A Novel Agent-based Computational Model for Liver-targeting, AAV-based Gene Therapies Could Predict Response Durability in Hemophilia B Patients Treated with Etranacogene Dezaparvovec

AMA691

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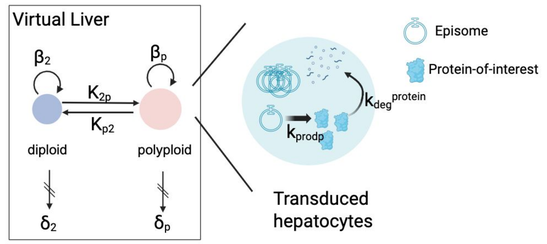
Introduction

- Adeno-associated virus (AAV) gene therapy offers a durable, single treatment for hemophilia B
- AAVs deliver DNA sequences into target cells, where the viral genome forms stable episomes, enabling the expression of therapeutic protein(s) by the host cell
- For self-renewing (i.e., not terminally differentiated) tissues or organs, the effects of cell turnover and episome propagation on durability of the therapeutic effect remain uncertain
- Differential equation-based models have been developed to predict AAV uptake and transgene protein production. However, capturing episome loss associated with target cell turnover is difficult in these models
- Here, an agent-based model (ABM) was developed to predict the long-term durability of coagulation factor IX (FIX) expression for gene therapy for hemophilia B, using simulation-based analyses on the impact of assumptions around cell biology, patient physiology and product characteristics

Methods

- An ABM was applied to etranacogene dezaparvovec (HEMGENIX®), a liver-targeting gene therapy for hemophilia B, with an AAV5 vector delivering a transgene encoding the Padua variant (R338L) of human coagulation FIX
- In the model, each agent represents an individual hepatocyte capable of cell division and death, and of being transduced with one or multiple AAV particles (**Figure 1**)
- Transduced target cells may pass episomes from mother to daughter cells during simulated cell division while all episomes were assumed lost upon host cell death
- The model was specified by nine kinetic parameters describing aspects of liver cell biology and AAV-mediated gene delivery (**Table 1**), and were informed by literature estimates
- The model was used to simulate FIX activity over 20 years following treatment
- Population variance was accounted for by creating a virtual patient population with age correlated with the age of patients that were enrolled in the HOPE-B trial (NCT03569891)
- Each virtual patient was parameterized via random uniform sampling on initial fraction of infected cells, number of episomes per transduced cell, patient age, and the maximum number of functional episomes expressed per cell (**Table 2**)
- 160,000 virtual patient simulations using a 1,000 agent-based representation of liver tissue resulted in reproducible statistics
- Model development, simulations and analyses were conducted in Julia 1.10.4.

Figure 1: Schematic of the agent-based model (ABM)



β_2 and β_p are the division probability of diploid and polyploid hepatocytes, respectively. δ_2 and δ_p are the death probability of diploid and polyploid hepatocytes, respectively. K_{2p} is the probability of diploid hepatocytes to change ploidy to polyploid hepatocytes. K_{p2} is the probability of polyploid hepatocytes to change ploidy to diploid hepatocytes. $k_{prodp}^{protein}$ is protein-of-interest production rate per episome per transduced cell. $k_{deg}^{protein}$ is the degradation rate for the protein-of-interest. Parameter values can be found in **Table 1**.

Table 1: ABM parameters describing hepatocyte dynamics and factor IX (FIX) production after treatment with etranacogene dezaparvovec

Name	Description	Value	Source
β_2	Proliferation probability of diploid hepatocytes per year	0.709	[1]
δ_2	Death probability of diploid hepatocytes per year	0.726	[1]
β_p	Proliferation probability of polyploid hepatocytes per year	0.027	[1], tuned
δ_p	Death probability of polyploid hepatocytes per year	0.019	[1], tuned
K_{2p}	Probability for a diploid cell transition to be a polyploid cell per year	0.0054	[1]
K_{p2}	Probability for a polyploid cell transition to be a diploid cell per year	0.0167	[1]
k_{prodp}	FIX production rate per episome per transduced cell (unit: molecules/year)	Diploid: 3.15×10^7 Polyploid: 6.3×10^7	[2–5]
$k_{deg}^{protein}$	FIX degradation rate	886.16 1/year	[6]

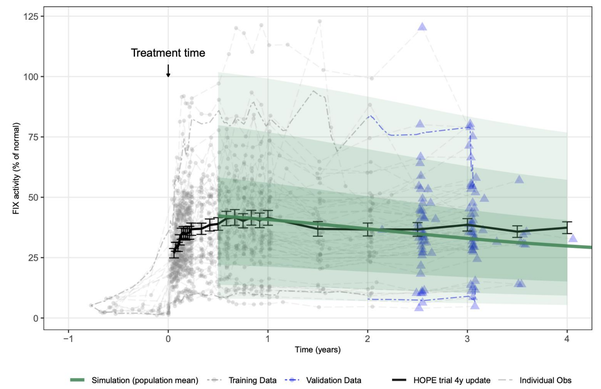
Table 2: Parameter ranges used to set up virtual populations treated with etranacogene dezaparvovec

Parameter	Parameter description	Value	Unit
Patient_age	Patient age	(20…80)	Years
Max_episome_express	Maximum number of episomes expressed per hepatocyte	(1…5)	Integer #
Initially_transduced_cells	Initially transduced cells	(10…70)	%
Init_Episome	Number of episomes per transduced cell	$10^{(1…3)}$	#/hepatocyte

