Comparative Effectiveness of Denosumab versus Bisphosphonates Among Treatment-Experienced Postmenopausal Women with Osteoporosis in the U.S. Medicare Program

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BACKGROUND

- Osteoporosis (OP) is a chronic disease warranting lifelong management, and emerging guidelines advise that patients who do not reach a bone mineral density (BMD) goal or experience fractures should undergo clinical reassessment and possibly a change in therapy1,2
- Although clinical trials have shown that transitioning from bisphosphonates (BP) to denosumab (Dmab) increases bone mineral density at key skeletal sites more than remaining on BP, evidence from head-to-head studies evaluating potential fracture outcomes is lacking3

OBJECTIVES

- To assess the comparative effectiveness of denosumab versus bisphosphonates on fracture outcomes among treatment-experienced postmenopausal women

METHODS

Study Population

- Medicare fee-for-service beneficiaries ≥66 years of age with prior history of treatment with an oral BP, who newly initiated (no prior history of) Dmab, a different oral BP (alendronate [Aln], ibandronate, or risedronate), Aln , or zoledronic acid (ZA) between Jan 1, 2012 to Dec 31, 2018
- Patients were followed from the date of second-line treatment initiation with either denosumab or a different BP therapy (index date) until earliest occurrence of fracture outcome, treatment discontinuation (end of prescription supply + 60 day allowable gap), switch to another OP medication, disenrollment, death, end of available data (Dec 31st 2019) or maximum follow-up of 5 years post index date.

Fracture outcomes

- Major osteoporotic (MOP; includes NV and HV)
- Hip
- Nonvertebral (NV; includes hip, humerus, pelvis, radius/ulna, other femur)
- Non-hip, nonvertebral (NHNV)
- Hospitalized vertebral (HV)

Statistical analyses

- Balance of 118 baseline (assessed during the 455-day pre-index period) covariates including demographics, comorbidities, medication use, healthcare utilization, and fracture history was assessed using standardized mean differences (SMDs), before and after weighting with inverse probability of treatment weights (IPTW).
  - SMDs > 0.1 indicate clinically meaningful imbalance between the 2groups.
  - Fracture history and prior OP medication use was assessed using all available data.
- Doubly-robust inverse probability of treatment and censoring (IPTCW) weighted function was used to estimate the relative risk (RR) of fractures associated with the use of Dmabvs oral BP, Aln, and ZA at 1, 2, 3, and 5 yrs. follow-up.

RESULTS

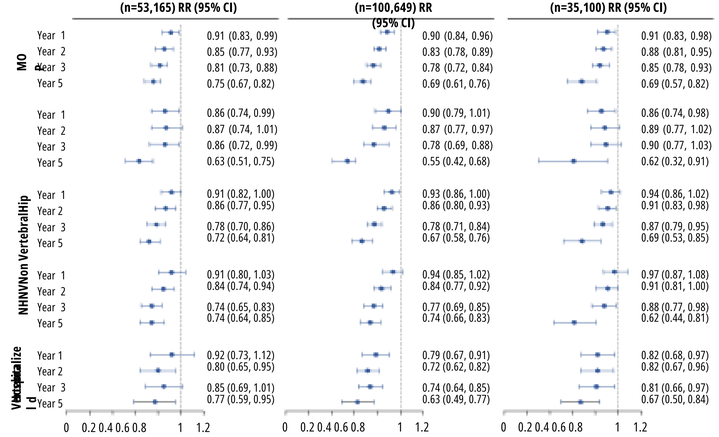
- Most patient characteristics were balanced between treatment groups before weighting
- However, Dmab patients were on average older, at greater risk for fracture, had more comorbidities, and used more medications, compared to Aln/Oral BP/ZA patients
- Average follow-up was ~1.7 yrs for Dmab, ~1.2 yrs for Aln, ~1.2 for oral BP and ~1.5 for ZA
- All variables were balanced after weighting with IPTW

Table 1. Baseline Characteristics of Treatment-Experienced Dmab, Aln, Oral BP and ZA Users Prior to Weighting with IPTW

N (%)	Dmab (N=109,061	Aln (N=53,864)	Oral BP (N=101,684	ZA (N=35,563
Mean age (SD)	77.3 (7.1)	77.2 (7.3)	76.6 (7.2)	76.1 (6.7)
History of any OP fracture*	29,168 (26.7)	10,842 (20.1)	19,341 (19.0)	8,768 (24.7)
Charlson Comorbidity Index ≥3	34,787 (31.9)	17,249 (32.0)	30,783 (30.3)	9,324 (26.2)
Vitamin D deficiency	25,566 (23.4)	9,060 (16.8)	17,354 (17.1)	7,945 (22.3)
Severe renal impairment	13,683 (12.6)	5,441 (10.1)	9,294 (9.1)	2,575 (7.2)
Any use of corticosteroids	54,398 (49.9)	23,446 (43.5)	45.206 (44.5)	18,904 (53.2)
Mean days of exposure to oral BP (SD)*	901.1 (828.8)	823.5 (817.7)	761.0 (778.1)	684.8 (700.2)
Mean # outpatient visits (SD)	15.2 (10.6)	13.4 (10.1)	13.5 (10.1)	14.8 (10.0)
Mean FRAX scores for MOP fracture (SD)**	21.8 (10.8)	19.7 (10.8)	19.2 (9.8)	20.8 (9.4)

