Advantages of Allometric Scaling Methods for Predicting Human Pharmacokinetics of Novel JAK Inhibitor -Baricitinib and Dose Extrapolation

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The primary motive of this study was to examine advantages of allometry scaling strategies for correct prediction of pharmacokinetics of Baricitinib in human from preclinical species. Baricitinib is basically Janus kinase (JAK) inhibitor used for the treatment of rheumatoid arthritis. Currently approved by FDA in combination with remdesivir for treatment of COVID-19 hospitalized patient. The literature published pharmacokinetic parameters (Cl and Vd) of preclinical species (Rat, Dog and monkey) were utilized for the allometry scaling of Baricitinib. The connection among the primary pharmacokinetic parameters [Volume of distribution (Vd) and clearance (Cl)] and body weight (BW) were studied across three preclinical species, we used the double logarithmic plots for prediction of the human pharmacokinetic parameters i.e. Cl and Vd with use of simple allometry and with additional correction factors for better prediction. The dose extrapolation of baricitinib was carried out by FDA guidelines. By application of the allometric scaling methods and principles correlation was found to be satisfactory for the prediction of intravenous human Cl and Vd for baricitinib. The volume of distribution (Vd) predicted by simple allometry (65.3 L) was found to be in agreement with the reported value (75.5 L); clearance (Cl) prediction by simple allometry was found to be at least 1.06 -closer to the reported value (245 mL/min); CF were used to predict the clearance. Both brain weight (B.W) and maximum life span potential (MLP) predicted the Cl with 0.52- and 0.61 -fold difference. The application of monkey liver blood flow predicted Cl with 0.81 fold which was also in close agreement with reported value. The Cl prediction was also extrapolated using LBF (Liver blood flow) method and observed that the higher species (Dog and Monkey) have predicted Cl with better accuracy than rat. Overall, the simple allometry (SA), monkey liver blood flow (MLBF) and application of liver blood flow (LBF) methods showed excellent correlation with human. The time vs. plasma concentration simulated graph also showed the similar closeness with human profile. The inclusion of plasma protein binding factor didn't improve the prediction accuracy. The FIH dose extrapolation were showed that PK guided approach and exponent for BSA based approach was found closer to actual human dose of 4.0 mg/Kg.

Keywords: Clinical Pharmacokinetics; FIH; Interspecies Scaling; Preclinical Pharmacokinetics; Simulations.

The novel JAK inhibitors tap down cytokine mediated signal via the JAK-STAT pathway, these have crucial role in immune regulation and growth. These 'small molecule' drugs are highly specific for blocking targets identified within cells that cause chronic inflammation[1]. Rheumatoid arthritis is categorized as autoimmune disease and occurred in females than males and more frequently in elder population. The occurrence rate mentioned in year 2002 ranged from 0.5% to 1%[2]

Though allometric scaling methods needs supplementary refinements and has certain limits, it is still considered as potential tool and balanced option for the estimate of pharmacokinetic parameters in species for which there are no data reported or to get good interpret preclinical efficacy and safety trials[3]. Rheumatoid arthritis is a devastating disease that affects the quality of life and efficiency of millions worldwide. This disease is characterized by inflammation of the joints that leads to damage to the cartilage[4].

Baricitinib have anti-inflammatory, immunomodulatory and antineoplastic activities. It binds to JAK1/2 and inhibitsits activation and leads to the inhibition of the JAK-STAT signaling pathways. This inhibition lowers the production of inflammatory cytokines and prevents an inflammatory response and reduces tumor cell growth.

Baricitinib approved for the treatment of moderate- to-severely rheumatoid arthritis in adults and was hypothesized to be a better therapeutic option for COVID–19. It was measured amongst all molecules studied to have a four role by inhibiting relevant cytokine signaling and have activity against NAKs, AAK1, and GAK 2,3 , which stimulate AP–2-linked host viral propagation[5–7]. Approved by the FDA for RA in June 2018 However, currently in phase 2 trials for psoriasis and AD[8]

BenevolentAI identified this compound as a prospective treatment for COVID-19 in its AI-based hypothesis.