Table 3: FIX activity simulated in virtual patient population compared to clinical observations

	Simulated FIX activity (%)		Observed FIX activity (%)	
Year	Median	95% Confidence Interval	Median	Range
1	35.5	7.82–99.1	41	5.9–113
2	31.8	7.01–91.7	35	9.1–99.2
3	28.2	6.12–83.5	45.3	13.7–80.3
10	21.8	4.42–68.6		
20	22.6	4.58–71		

Figure 2: ABM-simulated and observed FIX activity from the HOPE-B study over the first 4 years post-treatment



Light gray points represent individual clinical observations in the training data, blue triangles represent observations in the validation data. Light grey dash lines connect observations from the same subject. The green solid line represents the simulated mean FIX activity, and the shaded areas represent the 50%, 80% and 95% CIs (the darker shading corresponds to the tighter CI), and the shaded area represents the corresponding CI. The solid black line represents summarized clinical data of mean FIX activity observed in 47 patients enrolled in the HOPE-B trial over 4 years, the black bars represents the standard error.
ABM, agent-based model; CI, confidence interval; FIX, factor IX.

Results

- Model-predicted FIX activity for patients receiving etranacogene dezaparvovec was compared with clinical observations for 3 years following treatment (**Table 3**, **Figure 2**)
- The model-predicted sustained elevation of FIX activity over 20 years (**Figure 3**)
  - The 5% percentile prediction of 20-year FIX activity exceeds the FIX activity threshold (2% FIX activity) reported to allow patients to 'lead normal lives', with a decrease in bleed number and long-term preservation of musculoskeletal function (7,8)
- Sustained elevation of predicted FIX activity was driven by FIX expression in polyploid hepatocytes (**Figure 4**)
  - FIX expression from polyploid hepatocytes (half life ~5 years [1]) was predicted to be stable, and resulted in sustained elevation of FIX activity over 20 years
  - FIX expression from diploid hepatocytes was predicted to decrease ~5 years after receiving etranacogene dezaparvovec due to episome loss related to cell turnover

References

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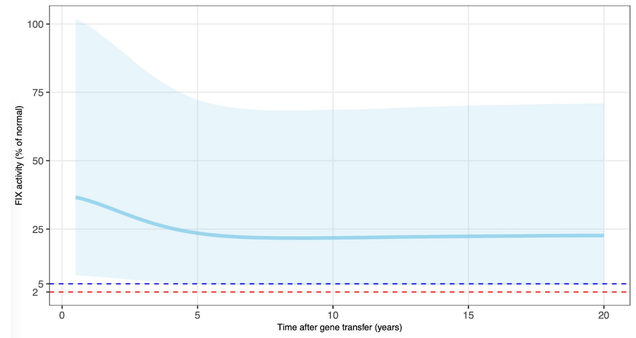
Acknowledgements

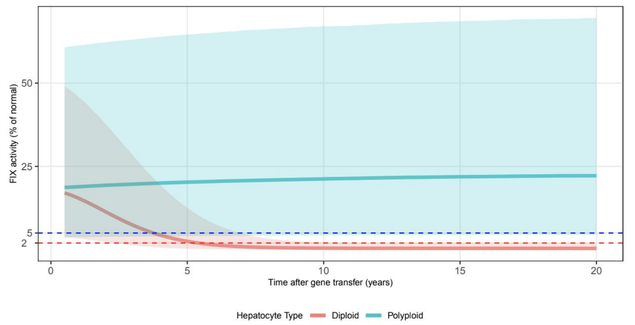
Editorial support was provided by Meridian HealthComms Ltd (part of the Bioscript Group Ltd), funded by CSL Behring. All authors reviewed the results and approved the final version of the poster.

Figure 3: ABM-predicted FIX activity, represented as percentage of normal, versus time over 20 years post-treatment



The solid blue line represents the predicted median FIX activity, and the shaded area represents the 95% CI. Red and blue dashed lines represent the 2% and 5% thresholds of normal FIX activity, respectively.
ABM, agent-based model; CI, confidence interval; FIX, factor IX.

Figure 4: Contributions from diploid and polyploid transduced hepatocyte populations to overall ABM-predicted FIX activity versus time for 20 years post-treatment



The solid blue line represents the predicted median FIX activity, and the shaded area represents the 95% CI. Red and blue dashed lines represent the 2% and 5% thresholds of normal FIX activity, respectively.
ABM, agent-based model; CI, confidence interval; FIX, factor IX.

Conclusions

- There are many uncertainties around the long-term outcomes of AAV-based gene therapies
- ABMs can be used to predict how biological variables such as target cell turnover, liver physiology, viability and product characteristics may impact durability
- It should be noted that the model is conservative and currently projects values lower than observed
- While the model applied here is in the context of AAV gene therapy for hemophilia B, the computational framework could be adaptable to other AAV-based gene therapies and diseases

Disclosures

Y Li, T Knab, DC Kirouac and AK Wilkins are employees of Metrum Research Group. E Jordie was an employee of Metrum Research Group at the time of the study, currently at Bill and Melinda Gates Foundation. P Nandy, K Peppel and S Nuthalapati are employees of CSL Behring.

Funding

This study was funded by CSL Behring.

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Presented at the American Society of Gene & Cell Therapy (ASGCT) 2025 Annual Meeting, New Orleans, LA, USA, May 13–17 2025.