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Historical Review of In-Life Data From Studies Utilizing AAVs for Gene Therapy

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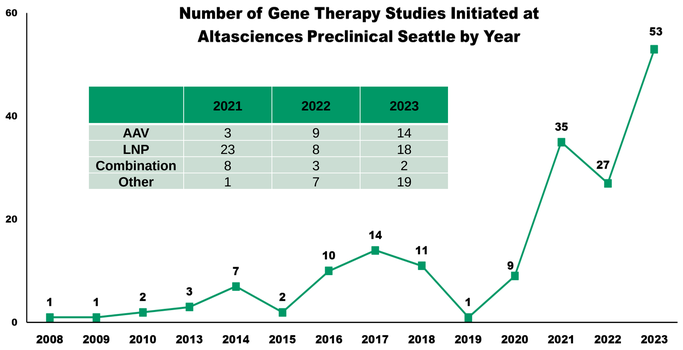
ABSTRACT

The field of gene therapy has made considerable progress over the past several years, specifically regarding Adeno-associated virus (AAV) vectors which have emerged as promising tools for *in-vivo* gene therapy. Prior to clinical trials, safety assessment studies of AAV vector-based therapeutics often utilize nonhuman primates (NHP) as the primary test species, which requires prescreening for naturally occurring neutralizing antibodies (nAb) against AAV prior to dosing. Additionally, pre-treatment with corticosteroids prior to AAV administration is often required to mitigate adverse immune responses. Given the unique challenges of executing successful preclinical AAV studies, we reviewed data from >20 studies conducted in the last 3 years to identify (1) the minimal number of NHPs needed for nAb prescreening; (2) successful corticosteroid premedication regimes; (3) common in-life findings. Only 38% (442/1219) of NHPs screened for nAb against AAV8 had low or negative viral titers indicating suitability for use on study, although nAb against other AAVs serotypes were less common (~80% suitable). Pretreatment with 2 mg/kg of dexamethasone approximately 1-2 hours prior to AAV administration was adequate to mediate adverse immune-related responses. Increases in complement fragment C3a concentrations were most often noted 6 hours post-dose on Day 1, at an average of 4.3-fold over baseline. No AAV-related effects were noted on body weights, and most abnormal clinical observations post-AAV administration were not significantly different than concurrent controls. In conclusion, this data review can serve as a guide to inform future AAV study designs and identify areas for reduction and refinement of animal use.

INTRODUCTION



	2021	2022	2023
AAV	3	9	14
LNP	23	8	18
Combination	8	3	2
Other	1	7	19

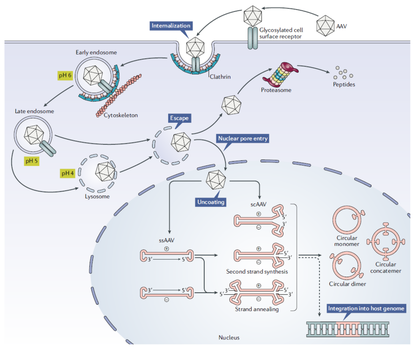


Figure 1. Diagram of rAAV transduction pathway.

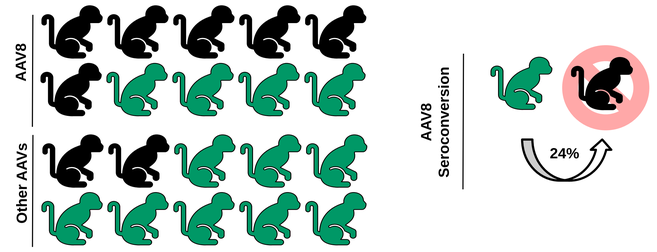
- Adeno-associated virus (AAV) is a non-enveloped virus that can be engineered to deliver DNA to target cells.
- Eleven serotypes of AAV have been identified that differ in the types of cells they infect making AAV a very useful system for preferentially transducing specific cell types.
- AAVs are the leading platform for gene delivery for the treatment of a variety of human diseases and are often utilized for delivery of CRISPR/Cas9 components for genome editing.

Wang, D., Tai, P.W.L. & Gao, G. Adeno-associated virus vector as a platform for gene therapy delivery. Nat Rev Drug Discov ***18****, 358–378 (2019). https://doi.org/10.1038/s41573-019-0012-9*

Neutralizing Antibodies (nAb) Prescreening and Seroconversion Rate:

Approximately 36% (442/1219) of Cambodian NHPs screened for nAb against AAV8 were suitable for study assignment based on established criteria for negative or low viral titers by AAV neutralizing antibody assay (≤ 5 nAb50 in HEK293 cells).

Animals were less likely to have nAb against other AAVs. Approximately 81% (123/152) of animals screened for AAV1 were suitable for use on study, 77% (23/30) for AAV2, 73% (22/30) for AAV3, 100% (30/30) for AAV5 and AAV6, 67% (20/30) for AAV7, 68% (81/120) for AAV9, and 80% (24/30) for AAV10.