Data from Eli Lilly'strial showed that baricitinib significantly reduces mortality in hospitalized COVID-19 patients by 38%. Review of the literature suggested that allometry scaling of novel JAK inhibitor Baricitinib hasn't been published.

METHODS

We used literature published database to find relevant articles of baricitinib for allometry scaling exercise. Baricitinib preclinical (Rat, Beagle dogs and monkey) and clinical data published were considered for allometry predictions. The observed human pharmacokinetic data were also gathered in order to enable the comparison of the predicted vs. observed pharmacokinetic data.

The published intravenous data of baricitinib in three preclinical species were used for the allometry scaling study of baricitinib. The correlation between the main primary PK parameters [volume of distribution (V_d) and clearance (Cl)] and body weight (BW) was studied across three pre-clinical species by using double logarithmic plots for prediction of the human pharmacokinetic parameters of Cl and V_d using simple allometry methods.

The collected data of volume of distribution (V_d) and clearance (Cl) values were transformed into L and mL/min, respectively. Table 1 shows the PK parameters collected from published literature from three animal species (Rat, beagle dogs and monkeys) that were used in this allometric scaling exercise.

The published studies indicate that the total body clearance is ~17 L/h and the renal clearance contribution is ~13.4 L/h in human healthy subjects; it showed that parent fraction of baricitinib is predominantly excreted via urine. The literature showed the major transporters involvement of P-gp, OAT-3 and MATE2-K for renal excretion[9].

So GFR and KBF factors were applied during scaling of Cl predictions.

Simple allometry

The scaling of V_d and Cl was carried out as per below equations.

$$V_d = aW^x \qquad \qquad ...(1)$$
$$Cl = bW^y \qquad \qquad ...(2)$$

Where, W is the body weight in kg of all species.

a and b are the coefficients and x and y are exponents of allometry.

The pharmacokinetic parameter (V_d or Cl) and W (Body Weight) were converted logarithmically and fitted to the below equation:

log (V_d or Cl) = log a + b log W, by linear least-square regression analysis.

The correction factors applied in this study are with consideration of mathematically derived constants like maximum life span potential (MLP), brain weight (BW) as well as the physiological process like kidney blood flow (KBF), monkey liver blood flow (MLBF) and excretory mechanisms as bile correction factor; Glomerular filtration rate (GFR).

Inclusion of correction factors (CF): These CF was summarized and was included into allometric equations are as below equation:

log (Cl × MLP/BrW/GFR/KBF/bile correction) = log b + y log W   ...(3)

Human Cl (Predicted) = Monkey Cl × (Human LBF/Monkey LBF)   ...(4)

The LBF method for prediction of human clearance (Cl) from each of the pre-clinical species as a fraction of liver blood flow as follows:
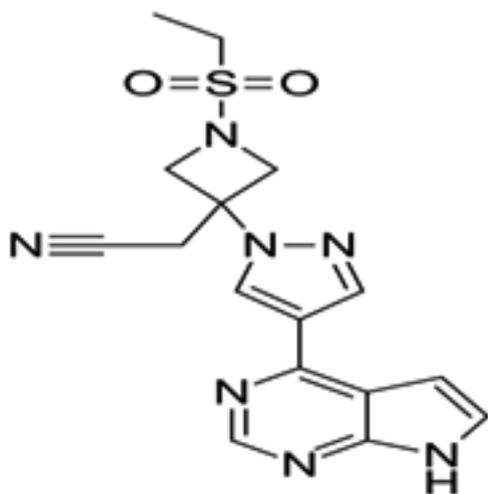
Fig. 1. Structure of baricitinib

Human Cl (Predicted) = Animal clearance * (Human LBF/animal LBF)   ...(5)[10]

The allometric scaling of the clearance (Cl); the physiological parameters were taken into consideration like as brain weight (BrW) or maximum lifespan potential (MLP) of each species were included as correction factor. The values for body weight, Brain weight and MLP used in for the exercise are presented in Table 2.

