PKPD model for cathepsin K inhibition with balicatib and changes in bone turnover biomarkers, in particular NTx

Nick Holford, Goonaseelan (Colin) Pillai, Nitin Kaila, William Collins, Sandip Roy,
Serge Cremers, Ulrich Trechsel, Florilene Bouisset, Jean-Louis Steimer

Dept of Pharmacology & Clinical Pharmacology, University of Auckland, Private Bag 92019, Auckland, New Zealand
Modeling & Simulation and Exploratory Development, Novartis, Basel, Switzerland and East Hanover, USA

Abstract

Background: Cathepsin K is a key enzyme for the breakdown of collagen during bone resorption. Balicatib inhibits cathepsin K. The drug may be active for treatment of osteoporosis.

Methods: Serum and urinary telopeptide data after oral dosing of healthy subjects and patients with post-menopausal osteoporosis were obtained during Phase 1 and Phase 2 of the clinical development of balicatib. Single doses of 5 to 400 mg and multiple daily doses of 5 to 50 mg were administered with intensive sampling on day 1 and at steady state, over up to 3 months in 140 patients and 12 months in 675 patients. A nonlinear mixed effects pharmacokinetic-pharmacodynamic model for balicatib effects on telopeptide formation was developed using NONMEM Version V Release 1.1.

Results: Serum C-terminal (CTx) and N-terminal (NTx) collagen telopeptide (TLP) concentration fell rapidly following the first dose of balicatib, as a %change vs baseline of 70-80 at the 50mg dose. They gradually increased over subsequent weeks with a rebound above baseline after stopping the treatment at 12 weeks. The initial attenuation of effect was describable with an empirical feedback model of decreasing serum TLP leading to increased TLP formation. Subsequent longer term changes were not well described by the empirical feedback model but could be described adequately by proposing accelerated turnover of bone formed during cathepsin K inhibition. The superiority of the accelerated turnover model was confirmed in studies of serum CTx and urinary NTx excretion over a 12 month treatment period but needs to be further investigated.

Computation

NONMEM Version V Release 1.1
FOCE with INTERACTION
SIGDIG=6
Source code patched and qualified with NMQUAL Version 4
Compaq Visual Fortran Version 6.6 Update C. Compiler options /fltconsistency /optimize:4 /fast.
Windows Server 2000, AMD Athlon MP2000

Objectives

The first objective was to develop a model for the time course of serum and urinary telopeptides during 12 weeks of treatment.
The second objective was to estimate the sensitivity of bone resorption inhibition (EC50) in order to predict suitable doses for a phase III study.

Patients

Healthy subjects (N=56)
Postmenopausal women with reduced bone mineral density (N=675)
Postmenopausal women with normal bone mineral density (N=191)

Models

Balicatib pharmacokinetics were described by a two compartment model with zero-order input and first-order elimination.
Bone collagen turnover (parameter COLEL) was assumed to drive formation of telopeptides (TLP) (Shown for NTx in Equation 1).
Parameters for cortical and trabecular bone turnover were calculated from literature values and FIXed. This allowed plausible numerical estimates of telopeptide volume and clearance.
The renal elimination of the N-terminal telopeptide (NTx) was used to describe renal and non-renal clearance of NTx. Urinary concentration of TLP was predicted relative to urinary creatinine (Equations 2 to 4) because all urinary NTx concentrations were reported relative to creatinine.
TLP fell initially but rose despite continued treatment and rebounded above baseline on discontinuation.
Two models were tried to account for the apparent development of tolerance to inhibition of collagen breakdown.
The Accelerated Turnover (Equation 5) model assumed that bone formed during cathepsin K inhibition had a quicker turnover than normal bone.
The Empirical Feedback (Equation 6) model assumed a rapid feedback through serum NTx to increase collagen breakdown.

Model Equations

$$\frac{dNTx}{dt} = (COLEL - NTx \cdot CL_{NTx}) / VNTx \quad \text{Equation 1}$$

$$uNTx/Cr = \frac{uNTx}{uCr} = \frac{\int_0^{Udt} CLrNTx \cdot sNTx dt \,/\, Uvol}{\int_0^{Udt} CLrCr \cdot sCr dt \,/\, Uvol} \quad \text{Equation 2}$$

