Item S1: Details about the case, methods, and model development.

Details about the Case:

- Kidney function was grossly estimated as an eGFR of 10 mL/min. Indeed, hemodialysis and amyotrophy precluded the formal application of the MDRD Study equation.
- Kidney biopsy showed amyloidosis with 25% fibrosis, 13% glomerulosclerosis, light chains tubular deposition and epithelial tubular lesions.
- Hepatic function was unremarkable.
- As multiple myeloma had been refractory to combined thalidomide, bortezomib and dexamethasone therapy, pomalidomide p.o. was introduced along with the fourth cycle of bortezomib and dexamethasone, while thalidomide was discontinued.
- No drugs affecting cytochrome P450 CYP3A4, CYP1A2 nor p-glycoprotein function were present in the co-medication.
- *Clinical course:* A good hematologic tolerance allowed increasing the dosage of pomalidomide up to 4 mg q.d. from the subsequent cycle onwards. The patient showed a moderately satisfactory response to this treatment combination, with pre-dialytic light chain levels decreasing from 3500 mg/L to 2000 mg/L (i.e. - 43%) after the first cycle. The treatment was therefore pursued, and further decreased light chains to the currently observed level of 283 mg/L after the 8^{th} cycle. However, kidney function did not recover and the patient still requires intermittent dialysis.

Methods:

- *Blood sampling schedule:* Samples were taken from days 1 to 7 of the first cycle of treatment. Blood samples were taken 5 hours post-dose, at the beginning, 3 hours after the beginning and at the end of 4 consecutive dialysis sessions. Post-filter and dialysate

samples were also drawn 3 hours after starting each dialysis session.

Model development:

A pharmacokinetic model was used to predict plasma concentrations of pomalidomide during HCO dialysis, based on published pomalidomide pharmacokinetic parameters, patient's renal and hepatic status on admission and dialysis settings. An *a priori* pharmacokinetic model was built up initially without taking into account our observations, and then compared to the observed plasma concentrations, to check whether they were consistent with the model.

Two-compartment kinetics best describe pomalidomide disposition according to the literature.[1] Pomalidomide normal total clearance ($CL_{Tot,N}$), hepatic extraction ratio (E_H), central volume of distribution (V_c), peripheral volume of distribution (V_p), intercompartmental clearance between central and peripheral compartments (Q), absorption lag time (A_{lag}), unbound fraction (f_u) and absorption rate constant (k_a) were obtained from the literature [1-3], as follows: $CL_{Tot,N}$ = 9.16 L/h, E_H = 0.978, V_c = 59.4 L (according to equation 5 below), V_p = 71.5 L, Q = 3.75 L/h, A_{lag} = 0.385 h, f_u = 0.71, k_a = 1.25 h^{-1}. Note that $CL_{Tot,N}$, V_c, V_p, Q are apparent values, incorporating bioavailability.

The patient's pomalidomide non-renal clearance (CL_{NR}, L/h) and renal clearance (CL_R, L/h) were calculated as:

$$CL_{NR} = CL_{Tot,N} \cdot E_H \quad (1)$$

$$CL_R = CL_{Tot,N} \cdot (1 - E_H) \cdot \frac{GFR_{Patient}}{6} \quad (2)$$

Where $GFR_{Patient}$ is 0.6 L/h (i.e 10 mL/min) divided by 6 L/h corresponding to a normal GFR.