Digitalization of reported pharmacokinetic data

The reported Phase-I patients pharmacokinetic data of Baricitinib (Xia Zhao *et al.,* 2020);[11] was collected from phoenix WinNonlin 8.1 using graphreader software as graph of time vs. plasma concentration was reported and no individual plasma concentrations was published. (Available at www.grpahreader.com ; accessed on 02 May. 2021) and Phoenix WinNonlin 8.1 software (Pharsight, Mountain View, CA, USA).

Prediction of intravenous plasma vs. time profiles of baricitinib in humans

Baricitinib plasma concentrations vs. time profile were derived by using simulation using Phoenix WinNonlin 8.1 software. The simulation of human intravenous profile were carried out at 2 mg/ kg dose employing one compartment model with bolus input (using WNL5 classic modeling, PK model #1).The pharmacokinetics of baricitinib in humans was characterized by rapid absorption with a long apparent elimination half-life; the decrease in plasma concentrations displayed a biphasic profile (Xia Zhao*et al.,* 2020).

Dose extrapolation

The retrospective analyses of baricitinib dose were done with applications of different dose extrapolations methods as follows:

As per FDA draft guidelines (USFDA, 2005) the dose by factor approach was applied

Table 1. Preclinical PK parameters of baricitinib from published data

Species	Body Wt.(Kg)	AUC_{0-t} (hr*ng /mL)	T½ (h)	Cl (mL/min/Kg)	V_d (L)
SD Rat	0.204	134	1.16	21.6	2.10
Beagle dogs	10.0	NA	3.47	6.66	1.40
Cynomolgus monkeys	8.00	NA	NA	5.99	1.10

PK Data from EMA assessment report [9]; NA: Not available.

using translation of animal doses to human equivalent doses.

Application of Rat NOAEL

As per published data (CDER, report 2018) reported NOAEL in rat was 8 mg/Kg; with application of BSA correction factor and safety factor the calculated HED the predicted dose was 47 mg in human.

$$HED = NOAEL \text{ of most sensitive species} \\ (mg=kg) \times BSA\text{-}CF \times 60 \text{ (kg)}$$

Application of Mice NOAEL

Mice NOAEL reported value is 300 mg/Kg; with application of BSA correction factor and safety factor the calculated HED was 1458 mg in human.

Application of exponent for body surface area (0.67)

By use of this method which applies an exponent for BSA (0.67) and consider for difference in metabolic rate (MR), to translate doses between animals and humans. Thus, HED is derived by the equation considering dog NOAEL:

$$HED \text{ (mg / kg)} = \text{Animal NOAEL (mg / kg)} \times \\ (\text{Weight}_{animal}[\text{ kg}]/\text{Weight}_{Human}[\text{ kg}])^{(1\text{-}0.67)}$$

The calculated dose by this method was 0.132 mg/Kg; for 60 Kg it was 8.0 mg/Kg; which was 2 fold higher than actual clinical dose.

