IMPLICATIONS OF DIFFERENCES IN MODEL PARAMETERISATION IN OSTEOPOROSIS

Stephan Schmidt[1], Teun M. Post[2], Lambertus A. Peletier[3], Massoud A. Boroujerdi[1], Meindert Danhof[1], Oscar E. Della Pasqua[1,4]

[1]Division of Pharmacology, Leiden-Amsterdam Center for Drug Research, Leiden University, Leiden, The Netherlands
[2]Merck Research Labs, MSD, Pharmacokinetics, Pharmacodynamics and Pharmacometrics (P3), Oss, The Netherlands
[3]Mathematical Institute, Leiden University, Leiden, The Netherlands
[4]Clinical Pharmacology Modelling & Simulation, GlaxoSmithKline, Stockley Park, UK

Objectives

Bone remodelling is a physiological process that allows continuous renewal and repair of bone structure. This process is highly regulated and involves both osteoclasts (bone resorption) and osteoblasts (bone formation). The RANK-RANKL-OPG system has been identified as a key player in the regulation of the osteoblast and osteoclast activity. Two models with partly conflicting RANK-RANKL-OPG parameterisations have been proposed in the literature (Lemaire et al. [1] vs. Pivonka et al. [2]) to characterise the bone remodelling process. The aim of our study was 1) to compare these two parameterisations based on a previously established model [3] and 2) to identify the parameterisation that best describes changes in bone turnover markers and bone mineral density (BMD) as a result of osteoblast and osteoclast activity.

Methods

Study Population and Design

Data was obtained from two identically designed randomised, double-blind, placebo-controlled dose finding studies. In these studies, 767 healthy post-menopausal women (1-4 years after menopause) were randomly assigned to once daily treatment with tibolone (0.3, 0.625, 1.25, and 2.5mg) or placebo [4]. All subjects received 500mg of supplemental calcium once daily.

Five different biomarkers were determined, characterising osteoblast activity (bone-specific alkaline phosphatase (BSAP), osteocalcin), osteoclast activity (urinary cross-linked N-telopeptide of bone collagen normalised to creatinine (NTX/Cr)) as well as bone mineral density (BMD) in lumbar spine (L1-L4) and total hip.

Disease System Analysis [5]

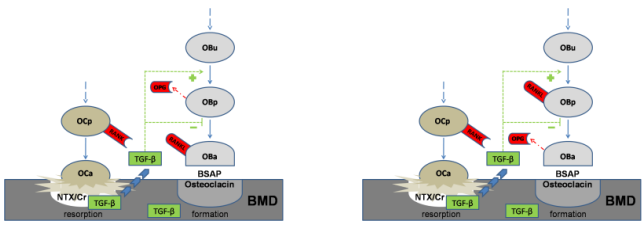

Figure 1. *Model structures proposed by Lemaire [1] (left panel) and Pivonka [2] (right panel). OBu: uncommited osteoblast progenitors, OBp: osteoblast precursor cells, OBa: active osteoblasts responsible for bone formation, OCp: osteoclast precursor cells, OCa: active osteoclasts responsible for bone resorption*

The disease systems proposed by Lemaire and Pivonka are very similar and differ only in the RANK occupancy ratio (π_L) as shown in equation 1.

$$\frac{dR}{dt} = D_R\pi_C - \frac{D_B}{\pi_C}R \qquad \pi_C = \pi_C(C) = \frac{C + fC_S}{C + C_S}$$

$$\frac{dB}{dt} = \frac{D_B}{\pi_C}R - k_B B \qquad \text{with} \qquad \pi_L(Lemaire) = \frac{\alpha K_L^P \pi_P B}{1 + \beta\left(K_O^P/\pi_P\right)R}$$

$$\frac{dC}{dt} = D_C\pi_L - D_A\pi_C C \qquad \pi_L(Pivonka) = \frac{\alpha K_L^P \pi_P R}{1 + \beta\left(K_O^P/\pi_P\right)B}$$

Equation 1. *Model parameterisation according to Lemaire [1] and to Pivonka [2]. R: responding osteoblasts, B: active osteoblasts, C: active osteoclasts, D_R: proportionality factor for the production of B from R, D_B: proportionality factor for the dissipation of R, D_C: rate of osteoclast precursor differentiation/apoptosis of C, π_C: TGF-β receptor occupancy; C_S: dissociation binding coefficient of TGF-β; π_L RANK occupancy ratio, which depends on the amount of RANKL attached to the osteoblast surface (K_L^P) and the rate of OPG production (K_O^P) .*

In order to evaluate the different time scales present in the disease model, the mathematical system (equation 1) was made dimensionless by converting the variables for R, B, and C into the dimensionless input functions x (= R/R_0), y (= B/B_0), and z (= C/C_0), where R_0, B_0, and C_0 are the respective baseline concentrations of R, B, and C [5].

