Title: Delayed Denosumab Injections and Fractures Risk Among Subjects with Osteoporosis: The Health Improvement Network (THIN) Primary Care Database

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Background

Denosumab is an effective anti-resorptive drug commonly prescribed for the treatment of osteoporosis. However, discontinuation of denosumab leads to rapid reversal of its therapeutic effect(1), bone turnover markers rebounds above baseline levels, leading to rapid loss in bone mineral density (BMD)(2,3).

This reversal of benefits raises concerns that discontinuing denosumab may expose patients to an increased risk of fractures(4–8). Since 2016, case series studies reported multiple vertebral fractures after discontinuation of denosumab(4). These fractures occur within a short off-treatment period (2 to 10 months after the denosumab therapeutic-effect has waned, i.e., 8-16 months from the last denosumab injection)(4), suggesting a potential association of denosumab discontinuation and increased fracture risk, highlighting the importance of timely administration(4,9).

Currently, the European Society of Endocrinology and the National Osteoporosis Foundation guidelines recommend that denosumab should not be delayed or stopped without subsequent antiresorptive to prevent rapid BMD loss and increased risk of fracture(10,11). However, this recommendation is only based on “ungraded good practice statement”(10). Evidence from large population-based studies is limited. Thus, the association between delayed denosumab injection and fracture risk is suspected but poorly defined.

Aims and objectives

The proposed analyses aim to examine the fracture risk of delayed denosumab injections among patients who used this medication for long-term osteoporosis management.

Methods

Study design

This is a retrospective cohort study, which takes advantage of naturally occurring variations in the timing of denosumab administration, allowing us to

examine variation in administration schedule's impact on fracture risk in routine clinical settings.

Data source

We will use The Health Improvement Network (THIN), an electronic medical record database from general practitioners in the United Kingdom (UK). THIN contains health information on approximately 17 million patients from 790 general practices in the UK 1987 to 2018. Specifically, during a consultation with patients, health information is recorded by general practitioners (GP) using a computerized system with quality control procedures to maintain high data completion rates and accuracy(12).

Study population and study design

Our study population will include individuals aged ≥45 years who used denosumab for the management of osteoporosis between 2010 and 2018. The osteoporosis indication will be defined by READ codes and the use of denosumab by British National Formulary (BNF) codes. This strategy of identifying the study population by using READ codes and BNF or ATC code has been adopted in prior studies using UK primary care database(13).

We will identify individuals who initiated denosumab through BNF codes, corresponding to the dose of 60mg subcutaneously every 6 months. Based on the research aim, we will set time zero as the date of the prior denosumab injection. Follow-up starts at day 181 and will continue through the earliest of the following dates: fracture, death, switch to another regimen (estrogen, selective estrogen receptor modulators, alendronate, risedronate, ibandronate, zoledronic acid, teriparatide, and other bisphosphonates), day 390 or end of study period (December 31, 2018).

Assignment to treatment strategy

We will compare three denosumab administration strategies shown in **Figure 1**. The strategies can be defined as:

1) No delay: receive the next denosumab injection between 150 days and 210 days (reference).
2) Short delay: receive the next denosumab injection between 210 days and 300 days (next injection delayed for 1-3 months).
3) Long delay: receive the next denosumab injection between 300 days and 390 days (next injection delayed for 4-6 months).

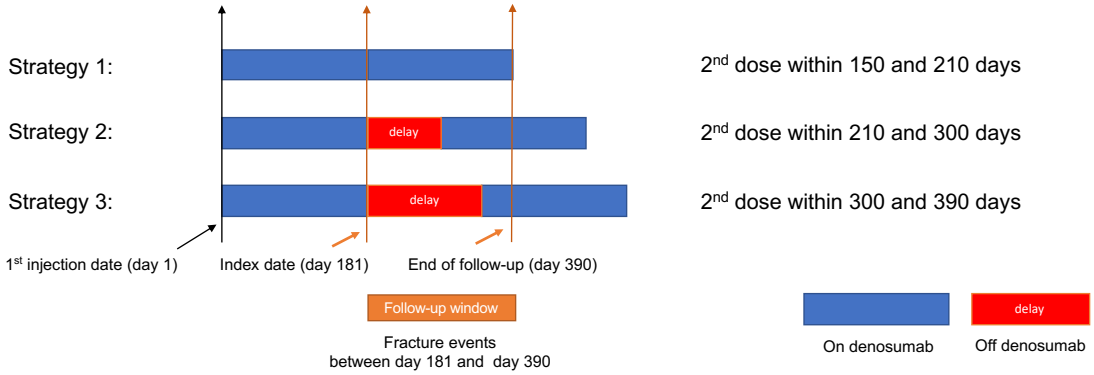

Figure 1 Study design

Assessment of outcomes

We will evaluate the fracture risk during the rebound period. In this study, we focused on the next following seven months when the effect of the prior denosumab wane, that is from day 181 to day 390. The primary outcome of interest is composite fracture including all types of fracture. Secondary outcomes include major fracture (hip fracture, vertebral fracture, wrist fracture, humerus fracture, pelvis fracture and rib fracture), vertebral fracture, and hip fracture. According to previous studies, READ codes will be used to define the occurrence of fracture(14,15). During the follow-up, the first fracture at each site would be counted.

