DELAYED DENOSUMAB INJECTIONS AND FRACTURE RISK AMONG SUBJECTS WITH OSTEOPOROSIS

STUDY PROTOCOL

Version 3.0

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Prior versions:

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History of Modifications

Version 2.0, Date: December 20, 2019

1. To increase statistical power, we used data from 2010 to 2019, rather than 2010 to 2018 only.
2. To increase the statistical power, we planned to perform sequential emulated trials and combine them. Studies will not be included if the total sample size <100 or no fracture occurred. However, due to the concern of selection bias from high loss to follow-up rate in later injections, we required the population in later studies to be at least 50% of the original population.
3. In the original protocol, the follow-up duration was seven months from time-zero. However, a 7-months follow-up period is not appropriate due to the following reasons. a. Since we combined multiple studies, there would be an overlapped follow-up for subjects who received their subsequent injection on time (the overlap ranges from 1 day to 1 month depending on when they receive subsequent injection). b. the overlapped follow-up would lead to an unfair comparison between delay regimen and on-time regimen because we will adopt the copying and censoring method. For example, if one subject in a later study receives subsequent injection at day 40, the one month overlapped follow-up will be copied and contribute to all the three treatment regimens, however, if one subject in later study receives subsequent injection at day 2, there will be a 28-days unique overlapped follow-up only contribute to on-time regimen. So we used a 6-months follow-up to avoid such bias.
4. Since we used a 6-months follow-up, we updated the secondary analysis examining the dose-response relationship between delay and fracture with a 6-months follow-up accordingly.
5. To accurately capture the time-varying covariates, we used week as the minimum time unit and updated time-varying covariates weekly. We used 4 weeks to approximate 1 month, and updated the definition of delay patterns

accordingly. (1) “on-time”, receiving the subsequent dose within 4 weeks after the recommended date; (2) “short delay”, receiving the subsequent dose between 4 week and 16 weeks after the recommended date; (3) “long delay”: receiving the subsequent dose after 16 weeks of the recommended date.
6. For computation convenience, we used robust SE to calculate the 95%CI of HRs instead of 500 times bootstrap.

Version 3.0, Date: May 15, 2020

1. Per the reviewers’ request, we added non-vertebral fracture as a secondary outcome and performed additional analysis for non-vertebral fracture.
2. Per the reviewers' suggestion, we estimated standardized cumulative risk (incidence proportion) of fracture over six months for each group with the method used in Danaei G et al.'s paper (Danaei G, García Rodríguez LA, Cantero OF, Logan RW, Hernán MA. Electronic medical records can be used to emulate target trials of sustained treatment strategies. Journal of Clinical Epidemiology. 2018;96:12-22).
3. Per the reviewers’ suggestion that unmeasured confounding may bias the estimates from this observational study, we examined the impact of unmeasured confounding with the E-values (VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. Ann Intern Med. 2017 Aug 15;167(4):268).

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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 a 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. We will emulate a sequential randomized controlled trial(RCT) comparing the three different strategies using observational data. The specification and emulation of a target trial is shown in **Table 1**.

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 from 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 2019. 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).

Table 1 Specification and Emulation of a Target Trial of Denosumab Delay and Fracture Risk Using Observational Data