Both models were reduced and changes in BSAP, NTX/Cr, and osteocalcin were related to y and z as shown in equation 2.
Changes in BMD of lumbar spine and total hip were characterised by the ratio of bone resorption (mediated by z) and formation (mediated by y).

$$\mathrm{BSAP} = \mathrm{BSAP}_0 \cdot y^{\tau_{BSAP}} \qquad \frac{dBMD(LS)}{dt} = k_{LS} \cdot \left(1 - \left(\frac{z}{y}\right)^{\tau_{BMD}}\right)$$

$$\mathrm{NTX} = \mathrm{NTX}_0 \cdot z^{\tau_{NTX}}$$

$$\mathrm{OST} = \mathrm{OST}_0 \cdot (y \cdot z)^{\tau_{OST}} \qquad \frac{dBMD(TH)}{dt} = k_{TH} \cdot \left(1 - \left(\frac{z}{y}\right)^{\tau_{BMD}}\right)$$

Equation 2. *Linking bone cell activity to changes in fast and slow biomarkers using transducer functions, where NTX_0, $BSAP_0$, and OST_0 are scaling parameters, while k_{LS} and k_{TH} are turnover parameters [5].*

Reduced kinetic-pharmacodynamic (K-PD) models were fitted to the tibolone data at all four dose levels (0.3mg, 0.625mg, 1,25mg, 2.5mg) and placebo using a non-linear mixed effect modelling approach in NONMEM 6.2. Different models were tested in order to identify the model that best describes changes in BMD following treatment with tibolone. Model selection and validation were based on statistical and visual diagnostic criteria.

Results

Both K-PD models converged successfully and allowed for sufficient fitting of BMD in lumbar spine and total hip. Parameterisation of the RANK-RANKL-OPG system according to Lemaire required the incorporation of a mixture model to identify responders and low-responders to tibolone treatment, while this was not necessary when using the Pivonka parameterisation. When evaluating model performance by simulating changes in BMD of lumbar spine and total hip for the entire treatment period, similar results were obtained for both models (Figure 2).

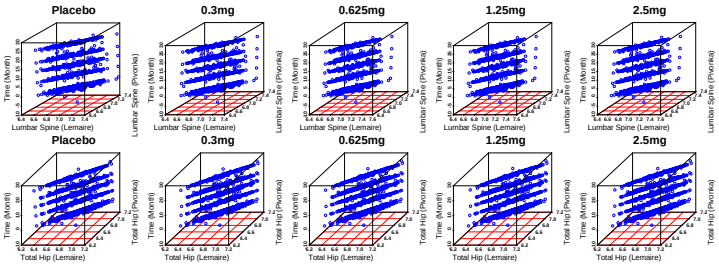

Figure 2. *Comparison of the simulated (blue dots, n=500) change in BMD of lumbar spine and total hip at five different dose levels (placebo, 0.3mg, 0.625mg, 1.25mg, and 2.5mg) using both model parameterisations.*

Our analysis further indicates that the dynamics of the fast biomarkers (BSAP, osteocalcin, NTX/Cr) were not appropriately captured (Figure 3). This is in part due to the structure of the data used for fitting both models. Simulations of the bone turnover dynamics show that changes in respective biomarker response are rapidly occurring (<200 days) and that a new homeostasis is already established at the time of the first (6 month) measurement (Figure 4).

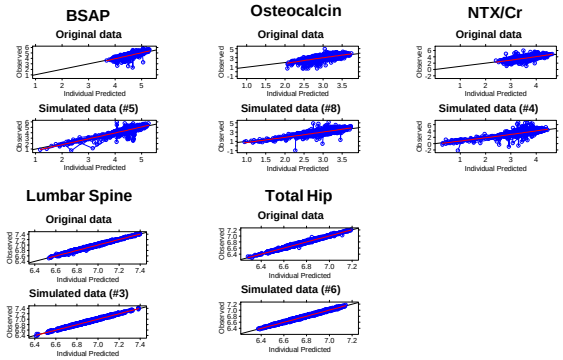

Figure 3. *Mirror plots for Pivonka parameterisation. Blue dots represent observed vs. individual model-predicted response of the bone turnover markers (BSAP, osteocalcin, NTX/Cr) as well as BMD in lumbar spine and total hip.*

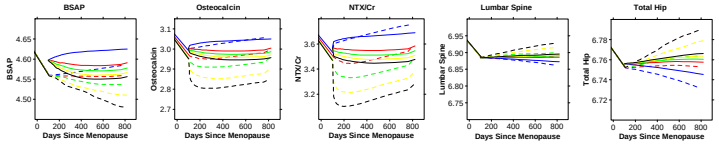

Figure 4. *Simulated change in median biomarker response at five different tibolone dose levels (placebo, 0.3mg, 0.625mg, 1.25mg, and 2.5mg). Treatment with tibolone is started at day 100. Solid lines represent the parameterisation according to Lemaire, while dashed lines represent the Pivonka parameterisation.*

Conclusion

Both models are structurally very similar, but the small difference in parameterisation by Pivonka allows between-subject variability in the data to be assigned to the maximum effect (I_{max}). In comparison, the model according to Lemaire required the incorporation of a mixture model (responders vs. low-responders) to describe the data.
Simulations based on the final parameter estimates of both models also indicate that bone resorption markers change more rapidly than corresponding bone formation markers. As a consequence, a more elaborate sampling scheme may be necessary when aiming to evaluate the relationship between bone resorption/formation processes and their impact on BMD. The use of a physiological frame work can support the optimization of a clinical study design, in particular with regard to sampling times.
Further work is needed to capture the effect of drugs with different mechanisms of action. Subsequently, the developed framework will be used to link the relevant biomarkers to fracture risk in different patient populations.

References

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Acknowledgement

This research was performed within the framework of project D2-104 of the Dutch Top Institute Pharma

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