Program # 1971

Prediction of duration of C3 inhibition with APL-2 in human eyes using a PK/PD binding model

Matthias Machacek, Pascal Deschatelets, Robert Kim, Patrick Johnson, Federico Grossi

OUTLINE

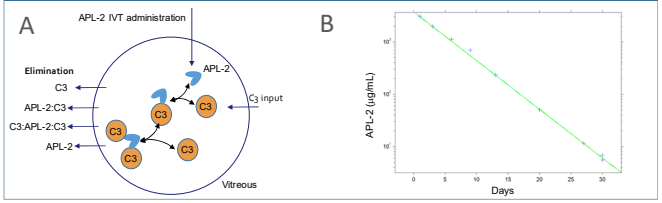
APL-2 is an anti-C3 PEGylated peptide in clinical development for geographic atrophy. The effect duration and the optimal treatment interval with intravitreal (IVT) administered APL-2 are under investigation.

Our goal was to develop a PK/PD binding model based on first principles, preclinical data from non-human primates (NHP) and published data to predict the duration of inhibition of free C3 by APL-2 in the human eye.

METHODS

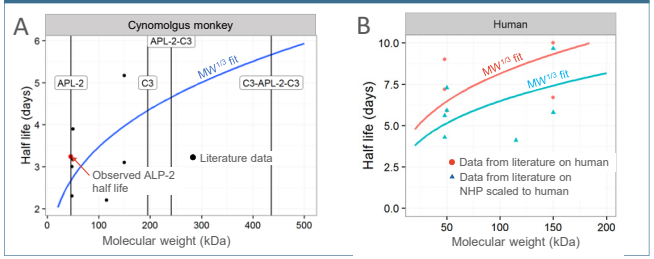
It was assumed that free C3 is a valid surrogate for the duration of effect. Based on this assumption a model was developed that describes the PK of APL-2 in vitreous and the binding of APL-2 to one or two C3 molecules (Fig 1A).

Figure 1. PK Model outline (A). APL-2 PK in NHP vitreous (B).



For PK modeling, a NHP study with APL-2 observations in vitreous after a single IVT dose of 10 mg were used (Fig 1B) and the vitreous volume of distribution and half-life were estimated. No data have previously been reported on C3 kinetics in vitreous. For purposes of the present study, it was therefore assumed that the half-life of C3 and the drug-target complexes were dependent on their molecular weights (MW). Data on molecules with a MW from 45 to 150 kDa were collected from literature and fitted with the relationship $T_{1/2} \sim MW^{1/3}$; assuming half-life is a result of diffusion limited distribution in the vitreous (Fig 2A).

Figure 2. Vitreous half life of different sized molecules in the vitreous of NHP (A) and human (B)



For scaling from NHP to human it was assumed that elimination from the vitreous is diffusion limited and that the eye radius *r* is the only difference between NHP and human eyes. From this assumption the relationship

$$T_{1/2,human} = T_{1/2,NHP}(r_{human}/r_{NHP})^2$$

was obtained. Fig 2B compares the observed $T_{1/2}$ in human (red) with the $T_{1/2}$ obtained through scaling from NHP (blue). While the scaled estimates underpredicted the actual $T_{1/2}$ by ~1 day, there was an overall good agreement supporting the validity of the scaling approach. For APL-2 to C3 binding a Kd = 0.52 nM based on surface plasmon resonance data for the APL-2 subunit was used. The model considered the binding of APL-2 to one or two C3 molecules. C3 concentration in vitreous was assumed to be 70 nM (1).

Table 1. $T_{1/2}$ estimates

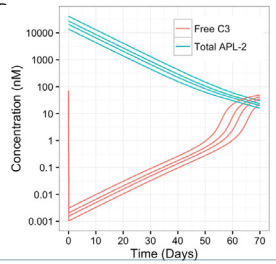
Molecule	$T_{1/2}$ vitreous (days)	
	NHP	Human
APL-2	3.2	6
C3	4.4	8.2
APL-2:C3	4.6	8.6
C3-APL-2:C3	5.6	10.5

RESULTS

Table 1 summarizes the vitreous $T_{1/2}$ that were identified; APL-2 $T_{1/2}$ in NHP through direct measurements and the other through considerations of the MW. All $T_{1/2}$ in human were obtained through scaling. Because of its large size, binding to C3 was predicted to prolong the residence time of APL-2 in the vitreous.

Simulations predicted that a single IVT dose of 15 mg of APL-2 inhibited free C3 for about 60 days in human vitreous (Fig 3). Reducing the dose to 5 mg reduced the effect duration on C3 by ~10 days.

Figure 3. Predicted total APL-2 and free C3 in human vitreous for IVT doses of 15, 10, 7.5 and 5 mg/eye



CONCLUSIONS

Model predictions support a monthly treatment interval with APL-2 and suggest also that a two-month interval is a reasonable hypothesis for testing in a clinical study.

References
1. IOVS 2012;53:6628–6637

This study was funded by Apellis Pharma. Contact email: pascal@apellis.com
Commercial relationships
Matthias Machacek, LYO-X GmbH (C); Pascal Deschatelets, Apellis (E), Robert Kim, Apellis (E), Patrick Johnson, JPharma Solutions (C), Federico Grossi, Apellis (E).