Pharmacokinetically guided approach

Starting dose = AUC in index species X Estimated clearance in human

Table 2. Body weight, Brain wt. and MLP values considered for allometry

Species	Weight (Kg)	Brain wt (Kg)	Maximum lifespan potential MLP (Years)
Rat	0.240	1.80	4.68
Dog	10.0	80.0	19.7
Monkey	8.00	100	8.01
Human	70.0	1400	93.4
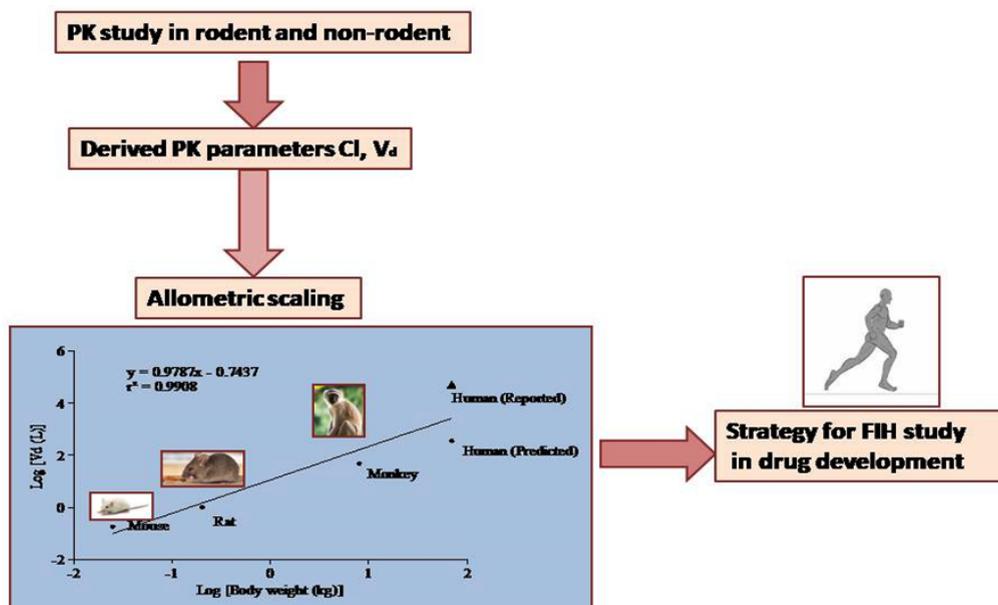
Fig. 2. Utility of allometric scaling in drug development

The AUC obtained at the NOAEL of dog (index species) reported AUC0-t (μM*hr) -1.21 and estimated clearance in human (L)-58.14
=1.21 X 58.14=70.18 mg

With application of safety factor of 10; the starting dose calculated was 7.0 mg for human[19]

Overall the PK guided approach and exponent for BSA based approach was found closer to actual human dose of 4.0 mg/Kg.

RESULT AND DISCUSSION

In order to understand the PK (Pharmacokinetics) predictions in human and providing an opportunity to refine various allometric scaling predictions this exercise

will guide the scientist from drug discovery to development.

A simple allometry correlation was found to be satisfactory for the prediction of intravenous human clearance (Cl)/volume of distribution (V_d) for baricitinib. The excellent correlation was observed between monkey and human as monkey liver blood flow method predicted the Cl value with 0.81- fold difference; the application of Cl based

Table 3. Comparative human digitalized values from graphreader with the reported values (Dose-2 mg/Kg)

PK parameters	Predicted	Reported*
T_{max} (h)	1.00	1.00 (0.50-1.50)
C_{max} (ng/mL)	23.7	24.6 (4.11)
$AUC_{inf,obs}$ (ng× h/mL)	138	140 (15.3)

*Source: Xia Zhao *et al.,* 2020

Table 4. Animal equivalent dose factors of different species BSA-CS [12]

