Predicting Nonlinear Changes in BMD Over Time using a Physiologically-Based Mathematical Model

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Abstract

A mathematical model has been developed that is able to reasonably predict nonlinear changes in mean BMD over a 4 year period for different denosumab dosing regimens from start of treatment to discontinuation of denosumab treatment, and provides a structure to be further generalized to accommodate other osteoporosis treatments.

Background

- Published literature on predicting BMD changes is predominantly on correlations (K-2 correlations and linear models), such as:
  - serum C-terminal cross-linking telopeptide of type I collagen (CTX), a marker of osteoclast (OC) function
  - bone formation markers, such as:
    - bone-specific alkaline phosphatase (BSAP) as osteoblast (OB) function
  - extracellular fluid Ca (ECF Ca) for denosumab available to develop BMD model component
  - other published physiologically based model of calcium and bone homeostasis that already considers calcium, bone matrix, and extracellular and endocrine long-term control of bone turnover

Methods

- Extract published mathematical model to predict longitudinal nonlinear changes in bone density (BMD) in healthy women over 4 years using (1) ultrasonometry (2) densitometry and (3) biochemical markers.
- Differential equation model linked the bone markers to BMD. Changes in BMD were described by
  - Equation links nonlinear changes in bone density (BMD) in healthy women over 4 years using (1) ultrasonometry (2) densitometry and (3) biochemical markers.
- Differential equations (BMD, CTx, and BSAP) describing on- and off-treatment effects of denosumab over 48 months from baseline, applied to five different denosumab dosing regimens over 48 months. The composite model was able to reasonably predict the percentage accumulation of lumbar spine BMD for the subcutaneously (SC) administered 30 mg every 3 months (q3M) and 210 mg q6M regimens from start of treatment to discontinuation of denosumab treatment, and provides a structure to be further generalized to accommodate other osteoporosis treatments.
- Differential equations were constructed to link the prior description of bone resorption and formation markers, scaled appropriately, to provide a prediction of BMD values following discontinuation of denosumab treatment, and provides a structure to be further generalized to accommodate other osteoporosis treatments.
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- Deterministic parameter estimates
- Simplex algorithm with least squares minimization (Curve Fitter). Modifying: x via
- Fit option
- Digitized data using Plot Digitizer, v 2.4.1

Model Predictions Following RanXL Inhibition With Denosumab (Figures 3-4)

- Circle (C) power show data and model predicted values were represented by the solid lines. A horizontal reference dotted line is included on Figure 3 and at the baseline value of 100%. Linear fits from 0 to 48 months indicate study extension periods (Figure 5). Observed values were interpolated from published data.

Summary

- A single differential equation linking longitudinal changes in bone formation and resorption markers described changes in BMD over a 4 year period of different denosumab treatment regimens.
- Differential and treatment-inhibition BMD, CTx, and BSAP changes were predicted without modifications of the previous single-compartment model due to RANKL inhibition.
- The multi-compartment model can be further expanded to accommodate different treatments, dosages, and measured markers by use of more hysteresis, and further generalization of the mathematically represented physiologic relationships.

References
