A Semi-mechanistic Approach to PK/PD Modeling of Complex Response Data: Bone Turnover Example for Odanacatib, a Cathepsin K Inhibitor

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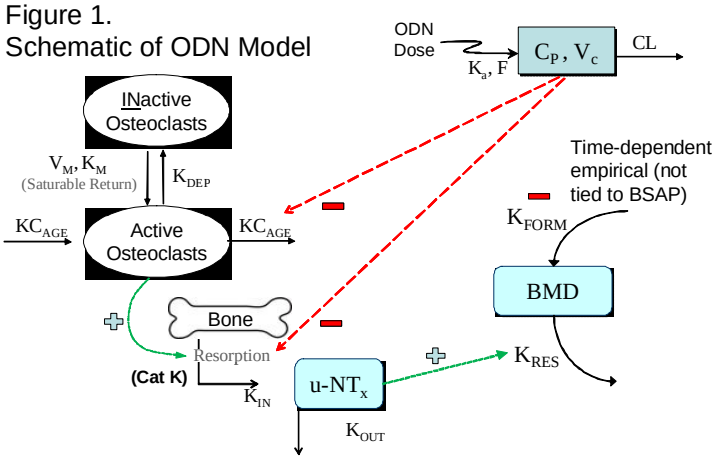
Background and Objectives

A variety of approaches can be taken to incorporate greater mechanistic understanding into PK/PD models, including a variety of bottom-up, middle-out, and top-down approaches. The osteoporosis field is rich with examples of various types, including several bottom-up examples that take advantage of systems biology methods and detailed biological interplay of various signaling pathways which are thought to mediate coupling of bone resorption and formation processes [1, 2]. However, application of these approaches requires assumptions about the quantitative interpretation of biomarkers often identified through qualitative associations in experimental data and additional assumptions regarding the applicability of relationships associated with other classes of anti-osteoporosis agents. Thus, such approaches may be sub-optimal for identifying which mechanism may be key or rate limiting to understanding response for a novel compound or class. For odanacatib (ODN) and the cathepsin K inhibitor class, drug effects on bone formation are unclear, with conflicting data prompting concerns that the traditional formation biomarkers (BSAP and P1NP) may not be quantitatively predictive of the true bone formation rate. For this reason, a top-down, semi-mechanistic approach was taken to model development which combined mechanistic and empirical strategies. Mechanistic model terms were incorporated early to capture well-understood phenomena that are likely to be highly influential. Empirical model terms were subsequently incorporated to capture less-understood aspects by finding functional forms that reproduce patterns seen in the observed data.

Methods

Data from 391 postmenopausal women receiving placebo, 3, 10, 25, or 50 mg odanacatib weekly for up to 2 years and 266 Japanese postmenopausal women receiving placebo, 10, 25, or 50 mg odanacatib weekly for 1 year were utilized. In the first study, patients who completed 2 years of treatment were re-randomized to placebo or 50 mg weekly odanacatib and followed for an additional 2 years, providing resolution of effect data in a subset of patients [3]. Odanacatib concentration, biomarker, and bone mineral density (BMD) data were collected periodically.

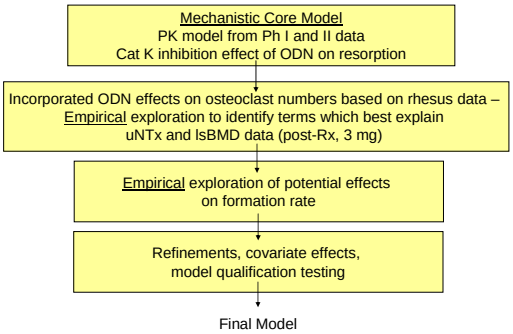
Figure 1.
Schematic of ODN Model



A population PK model (1-compartment, linear elimination, saturable bioavailability with dose) was used to estimate individual concentration-time profiles. An indirect response model (Figure 1) characterizes the time course of BMD as a function of bone formation and resorption, with the bone resorption biomarker, uNTx, described as a function of the bone resorption rate process only. Mechanism-based model elements included drug effects on: (1) uNTx, (2) rate of bone resorption and (3) osteoclast numbers (as seen in rhesus experiments). Empirical elements, such as the Emax terms for the exposure-response behaviors, the functional forms of the equations describing interplay between active and inactive osteoclasts, and the terms describing potential time effects on bone formation rate, allowed for flexible but parsimonious parameterization that results in acceptably precise estimation of parameter values for utilization of the model in simulation mode to predict untested dosing conditions (Figure 2).

Population PK/PD modeling was performed using NONMEM with the model simultaneously fit to both uNTx and BMD data from all treatments.