Species	BSA-CS (Divide human dose by)
Mouse	0.081
Hamster	0.135
Rat	0.162
Guinea pig	0.216
Rabbit	0.324
Dog	0.541
Monkey (Cynomolgus, Rhesus)	0.324
Marmoset	0.162
Baboon	0.541
Micro-pig	0.730
Mini-pig	0.946
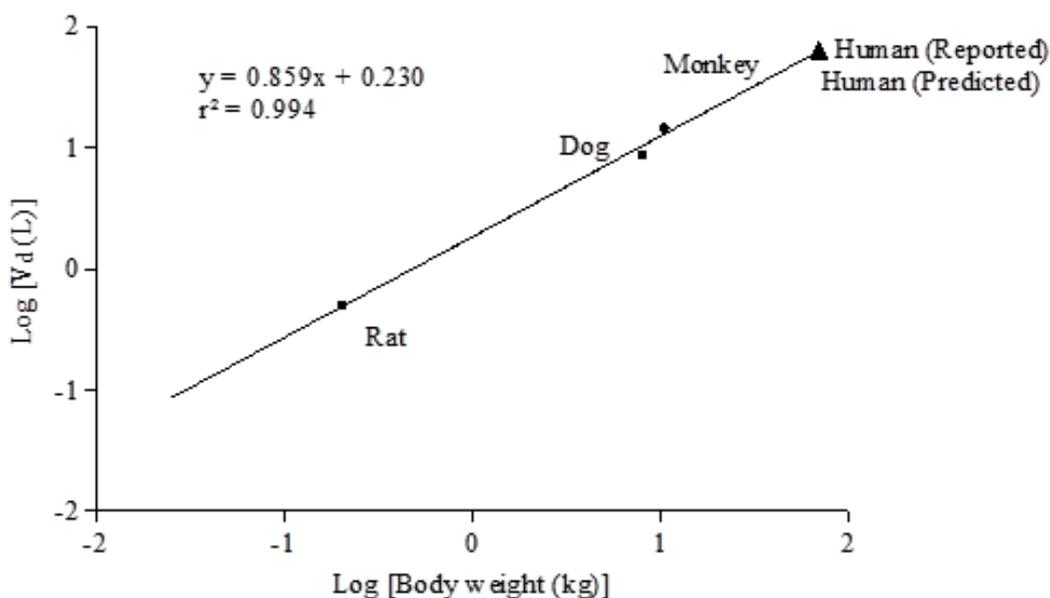
Fig. 3. Prediction of human Vd by Simple allometric scaling using rat, dog and monkey data

$y = 0.66x + 1.12$
$r^2 = 1.00$

4(a)

$y = 0.60x + 1.50$
$r^2 = 0.59$

4(b)