$$uNTx/Cr = \frac{CLrNTx \cdot \bar{s}NTx}{RuCr} \quad \text{Equation 3}$$

$$uNTx/Cr = \frac{CLrNTx \cdot sNTx}{CPR} \quad \text{Equation 4}$$

```
;Calculate bone rate constants from half-lives                          Equation 5
;for cortical (CRT) trabecular (TRB) and bone formed during CKI (BCK)
  KCRT = ln(2)/POP_T2CRT
  KTRB = ln(2)/POP_T2TRB
  KBCK = ln(2)/T2BCK

;Activity of CK and formation rates of telopeptide from 3 bone sources
  CKACT = 1- Caae/(EC50+Caae)
  OUTCRT = CRT*KCRT*CKACT
  OUTTRB = TRB*KTRB*CKACT
  OUTBCK = BCK*KBCK*CKACT
;Total telopeptide formation rate
  RIN = OUTCRT + OUTTRB + OUTBCK

;Switch between normal and accelerated bone turnover
;if CK activity is <=99%
  IF(CKACT.LE.0.99)THEN
    INCRT = 0
    INTRB = 0
    INBCK = INCRT+INTRB
  ELSE
    INCRT = POP_INCRT
    INTRB = POP_INTRB
    INBCK = 0
  ENDIF

;Define turnover rates for telopeptide and bone compartments
  dNTx/dt  = RIN - CL_NTx * NTx
  dCRT/dt  = INCRT - OUTCRT
  dTRB/dt  = INTRB - OUTTRB
  dBCK/dt  = INBCK - OUTBCK

;Feedback depends on current NTx and baseline NTx                       Equation 6
  FBACK = (NTx/NTxC0) ** FBC

;Formation rate is modified by CK inhibition and feedback
  RIN = COLEL * (1 - Caae/(EC50 + Caae)) * FBACK

  dNTx/dt = RIN - CL_NTx * NTx
```

Discussion

Serum NTx is a more consistent marker of bone resorption than serum CTx or urinary NTx/Cr because turnover of C-terminal telopeptide (CTx) is more rapid (half-life 1 h) than NTx (half-life 11h). The short CTx half-life is associated with additional variability (e.g. diurnal variation).
Cathepsin K inhibition with balicatib causes a prompt fall in NTx and CTx but the effect is not constant.
The loss of effect is relatively slow and was described better by an effect on bone turnover than immediate feedback through serum TLP.

Conclusions

The balicatib PKPD model for effects on telopeptides was able to describe the central shape and variability in changes in serum NTx (shown in this poster) and serum CTx and urinary NTx/Cr. Accelerated turnover of bone formed during treatment may be the cause of loss of treatment effect on the biomarker TLP measurements.

The EC50 for cathepsin K inhibition by balicatib based on 12 months treatment can be used to predict 75% inhibition of bone turnover with a dose of 50 mg/day.

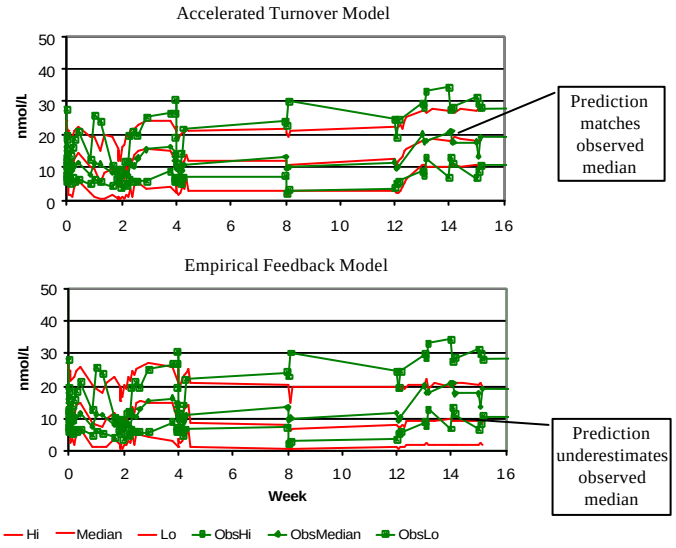
Acknowledgments:
The authors gratefully acknowledge Aurelie Gautier and Vincent Buchheit for their programming skills.

PKPD Parameter Estimates for Balicatib and NTx Turnover

Description	Units	12 week+ estimate	12 month++ estimate	12 week PPV	12 month PPV
Rate of cortical bone turnover	nmol/h	43.5 FIX	43.5 FIX	.	0.232+++
Rate of trabecular bone turnover	nmol/h	109 FIX	109 FIX	.	.
Half-life of cortical bone	y	23.1 FIX	23.1 FIX	.	.
Half-life of trabecular bone	y	2.31 FIX	2.31 FIX	.	.
Half-life of CKI bone	y	1.4	2.15	0.926	1.10
Balicatib EC50	mcg/L	40.6	19.1	0.493	0.407
NTx non-renal clearance	L/h/70kg	6.89	6.89 FIX	0.266	0.266 FIX
NTx renal clearance	L/h/70kg per 6 L/h CLcr	2.1	1.34	0.215	0.225
NTx half-life	h	10.8	11.8		
NTx Additive residual error	nmol/L	5.2	-	0.187	-
uNTx/Cr Additive residual error	(nmol/L)/(mmol/L)	52.2	16.7	.	.

PPV=Population Parameter Variability (SQRT(OMEGA)
+=Based on serum NTx, ++=Based on urine NTx/Cr
++=PPV for combined cortical and trabecular bone turnover.

Visual Predictive Check For Serum NTx 90% Prediction and Observation Intervals



NOVARTIS