For AAV8, rescreening of animals 5 to 7 months following initial viral titer assessment revealed 24% (32/135) were positive (≥10 nAb50 in HEK293 cells) for nAb when they previously had low to negative viral titers.

Predose Corticosteroid Administration Prior to Dosing:

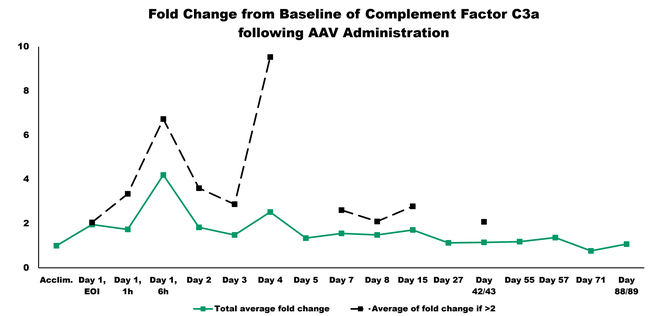
Pretreatment with 2 mg/kg of dexamethasone IV at approximately 1-2 hours prior to AAV administration was adequate to mediate immune-related responses. Of the studies reviewed, 42% (13/31) utilized pretreatment.

AAV Dose Administration:

Common AAV study designs include the administration of AAVs alone or in combination with other Test Materials at viral concentrations of 1.5 x 10^{11} to 6 x 10^{13} vg/mL. Dose administration typically occurs via IV bolus injection or IV infusion at durations of up to 1 hour.

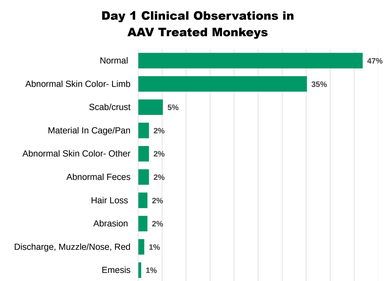
Activation of Complement factor C3a:

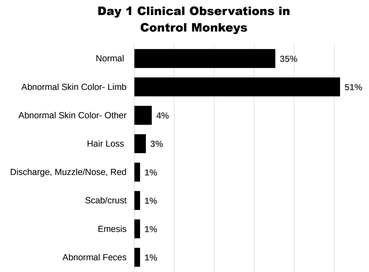
Increases in average complement factor C3a concentrations were most often noted 6 hours postdose on Day 1 at an average of 4.3-fold over baseline (9 AAV studies; 5 with pretreatment with 2 mg/kg dexamethasone and 4 without pretreatment). Further assessment of average C3a concentrations only in groups with an activated complement cascade (C3a concentrations greater than 2-fold) highlights the magnitude of changes seen.



Common Clinical Observations in Animals Administered AAVs on Day 1:

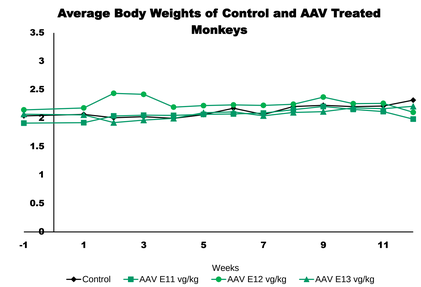
The most common clinical observations on Day 1 in animals administered AAVs were similar to those observed in control animals and typical of animals housed in similar laboratory conditions. Observations included bruising/abnormal skin color, abnormal feces, hair loss, abrasion, and scab/crust. Compared to controls (1 observation), increased incidence of emesis or evidence of material in the cage/pan (11 observations) in animals administered AAV without pretreatment with corticosteroids may be indicative of immune activation.





Body Weight Changes in AAV vs. Control Animals:

Body weight changes assessed over 12 weeks post-AAV administration were comparable to concurrent control animals in both males and females.



CONCLUSION

The number of safety assessment studies run at Altasciences utilizing adeno-associated viral (AAV) vectors for gene therapy application has increased significantly in the last few years. Prior to the initiation of a program utilizing AAVs, it is important to understand the necessity and constraints of screening animals for neutralizing antibodies (nAb) against the specific AAV serotypes. Once animals are selected, the AAV is typically administered by IV bolus injection or infusion depending on the viral concentration and dose volume constraints. Premedication with corticosteroid may help to mediate immune-related responses to AAV administration. Clinical observations on Day 1 in AAV animals are similar to control animals and typical of animals housed under laboratory conditions. Observations indicative of emesis may be related to AAV administration in animals which were not pretreated with corticosteroid but are typically limited to Day 1. If the complement cascade is activated by AAV administration, increased concentrations of C3a are most often observed at 6 hours postdose on Day 1. Over the course of the study significant body weight changes are not observed following AAV administration.