# Hemophagocytic Lymphohistiocytosis (HLH)/ Hyperinflammatory Syndrome Following High Dose AAV9 Therapy

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# Disclosures

Travel honoraria with Neurogene

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# Hemophagocytic Lymphohistiocytosis (HLH)

- **HLH is a rare, life-threatening hyperinflammatory syndrome** characterized by immune dysregulation, cytokine storm, and multi-organ damage[1-3]
  - Most cases are triggered by infections, malignancy, autoimmune disease, or CAR-T (3.5% incidence)
- **Over 90% of patients present with the initial "three Fs" seen in the HLH-2004 study: Fever, elevated Ferritin, and Falling blood counts (cytopenia)[4]**

**Monitoring for HLH is not part of standard monitoring in AAV therapy trials and we believe should be implemented**

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[1]Soy et al. Rheumatol Int. 2021;41(1):7-18. [2]Mérad et al., 2019; [3]Jordan et al. Blood. 2011;118(15):4041-52; [4]Henter J et al 2007 Feb; 48(2):124-31

# HLH has been Rarely Reported Following High-dose AAV Gene Therapy

- Only one published case report[1] and mention of similar cases[2] reported HLH-like symptoms with high-dose systemic AAV treatment (1E14 vg/kg or higher)
- Symptoms: **Elevated ferritin within the first few days, fever**, **pancytopenia,** rash, hepatosplenomegaly[1]
- Cases treated successfully with early administration of either **high dose steroids or anakinra (IL-1 receptor antagonist)**
- **No HLH events have been reported at AAV doses below 1E14 vg/kg**

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[1]Galletta et al. J Clin Pharm Ther. 2022:47(9):1478-1481.; [2]Byrne et al Mol Ther. 2022;30(12):3503-3504.

# Case Presentation: HLH/Hyperinflammatory Syndrome in AAV Study

- Participant in RTT-200 trial: Participant with classic Rett syndrome; received **3E15 total vg (1.5E14 vg/kg)**[1] of NGN-401
- Prophylactic immunomodulation: Steroids/sirolimus/rituximab
- Two other participants had been treated with the 3E15 vg dose and did not have any hyperinflammatory reactions; 1E15 vg NGN-401 dose believed to be generally well-tolerated with no cases of hyperinflammation
- Participant developed fever prior to discharge

**Day after discharge:** Developed fever, lethargy, vomiting, somnolence, cough, and poor oral intake → returned to hospital

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[1]Rosenberg et al. Hum Gene Ther. 2023 Nov 15;34(21-22):1095–1106.

# HLH Suspected and Maximal Care Provided

**At re-admission:** Diagnosed with dehydration; started on IV fluids and oxygen

**Treatment:** Antibiotics, high-dose hydrocortisone

**Labs:** Thrombocytopenia, elevated liver enzymes and LDH, coagulopathy

**Rapid clinical decline with respiratory failure, acute kidney injury, hypotension; intubated, admitted to ICU and placed on CVVH and inotropic support**

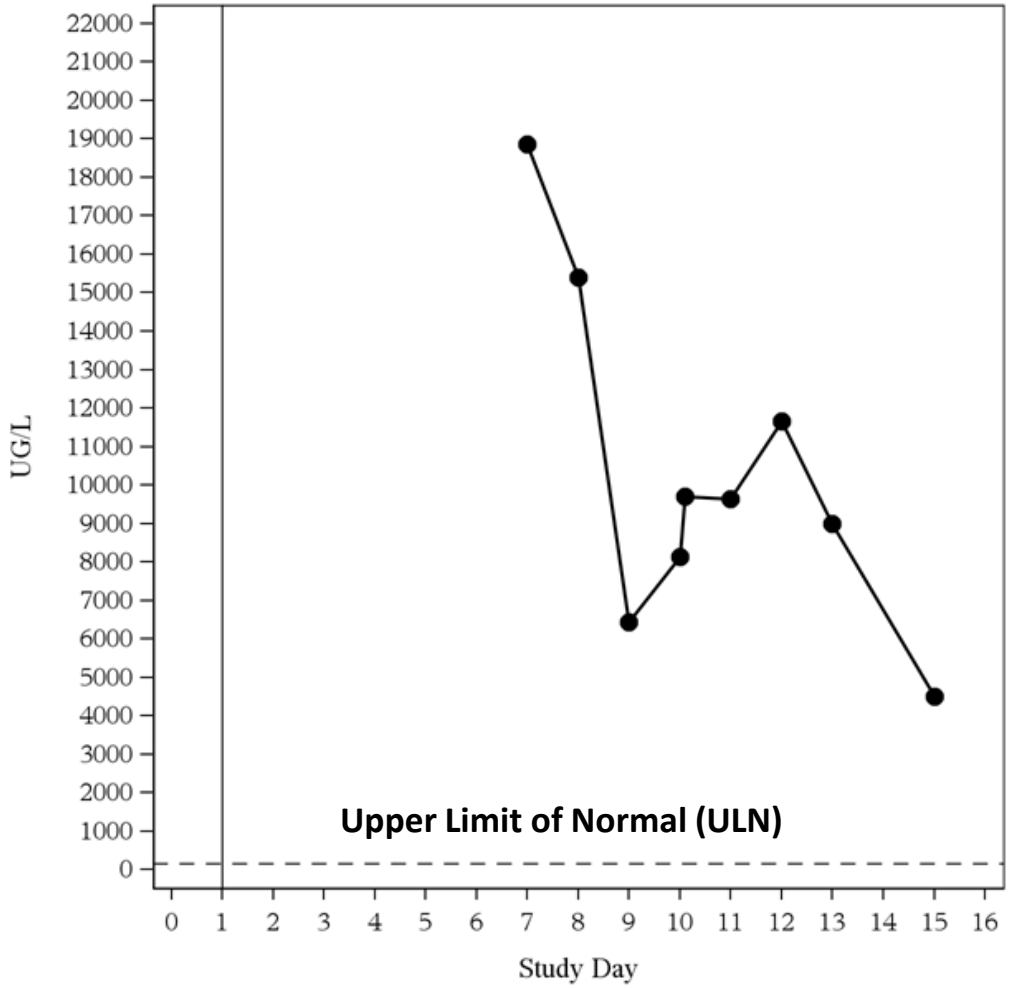
- Markedly elevated ferritin with labs and symptoms consistent with HLH/hyperinflammatory syndrome
- TMA considered unlikely (negative blood smear)