$y = -0.27x + 2.05$
$r^2 = 0.93$
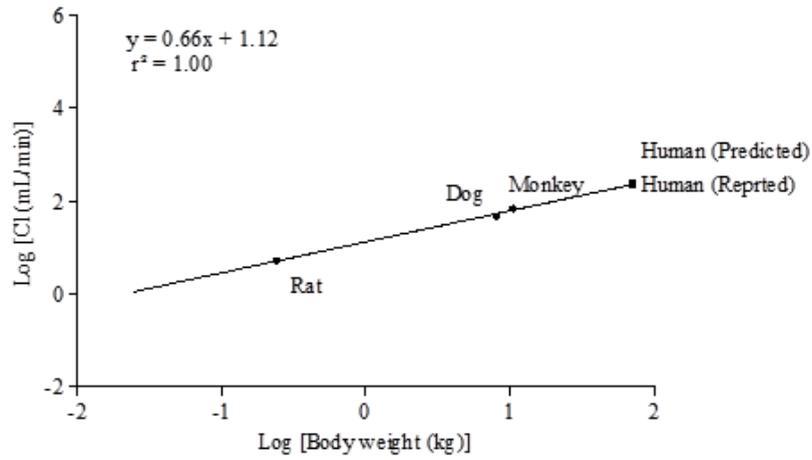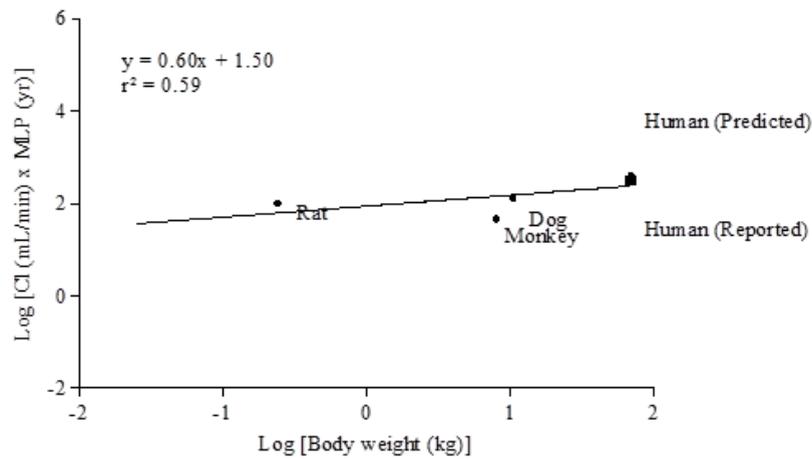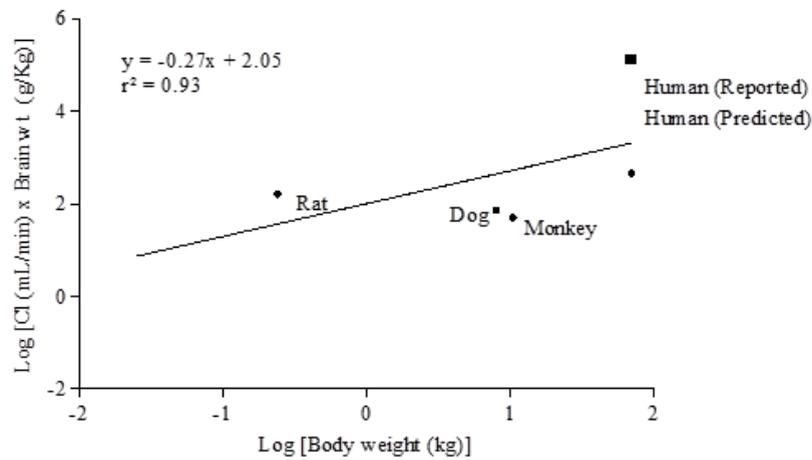
4(c)
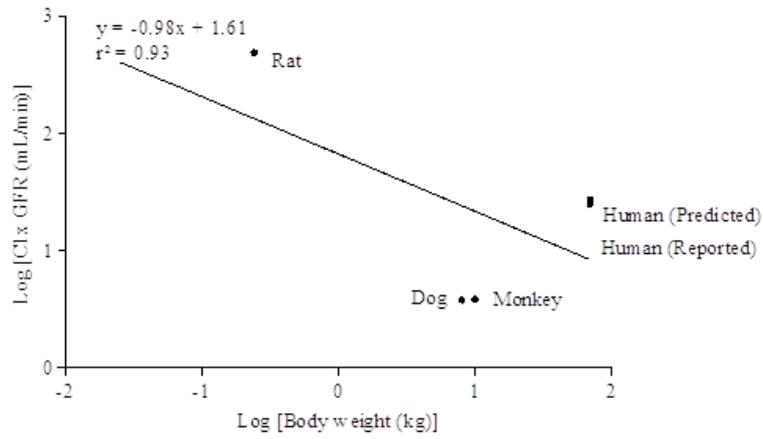
4(d)
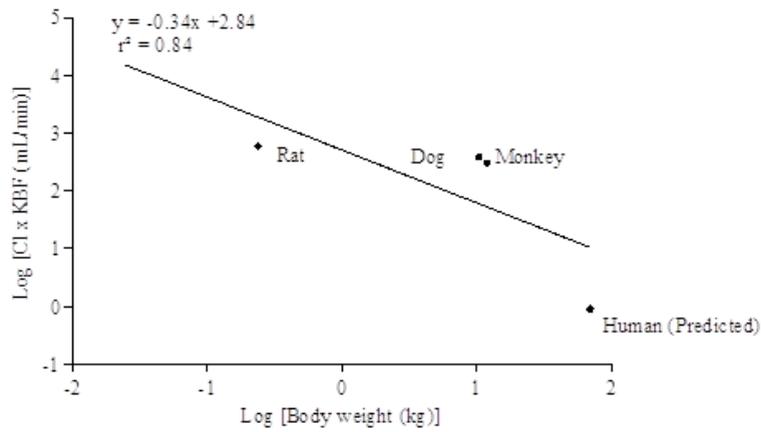
4(e)
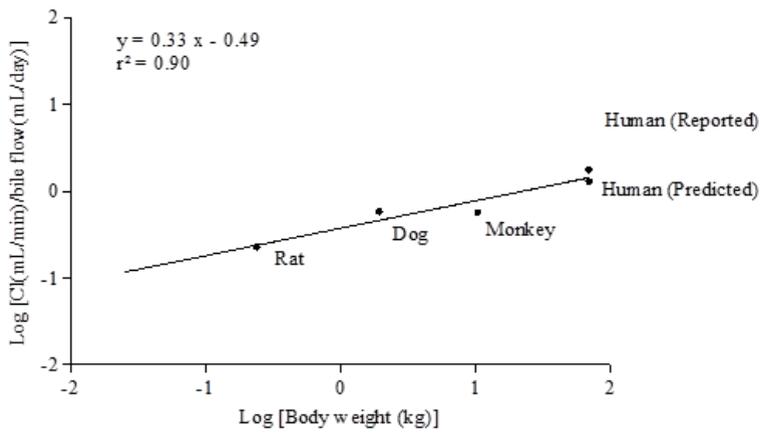
4(f)