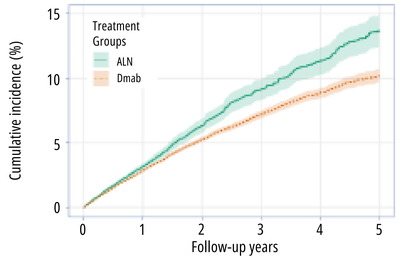
*Assessed using all available data **Among a subgroup of patients with linked EHR data (Aln N=5,309, oral BP N=13,401, Dmab N=33,765, ZA N=9,980)

Figure 1: Forest Plots of Relative Risks of Fracture Outcomes Comparing Dmab** to Aln, Oral BP and ZA*



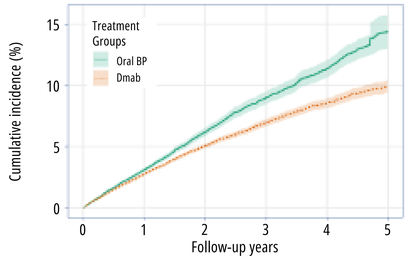
*After IPTW weighting and applying a 1% trim
**Dmab n~108,000

Figure 2: Cumulative Incidence of MOP Fracture: Denosumab vs Alendronate



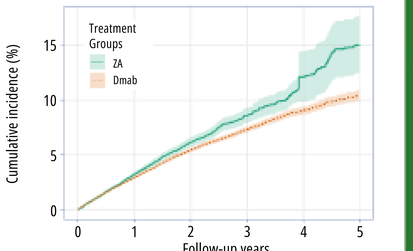
Persons @ risk	0	1	2	3	4	5
Denosumab Aln	108,130	65,176	30,928	15,438	7,749	3,663
	53,165	20,204	10,057	5,146	2,724	1,242

Figure 3: Cumulative Incidence of MOP Fracture: Denosumab vs Oral BP



Persons @ risk	0	1		3	4	5
Denosumab Oral	107,988	65,079		15,442	7,757	3,665
BP	100,649	38,007		9,307	4,814	2,191

Figure 4: Cumulative Incidence of MOP Fracture: Denosumab vs ZA



Persons @ risk	0	1	2	3	4	5
Denosumab ZA	108,076	65,191	30,878	15,408	7,722	3,642
	35,100	28,706	8,717	3,573	1,385	563

STRENGTHS AND LIMITATIONS

Strengths

- Largest comparative effectiveness study among treatment-experienced patients evaluating fracture outcomes between Dmab vs. Aln/ Oral BP/ ZA
- A gating framework using negative control outcomes was used to ensure balance between treatment groups (i.e., minimize unmeasured confounding)
- A validated algorithm based on Medicare claims data linked to radiographic imaging through EHR was used to identify incident fracture outcomes (>95% positive predictive value)4
- Higher FRAX scores among Dmab patients indicates that availability and adjustment for FRAX/BMD would have likely resulted in a larger treatment effect (i.e., greater fracture risk reduction) than what was observed

Limitations

- Residual confounding cannot be fully ruled out because of missing data on important risk factors (e.g., BMD for the entire cohort)
- High rates of patient attrition (i.e. loss to follow-up) due to treatment discontinuation, particularly for Aln/ oral BPs
- Results for hospitalized vertebral fractures, as clinically severe fractures, may not be generalizable to vertebral fractures overall, which are often asymptomatic and difficult to capture in claims databases due to lack of radiographic imaging

CONCLUSIONS

- Over a maximum of 5 years of follow-up, we observed robust and clinically meaningful reductions in the risk of hip, NV, NHNV and MOP fractures for patients who were switched to Dmab vs. other OP treatments (Aln, Oral BP and ZA) in the second-line setting
- We observed greater reductions in fracture risk with longer durations of exposureto Dmab
- As fractures are associated with significant morbidity and mortality, our results may help guide physicians, patients and policymakers on optimal treatment strategies for second line management of OP

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DISCLOSURES

This study was funded by Amgen. MK, VCB, LS, MM, BDB, and TCL are employees and own equity in Amgen. RKS was a former employee of and owns equity in Amgen. JRC has received consulting funds and research grants from Amgen. TA and YL have nothing to disclose.