Protocol component	Target pragmatic trial specification (a hypothetical RCT that is ideal for answering this question)	Target trial emulation (using observational data to to best approximate the RCT comparison)
Eligibility criteria	We set a 6-months (180 days) "run-in" period to assess eligibility. Age≥45, between 2010 and 2019; Receive a prior dose of denosumab 180 days ago. Not receive any other anti-osteoporosis drug in the prior 180 days. At least 1 year of up-to-standard data in a THIN primary care practice;	Same as the target trial, except that patients could be eligible multiple times. Thus we will emulate sequential trials and combine them. We will collect baseline covariates during the past 2 years.
Treatment strategies	(1) On-time: receive a subsequent dose of denosumab within 4 weeks after randomization. (2) Short delay: receive a dose of denosumab between 4 and 16 weeks after randomization (3) Long delay: receive a dose of denosumab after 16 weeks after randomization. In the three strategies, patients are not allowed to switch to any other anti-osteoporosis drug (i.e. estrogens, selective estrogen receptor modulators, bisphosphonates, teriparatide, or combination of these medications)	Same as for the target trial. We define the date of denosumab injection using the date of denosumab prescription. In clinical practice, patients who receive subsequent dose early (i.e., between 5 to 6 months after the prior dose) are also viewed as on time. We will classify these injections as "on time" in the primary analysis and exclude them in the sensitivity analysis.
Treatment assignment	Eligible individuals are randomly assigned to one of the three "treatment strategies" and are aware of the strategy to which they have been assigned	We classified patients according to the strategy that their data were comparable with at time zero and emulate randomization by adjusting for baseline confounders
Outcomes	Composite fracture (including all types of fracture), major osteoporotic fracture (hip, vertebral, wrist, humerus fracture, pelvis, and rib fracture), vertebral fracture, and hip fracture	Same as for the target trial
Follow-up	Starts at the time of assignment to a strategy, and ends at the earliest of first fracture, death, 6 months after time zero or administrative end of follow-up.	Starts the day after the end of the "run-in" period.
Casual contrasts	Intention-to-treat (ITT) effect, Per-protocol effect	Observational analog of the per-protocol effect
Statistical analysis	ITT analysis; Per-protocol effect (45): censor patients when they deviate from their assigned treatment strategy (not follow the pre-defined protocol, die or switch/add other osteoporosis medications). The analysis will adjust for pre-randomization and post-randomization prognostic factors that predict adherence to the protocol and loss to follow-up.	Observational analog of the per-protocol effect: same as target trial, except that we created 3 individuals (clones) per eligible person and assigned 1 to each treatment strategy. The analysis will adjust for baseline and post-baseline prognostic factors that predict adherence to the protocol and loss to follow-up.

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 6 months after the date of the prior denosumab injection. Follow-up starts at time zero 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), 6 months or end of study period (April 31, 2019).

Assignment to treatment strategy

The subsequent dose of denosumab is recommended to be given six months after a prior dose; so we compared the effect of the following three delay patterns:

(1) “on-time”, receiving the subsequent dose within 4 weeks after the recommended date;

(2) "short delay", receiving the subsequent dose between 4 weeks and 16 weeks after the recommended date;

(3) “long delay”: receiving the subsequent dose after 16 weeks of the recommended date.