Fig. 4. Human Cl prediction by allometry from preclinical species (a) simple allometry (b) MLP correction factor (c) BW. correction factor (d) GFR correction factor (e) KBF correction factor (f) bile flow correction factor

on LBF methods showed that higher species have better correlation than rat.

The predicted values of clearance observed were within 2.0 fold of values by simple allometry this showed success of allometry scaling methods for baricitinib.

Based on our study and reviewed literature it is well identified that volume of distribution can be predicted using simple allometric scaling; still, the clearance was not establishing to be agreeable for simple allometry and therefore, from long time correction factors has been proposed and in many cases the use of such correction factors (CF) has led to improved predictions of clearance and half-life. (Mahmood I.)[13] Studied and clarified the significance of correction factors that may further

convey allometry as a proficient predictive tool. Therefore, in this study we explored advantages of these methods which were not applied for novel JAK inhibitors.

The application of simple allometry resulted in a predicted Cl value of 231 mL/min, which was close agreement (1.06) with reported human value of 245 mL/min. The use of correction factors (CF) was generally considered to provide a better estimate of the human Cl.

The application of correction factors (CF) as bile flow and glomerular filtration rate of each species can also be applicable for drug classes that show similarity in the drug disposition as compared to baricitinib. In agreement, the inclusion of GFR, KBF and bile correction factor resulted in
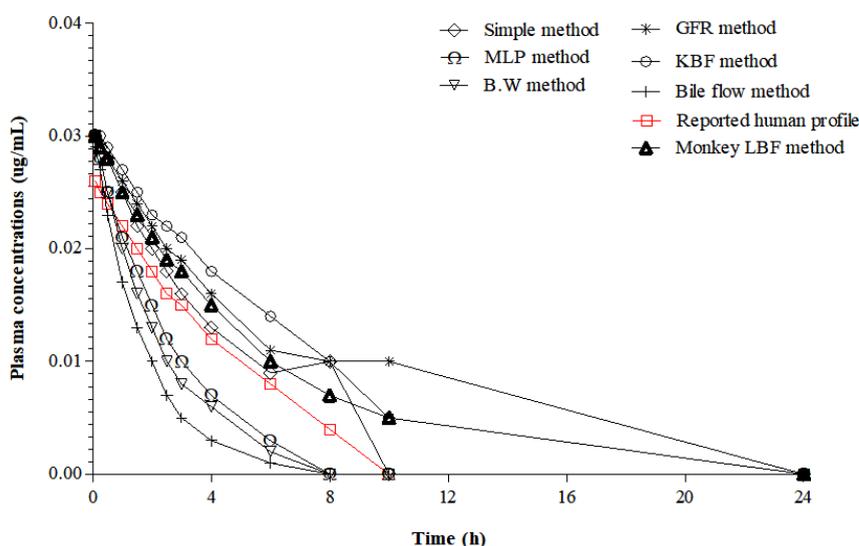
Fig. 5. Comparison of multiple simulation methods with the reported human pharmacokinetics profile of baricitinib at 2 mg/kg