Covariates

We will use READ codes or BNF codes to define the baseline covariates occurring in two years prior to the index date. The following variables will be included: sociodemographic factors (age, sex, ethnic origin, Townsend Deprivation Index score), body mass index, lifestyle factors (i.e., smoking, alcohol use), parental history of osteoporosis or hip fracture in a first degree relative, comorbidities, fracture history and medication use prior to the index date. In addition, cumulative bisphosphonates exposure length, Charlson Comorbidity Index (CCI)(16), and Q-fracture risk score will be calculated(17). Time-varying covariates are same set variables used in Q-fracture risk score, but updated weekly.

Statistical analysis

We will emulate a sequential randomized controlled trial(RCT) comparing the three different strategies using observational data, and then combine the results of sequential RCTs to provide accurate estimates of fracture risk. The design will follow the recommendation of using electronic medical records to emulate target trial(18,19). For example, the design of the 1st study focused on the 2nd injection delay from individuals who received two or more injections

(**Figure 1**). To avoid immortal bias, we will use the "clone and censor" method used in prior studies(21–23). This method allows us to align the start of follow-up, specification of eligibility, and treatment assignment(18). Briefly, we will create a dataset with three copies of each eligible subjects at baseline and assign each of the replicates to 1 of the three treatment strategies. Replicates assigned each treatment strategy will be censored if and when they deviate from the assigned treatment strategy. To increase the statistical power, we then perform sequential emulated trial by focusing on the i^{th} injection from individuals who received i or more doses ($i \geq 2$). Studies will not be included if the total sample size <100 or no fracture occurred.

We will fit a pooled logistic regression model for each fracture outcome. Final models will include an indicator for the treatment strategies, month of follow-up (linear and quadratic term), a cluster indicator of individual and the potential confounders for the effect of denosumab administration on fracture. Because the outcome of the models is rare at all times, the odds ratio from this model approximates the hazard ratio (HR). We will calculate the cumulative incidence of fracture since the index date for each treatment strategy.

Because the censoring required by our analytic approach has the potential to introduce selection bias due to post-baseline variables, thus, we additionally assign time-varying inverse probability weights to ameliorate this selection bias issue(24). We will define discrete unit time interval in which we can define time-varying covariates that can predict deviation from assigned treatment. Weights will be truncated at the 99.5th percentile. We will use a nonparametric bootstrap with 500 samples to appropriately compute the 95% confidence intervals (CIs) for the HR and cumulative incidence estimates from the pooled data set.

Secondary analytic strategies:

1) Based on our previous study(unpublished data), 30-40% patients will delay next denosumab injection over one month, and 10-20% patients delay over four months. If the sample size or outcome events in strategy 2 and strategy 3 are small or rare, we will perform a secondary analysis by combining strategies 2 and 3.
2) To better evaluate the association between injection delay and fracture risk, we will extend the analysis from 2 or 3 strategies to 30 strategies of the form "delay the next denosumab injection by x weeks" where x takes values from 1 to 30 in increment of 1. Similar to the main analysis, we will emulate a randomized experiment and use the same "clone and censor" method, but involving 30 regimes. We will estimate the delay effect by smoothing over the 30 treatment regimes using the cubic function of "delay (weeks)."(24–26) This type of analysis will allow us to estimate the non-linear relationship

between denosumab injection delay and fracture risk.

Power calculation

We estimated that approximately 10,000 valid follow-up denosumab injections could be pooled from osteoporosis patients in THIN during the period 2010-2018. And based on the fracture risk in general population over 50 years old[30], with type 2 error=0.05, 80% power, and the expected hazard ratio of 1.8 to 2.2 (long delay compared to no delay), the sample size of valid denosumab injections are listed below. The fracture risk in severe osteoporosis population is much higher than that in general population, so the sample size we need may be much smaller. Current THIN data may not have enough sample size for site-specific fracture (hip or vertebral fracture) but have enough sample size for composite fracture.

Table 1 Estimated sample size for outcomes with different expected HRs

	HR	Composite fracture	Major osteoporotic fracture	Vertebral fracture	Hip fracture
Fracture incidence*	-	31/1,000	15/1,000	9.7/1,000	6.6/1,000
Situation 1	1.8	4571	9447	14600	21470
Situation 2	2.0	3287	6793	10505	15439
Situation 3	2.2	2541	5250	8119	11932

Fracture risk is estimated in general population over 50 years.

Limitations

First, current THIN data may only have enough sample size for composite fracture outcome, but perhaps not for specific fracture, like hip fracture or spine fracture. However, the current study design emulates multiple trials and combine the result, which will significantly improve the statistical power. Second, while every effort will be made to control for the potential confounders, we still could not rule out the residual confounding bias that may affect our study findings.

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