**Treatment:**

- Dexamethasone
- Anakinra
- Single dose of eculizumab given despite negative blood smear

Multi-system failure was too far advanced and despite maximal supportive care, the participant's clinical status declined and the participant passed away approximately two weeks post-dosing

**Ferritin level 18,850 ug/L (normal <150 ug/L)**




CVVH = Continuous Veno-Venous Hemofiltration
LDH = Lactate Dehydrogenase

# FAERS Database Shows HLH/HLH-Like Symptoms Following High-Dose Systemic AAV (>1E14 vg/kg)

**While HLH is extremely rare, emerging post-marketing data suggests that HLH-like immune responses may occur in a small subset of patients treated with high-dose systemic AAV gene therapy[1]**

- **HLH-Related Findings (N=15):**
  - **1 confirmed case of HLH**; **11 hyperferritinemia**, **3 elevated blood iron**
  - Common reported symptoms: fever (80%), ↑ALT and/or AST (100%), thrombocytopenia (60%)
- **Incidence Estimates**:
  - **HLH-like:** 1.3% of SAEs, ~0.3% of total exposures
  - For comparison: **TMA:** 3.1% of SAEs, ~0.8% of exposures
- **HLH-like cases are separate from TMA:** No overlap in ferritin elevation or diagnosis between the two

**Data indicate standard monitoring for HLH after dosing with AAV should be implemented, similar to standard monitoring for TMA**

[1]Analysis based on 4,500 cases of Zolgensma treatment
Data cut-off date: December 31, 2024
FAERS = FDA Adverse Event Reporting System

# HLH Risk Mitigation Strategy Should be Implemented for AAV Gene Therapy

- **Dose level above 1E14 vg/kg not allowed**
- **In the first week post dosing: employ daily monitoring of ferritin, fever, and falling blood counts (cytopenia)**
- Exclude subjects with:
  - Any illness within 30 days of dosing, including EBV and CMV
  - COVID within 6 weeks of screening
- Prior to dosing, require sites to have anakinra available and encourage availability of a local HLH expert prior to dosing
- **Include HLH treatment algorithm within protocol**
  - **1st line of defense high-dose corticosteroids, 2nd line: anakinra**

Risk Mitigation Now Included in RTT-200 Clinical Trial

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EBV = Epstein–Barr virus; CMV = Cytomegalovirus

# Key Conclusions: HLH can be Reversed if Recognized Early

- HLH is rarely described but has occurred in the setting of high-dose AAV therapy
- Key early signs and symptoms include **fever, elevated ferritin, and falling blood counts (cytopenias)**
  - Fever within the first few days post-dosing warrants further diagnostic workup
  - While elevated ferritin can serve as an early warning indicator, it must be interpreted within the broader clinical context - ferritin elevation alone is not diagnostic of HLH
- Delayed recognition of HLH can lead to rapid clinical decline and may be life-threatening
- Early monitoring and prompt treatment, typically with high-dose corticosteroids and/or anakinra, have proven effective in reversing the course of HLH in the setting of AAV gene therapy

**Frequent <u>monitoring</u> in the first week post dosing is key to recognizing signs and symptoms**
**<u>Treat</u> with high-dose corticosteroids, and keep anakinra on standby**

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# Thank You, and Acknowledgments


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- HLH and gene therapy experts who consulted on this case


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