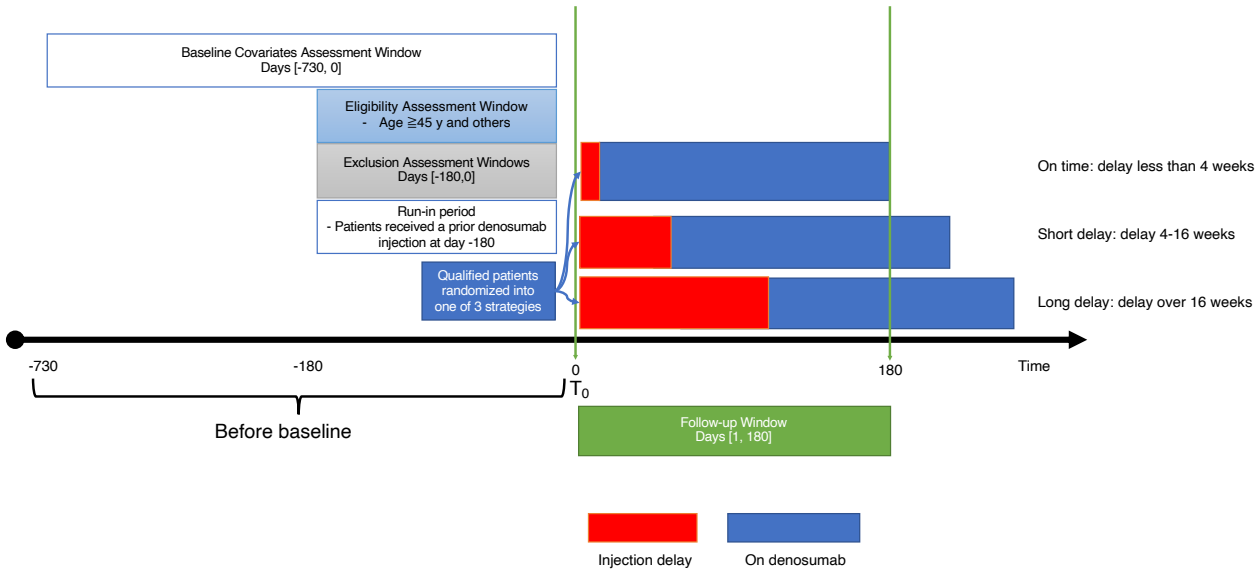

Figure 1 Study design

Assessment of outcomes

We will evaluate the fracture risk during the rebound period. In this study, we focused on the next following six months when the effect of the prior denosumab wane, that is from the recommended date to the following 180 days. The primary outcome of interest is a composite fracture, including all types of fractures. Secondary outcomes include major fracture (hip fracture, vertebral fracture, wrist fracture, humerus fracture, pelvis fracture, and rib fracture), vertebral fracture, hip fracture , and non-vertebral 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 the same set variables used in the 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 trials(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**). 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 ($i \geq 2$). Due to the concern of selection bias from high loss to follow-up rate in later doses, we required the population in later doses to be at least 50% of the original population

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 time intervals 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 robust SE to compute the 95% confidence intervals (CIs) for the HRs.

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 23 strategies of the form "delay the next denosumab injection by x weeks" where x takes values from 4 to 26 in an increment of 1. Similar to the primary analysis, we will emulate a randomized experiment and use the same "clone and censor" method, but involving 23 regimes. We will estimate the delay effect by smoothing over the 23 treatment regimens 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.

Potential sensitivity analyses:

1) If the fracture events are between 150-200, we will use outcome regression to adjust the above mentioned baseline covariates
2) In case the fracture events are rare, and the outcome models could be potentially overfitted, we may consider using inverse probability treatment weights (IPTW) or matching weights to address the confounding issue[28,29]. In this situation, the final weight for a given time point will be constructed as the product of the observation-specific time invariant IPTW and the observation-specific, time point-specific time-varying IPCW and was normalized to represent the sample size of each treatment group at each time point(28).
3) In the primary analysis, patients who fractured during the “run-in” period were eligible. However, patients with recent fractures have high risk of further fractures and could be more adherent to denosumab. The primary

analysis could potentially underestimate the fracture risk difference between long delay and on time of subsequent dosages; therefore, we will repeat the analysis by excluding patients who had fractures during the “run-in” period.

4) Repeat the main analysis only examining the relationship between delay and fracture risk of the 2nd dose only.
5) In our study population, only a proportion of the study population received the 3rd dose and 4th dose. Due to the concern of potential selection bias of patients attrition in the later emulated trials, we will create an additional inverse probability weights to address potential selection bias.
6) We will perform a sensitivity analysis in a subset population who received their subsequent injection in 6 months;
7) In clinical practice, patients who receive subsequent dose “early” (i.e., between 5 to 6 months after the prior dose) are also viewed as on time; we will classify these injections as "on time” and perform a sensitivity analysis by excluding those “early” injections.
8) We will perform imputation analyses to account for missing data. Variables include BMI, smoking, alcohol use and other variables. To minimize random error, we will impute 5 data sets, calculating effect estimates from each imputed data set and averaging estimates and their CIs obtained from each imputed data set using Rubin’s rules.
9) Unmeasured confounding (e.g., Vitamin D/calcium, diet, and activity level) may bias the estimates from this observational study, which we examined using the E-value(31).

Potential subgroup analyses:

1) age >85 (or the median age of study population);

2) gender (male or female);

3) prior bisphosphonate duration (<=3 years or > 3 years, or cutoff can be defined later by the median value of the study population);

4) baseline Q-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 2010-2019. And based on the fracture risk in the 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 (Table 2). The fracture risk in severe osteoporosis population is much higher than that in the 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 2 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 the 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 fractures, 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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