and the bDMARD groups. bDMARD, biologic disease modifying antirheumatic drug.



**Figure 2.** Kaplan–Meier curve for patient reported disease worsening-free survival for the bDMARD/denosumab and the bDMARD groups. bDMARD, biologic disease modifying antirheumatic drug.



**Figure 3.** Kaplan–Meier curve for persistence on bDMARD treatment for the bDMARD/denosumab and the bDMARD groups. bDMARD, biologic disease modifying antirheumatic drug.

ing the bDMARD treatment at 24 months (Kaplan–Meier survival analysis is shown in Figure 3). As for the previous outcomes, denosumab administration did not represent a significant risk factor for bDMARD interruption on Cox regression analysis (HR: 1.141, 95% CI: 0.472–2.757,  $P = .770$ ). Denosumab was interrupted by 3 (10.7%) patients, all for safety events.

## Discussion

Our data show that the addition of denosumab to bDMARD did not modify the efficacy, the safety profile, and the persistence on treatment of bDMARD in patients with inflammatory RMD and CTD.

Denosumab is a valuable option in the second-level treatment of OP, both as a primary condition and as a secondary complication to RMDs and glucocorticoid administration.<sup>14–16</sup> Moreover, it showed additional beneficial effects on RA evolution in different RCT. Denosumab significantly inhibited disease radiographic progression measured with the mTSS and reduced the disease-related erosive burden.<sup>17–19</sup> These studies included RA patients treated with csDMARD combination regimen,<sup>17–19</sup> raising concerns regarding the possible additional effect of double monoclonal antibody treatments on safety profile in patients treated with the bDMARD and denosumab combination.

In a recent metaanalysis, denosumab was shown to increase the rate of serious infectious adverse events when compared to placebo,<sup>21</sup> but this datum was not confirmed by studies testing denosumab in RA. The rates of serious adverse events, in particular infectious events, ranged between 4 and 10% in RA patients<sup>17–19,22,23</sup> and were not different in comparison to placebo. This is in line with the data in our cohort, in which the rate of serious adverse events was similar in the two groups. Similarly, the rate of non-serious adverse events was not different among bDMARD patients with or without denosumab combination, presenting in about 80% of the patients, mostly represented by infectious adverse events, in line with previous reports on both csDMARDs<sup>17–19</sup> and bDMARD patients.<sup>20</sup>

In our study, we reported clinically defined disease flares were in both groups, with a numerically higher prevalence in the *combination* group. Cohen et al.<sup>19</sup> found similar rates of RA flares in their study, afflicting almost a third of their study population. Similar prevalence and difference between the groups were confirmed also when we evaluated patient reported disease flares, despite the subjective nature is not based on specific patient reported outcome measures.

When considering disease activity, Hasegawa et al.<sup>20</sup> did not report any significant difference in patients treated with bDMARD with or without denosumab association. This is not in line with our data, as we observed a statis-

tically significant higher change in inflammatory markers, TJC, and SJC over the first year favoring the *monotherapy* regimen. Our results should take into account the different baseline time point in the two groups. In fact, baseline corresponded to the first overlapping administration of the two monoclonals in the *combination* group, mainly composed of bDMARD experienced patients, in which the drug had already reached a steady state and positive disease modifying effect. In the *monotherapy* group, the baseline visit corresponded to the bDMARD initiation visit, characterized by a high disease activity, and therefore determined a significantly higher change over 12 months in the efficacy measures. Considering that the majority of patients had reached a stable disease status after 1 year of bDMARD therapy, we did not find a statistically significant difference in changes in inflammatory serological markers and TJC/SJC over the second year of therapy. This could then support the hypothesis of a non-impacting effect of denosumab on the efficacy of the bDMARD in controlling disease activity, therefore confirming the data of other groups.<sup>20</sup>

Finally, denosumab did not determine a significant impact on bDMARD treatment persistence over the first 2 years of administration, and there was no statistically significant difference in bDMARD withdrawal among the two groups during the first 2 years. Taken together, these data confirm that denosumab does not have an additive value on the clinical and serological manifestation of the RMD/CTD disease but, most importantly, did not impair the efficacy and persistence of other treatments, specifically ongoing bDMARD.

Our study represents the first multidisease confirmation of previous data available only for RA patients, including also patients with other RMD (PsA and AS) as well as patients with CTD (in particular, systemic sclerosis and overlap syndromes). Moreover, to the best of our knowledge, this is the first study evaluating the impact of denosumab on bDMARD survival.

Despite these positive aspects, our paper presents many limitations: the data collection was performed retrospectively, with possible bias on safety reporting. Our study included low number of patients, which, therefore, requires validation in larger multicenter cohorts; in addition, the low number of patients did not allow subgroup analyses and could not, therefore, verify the replicability of the results among the different diseases. We did not use standardized definitions of disease relapse based on clinimetric evaluations of validated scores, and, similar-

ly, no patient reported outcome measure was available in our cohort. We acknowledge the subjective nature of our survival outcomes, both the physician detected disease relapse and the patient perception of disease worsening. Despite this, both terms have allowed us to include patients from different diseases in a heterogeneous group and to consider also nonarticular disease relapses. Imaging data were also not available, therefore not allowing to measure the anterosive and disease progression modifying effect of denosumab. Finally, our cohorts do not include biosimilars and targeted synthetic DMARDs, which represent a reality in recent years and, therefore, should be evaluated in future studies.<sup>25-27</sup>

In conclusion, denosumab might be a meaningful therapeutic option in RMD and CTD patients who develop secondary OP while on bDMARD treatment, without altering its safety profile and persistence. If confirmed by prospective randomized studies with dedicated clinical, clinimetric, and imaging outcomes, denosumab could be suggested as a therapeutic option for OP in all patients with RMD/CTD being treated with other bDMARDs.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the Comitato Etico Regionale per la Sperimentazione Clinica della Regione Toscana - Sezione Area Vasta Centro (Approval Date: March 31, 2020; Approval Number: Protocol CEAVC 15659).

**Informed Consent:** Written informed consent was obtained from the patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept - C.B., F.N., S.B.R., S.G., G.F., M.M.C., G.T., F.B., L.C.; Design: C.B., C.C., M.M.C.; Supervision - C.B., M.M.C., G.T.; Materials - C.B., M.M.C.; Data Collection and/or Processing - C.C., G.T.; Analysis and/or Interpretation - C.B., F.N., S.B.R., S.G., G.F., C.G., M.M.C., G.T., F.B., L.C.; Literature Search - C.B., M.M.C.; Writing Manuscript - C.B., C.C., M.M.C.; Critical Review - C.B., F.N., S.B.R., S.G., G.F., C.C., M.M.C., G.T., F.B., L.C.

**Conflict of Interest:** C.C., G.T., L.C., F.B., G.F., F.N., S.B.G., and S.G.: none to declare. C.B. received honoraria from Actelion and Eli-Lilly. M.M.C. reports receipt of grant/research support and/or speaker's bureau attendance from Actelion, Pfizer, GlaxoSmithKline, Bristol-Myers Squibb, Bayer—MSD, Biogen, Eli Lilly.

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