Pomalidomide dialytic clearance (CL_{Dial}, L/h) was estimated based on blood flow (Q_{Blood}), unbound fraction (f_u) and blood/plasma concentration ratio (r_{bp}).

$$CL_{Dial} = Q_{Blood} \cdot f_u \cdot r_{bp} \quad (3)$$

The r_{bp} was taken as 1 minus the hematocrit, i.e. 0.73 in this patient, in line with the value of 0.75 – 0.90 already published.[2]

The patient's pomalidomide total clearance $CL_{Tot,patient}$ (L/h) was equated to the sum of renal clearance (CL_R), non-renal clearance (CL_{NR}) and dialytic clearance (CL_{Dial}):

$$CL_{Tot,patient} = CL_R + CL_{NR} + CL_{Dial} \quad (4)$$

Central volume of distribution (V_c) was calculated as:

$$V_c = 58.3 \cdot \left(\left(\frac{\text{Body Weight}}{78.3}\right)^{0.686}\right) \cdot \left(1 + 0.00609 \cdot \left(\text{Total proteins} - 73.0\right)\right) \quad (5)$$

giving 59.4 L with a body weight of 84.9 kg and a value of total proteins of 67 g/L.

The amount of pomalidomide (µg) in the central (A_c) and peripheral (A_p) compartments were calculated over time according to the following differential equations:

$$\frac{dA_c}{dt} = k_a \cdot A_a - \frac{CL_{Tot,Patient}}{V_c} \cdot A_c - \frac{Q}{V_c} \cdot A_c + \frac{Q}{V_p} \cdot A_p \quad (6)$$

$$\frac{dA_p}{dt} = \frac{Q}{V_c} \cdot A_c - \frac{Q}{V_p} \cdot A_p \qquad \text{with } A_c = 0 \text{ and } A_p = 0 \text{ at } t = 0 \quad (7)$$

Where A_a is the amount of pomalidomide in the absorption site, evoluting over time according to:

$$\frac{dA_a}{dt} = -k_a \cdot A_a \qquad \text{with } A_a = \text{dose (µg) at } t = 0 \quad (8)$$

The predicted concentration C_c (µg/L) of pomalidomide in the central compartment was calculated as:

$$C_c = \frac{A_c}{V_c} \quad (9)$$

The area under the curve (AUC) was eventually calculated by numerical integration over 24 hours as:

$$AUC = \int_0^{24h} C_c \cdot dt \quad (10)$$

Mean AUC_{24h} values were calculated over one week, either with HCO dialysis 4 times a week (on-dialysis) or without any HCO dialysis (off-dialysis).

Pomalidomide extraction coefficient (E) was calculated from pre-filter (C_a) and post-filter (C_v) concentrations measured during HCO dialysis:

$$E\ (\%) = \frac{(C_a - C_v)}{C_a} \cdot 100 \quad (11)$$

Half-life ($t_{1/2}$) is calculated as:

$$t_{1/2,\ \text{on-dialysis}} = \ln(2) \cdot \frac{V_{ss}/F}{CL_{Tot,patient} + CL_{Dial}} \quad (12)$$

$$t_{1/2,\ \text{off-dialysis}} = \ln(2) \cdot \frac{V_{ss}/F}{CL_{Tot,patient}} \quad (13)$$

The predictions based on this model were compared to the observed concentrations. The model was implemented and optimized using Microsoft Excel 2007 (Microsoft Corp., Redmond, WA) with the Solver™ add-on. It could be further refined by revising $CL_{Tot,Patient}$ to 3 L/h, V_c to 63 L, V_p to 69 L, Q to 1.44 L/h, k_a to 0.82 h^{-1}, in order to improve the model fit and to obtain the most likely description of pomalidomide concentrations between and during HCO dialysis sessions (Fig. 1). The estimated AUC_{24h} amounted to 475 µg·h/L for a dosage of 2 mg q.d. The mean AUC_{24h} off-dialysis was estimated to 574 µg·h/L for the same dosage. Pomalidomide dialytic extraction ratio was estimated as 38%, 37%, 65% and 38% during the first, second, third and fourth dialyses respectively. These values are consistent with our initial estimation of the $f_u \cdot r_{bp}$ (51%).

Works Cited:

1. Li Y, Xu Y, Liu L, Wang X, Palmisano M, Zhou S. Population pharmacokinetics of pomalidomide. *Journal of clinical pharmacology.* 2015;55(5):563-572.
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