Figure 2.
Process to Develop ODN Model Elements



Results

In building the odanacatib model, several features in the patterns of response in the Phase II dose-ranging studies were important to capture, including: (1) sustained suppression of uNTx and near linear increase in BMD throughout 4-year treatment at higher doses; (2) enhanced uNTx levels after cessation of treatment and associated resolution of BMD effects; and (3) a non-monotonic dose-response relationship for uNTx and BMD, as the very low dose (3 mg) tended to have slightly enhanced uNTx and slightly reduced BMD relative to placebo at later treatment timepoints [3] (Figure 3). Transient elevation of bone resorption biomarkers after cessation of treatment was successfully described by incorporating active and inactive osteoclast numbers as system variables and including an osteoclast turnover component with an inhibitory sigmoid Emax function describing odanacatib inhibition of osteoclast apoptosis rate to generate an increase in osteoclast numbers during therapy. A modest shift in the exposure-response relationship of odanacatib on osteoclasts and anti-resorptive effects, such that at very low doses the osteoclast effect was more sustained than the anti-resorptive effect, was able to account for the non-monotonic dose-response. Empirical time-dependent terms for effects on formation rates were evaluated two ways: applied only to active treated patients or applied to all patients. Formation effect applied to all patients provided improved fit and suggests that the most prominent "formation" effect was a rapid burst of BMD increase after study start, possibly related to remineralization in patients receiving supplemental calcium and vitamin D, and that further odanacatib-based changes in underlying bone formation were not needed to describe the available data. Figure 4 illustrates how the predicted drug- and time-dependent effects on rates of bone resorption and formation create the net bone turnover rates which are seen in the lumbar spine BMD time course.

Figure 3. ODN Model Captures Key Features in Ph II Data

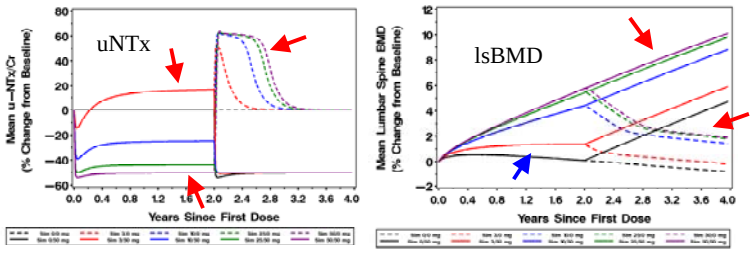
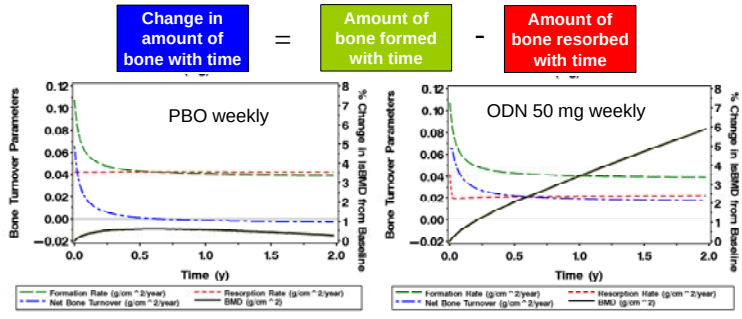


Figure 4. Model Predicted Changes in Bone Turnover Processes (over 2 Years)

- Simulation of "mass balance" elements from bone turnover for ODN vs PBO



Goodness of fit diagnostics and visual predictive checks indicate that the model well characterizes the uNTx and BMD data. The model supports that a combination of drug effects on bone resorption (Emax 67.9%, EC50 38.1 nM) and osteoclast cycling (Emax 72.0%, EC50 17.9 nM) can generate the range of behaviors observed in the Phase II data, including a non-monotonic dose-response relationship and enhanced bone resorption post-cessation of therapy. The model also suggests that odanacatib has, at most, only modest effects on bone formation rate with long-term therapy.

Conclusion

The semi-mechanistic approach used in development of the odanacatib PK/PD model allowed for:

- Identification of a "minimal" model necessary to reproduce key features in the data
- Parameter estimation through data fitting, including covariate effects and variability characterization
- Use of data to drive model interpretations for less well-understood aspects
- Improved understanding of which phenomena are most influential (drug effects on bone resorption and osteoclast numbers) and which are relatively less influential (formation effects) for odanacatib response

References

[1] Lemaire et al. Journal of Theoretical Biology 229 (2004) 293–309

[2] Peterson and Riggs. Bone 46 (2010) 49–63

[3] Bone et al. J. Bone and Mineral Res. 25 (2010) 937–947