Table 5. Evaluations of scaling methods

Parameter	Types of Scaling	Predicted values	Reported values	Fold differences
V_d (L)	Allometric scaling by simple method (for V_d)	65.3	75.7	0.86
Cl (mL/ min)	Simple allometry	231	245	1.06
	MLP correction factor	405		0.61
	Brain weight (B.W) correction factor	467		0.52
	Glomerular filtration rate (GFR) correction factor	145		1.69
	Kidney blood flow (KBF) correction factor	180		0.74
	Bile correction factor	627		0.39
	Monkey liver blood flow	200		0.81

Table 6. Prediction of Cl based on LBF method (equation 5)

Species	Predicted human Cl (mL/min)	Actual reported Cl of Human (mL/min)	Fold difference
Rat	551	245	0.44
Dog	311		0.79

Table 7. Free fraction data values of preclinical species extracted from literature

Species	Free fraction in serum (%)
Rat	47
Dog	61
Monkey	49
Human	50

*Source: EMA assessment report [9]

prediction of 0.74 -fold, 1.69-fold and 0.39 fold respectively; lower Cl value by KBF and GFR methods and higher by biliary clearance method than the reported human value.

In the absence of human PK data the application of monkey liver blood flow (MLBF) has been proved as better tool for getting a good correlation to the human values as monkey have better correlation to human. The application of species specific liver blood flow led to the prediction of human Cl within 0.81-fold to the reported value.

The prediction of human V_d of baricitinib by simple allometry resulted in an exponent of 0.85, which is within the satisfactory range of 0.8-1.10 the similar results were observed in the literature for most of the compounds; this resulted in a predicted value of 65.3 L which was observed in close of the observed human value of 75.7 L.

The additional efforts were tried to find out impact of plasma protein binding factors (Table 7) and observed that the prediction was not improved for simple allometry and for rest of the methods; as protein binding are not different form rodent to human. The many literature studies showed that protein binding factor were successful for vertical allometry and drugs with high extraction rate.

Dose extrapolation study showed that PK guided approach and exponent for BSA based approach was found to predict FIH dose within two fold of 4.0 mg/Kg.

CONCLUSION

Retrospective assessment of human pharmacokinetics prediction is necessary for improving prediction techniques and strategies for future candidate drugs.

Allometric scaling retrospectively predicted V_d and Cl parameters well within two fold of observed values. The overall PK of the baricitinib predicted with excellent accuracy with few exceptions of biliary corrections factor and could be used as a forthcoming tool for this class of drugs.

The correction factors evaluated in this study of baricitinib can be applicable for other or similar classes of drugs having similar metabolism and excretion pathways observed for baricitinib.

The reason for over prediction of biliary clearance may be due to lower recovery of baricitinib in feces as reported in published articles (Baricitinib recovery 15 % in feces by Sarah *et al* 2020) [14].

Allometry scaling will continue a method of choice for the prediction human PK parameters and the selection of first in human dose based solely on existing PK data of preclinical species.

Allometric scaling approaches will be decisive tool for scientists to optimize doses among species from preclinical to clinical stage of development.

Conflict of interest

The authors wish to declare that there are no conflicts of interests in the contents of the manuscript.

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