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Preliminary Analysis of Safety, Tolerability, and Efficacy of a Prophylactic Sirolimus Protocol for Patients Receiving Delandistrogene Moxeparvovec-Rokl Gene Therapy

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Background

- Delandistrogene Moxeparvovec-Rokl (DMR) is the only FDA-approved gene therapy for patients with Duchenne muscular dystrophy (DMD).
- Acute liver injury (ALI) has been reported in up to 40% of patients receiving DMR.
- Two patients have died due to acute liver failure (ALF) from DMR, and death from ALF is a known complication after gene therapy.
- After these deaths, our center began prophylaxis with sirolimus to help prevent ALI.

OBJECTIVE:

The objective of this abstract is to report the initial safety, tolerability, and efficacy of sirolimus prophylaxis.

Methods

Twenty DMD subjects have received DMR at our institution. The first 14 underwent DMR with a standard protocol including corticosteroid intensification based on the FDA package insert but no additional immunosuppression. The remaining 6 subjects underwent a modified immunosuppression protocol with sirolimus (with the first 2 patients starting at 1 and 2 weeks after DMR infusion). The modified protocol is listed below:

- Begin sirolimus 1 week prior to infusion with dose of 1mg for patients <40kg and 2mg for patients ≥40kg. Give 0.5mg tablets for dose flexibility. Give steroids based on standard protocol.
- Obtain first sirolimus trough on day of infusion; goal sirolimus 4-6.
  - If sirolimus levels within goal, check at
    - Week 1
    - Week 2
    - Week 4
    - Then monthly
  - If not in goal, determine timing of next level based on adjustments
- Start Bactrim 1 single strength tablet daily (80mg TMP) for patients ≥16kg (5-10mg/kg/day of TMP daily for patients <16kg)
- Check TG and cholesterol levels at baseline and with sirolimus levels
  - If TG>250, start omega-3 capsules 1g daily
- If evidence of rising LFTs/GGT, treat each patient on an individual basis. General approach as below
  - Double dose of oral steroids
  - Consider early admission to hospital for pulse steroids
  - Administer IVIG
  - Increase sirolimus dose to target higher levels
- Wean steroids back to baseline starting at 60 days post-infusion if liver function tests (LFTs) in normal range
  - Stop sirolimus after 12 weeks if no evidence of elevated LFTs and *back to baseline steroid dose*
  - Stop bactrim when sirolimus is discontinued

The clinical course of patients receiving sirolimus prophylaxis was retrospectively evaluated and compared to those who did not receive sirolimus. Laboratory testing, particularly gamma glutamyl transferase (GGT), other LFTs, and sirolimus testing was collected.

A Fisher's exact test was used to assess for a difference between groups.

Please email jonathan.h.soslow@vumc.org with any further questions.

Results

Table 1: Demographics

	All DMR Median (IQR)	Standard Immunosuppression Median (IQR)	Sirolimus Prophylaxis Median (IQR)
Age (years)	7.5 (5, 12); range 4-21	5.5 (5, 12); range 4-21	10.5 (8, 12); range 6-15
Height (cm)	124 (110.5, 142.5)	115.5 (110, 146)	135 (132, 141)
Weight (kg)	29.0 (20.4, 52.1)	22.9 (20.4, 39.8)	45.9 (30.5, 56.5)
Ambulatory	16 (80%)	11 (%)	5 (83%)
Race			
Caucasian	17 (85%)	12 (86%)	5 (83%)
African American	1 (5%)	1 (7%)	0
Unwilling to provide	2 (10%)	1 (7%)	1 (17%)
Ethnicity			
Hispanic	2 (10%)	1 (8%)	1 (17%)
Unwilling to provide	2 (10%)	1 (8%)	1 (17%)

- Sirolimus levels were maintained within range in most patients without significant dose changes.
- All patients had elevated triglycerides and were started on Omega-3. No other side-effects were documented.

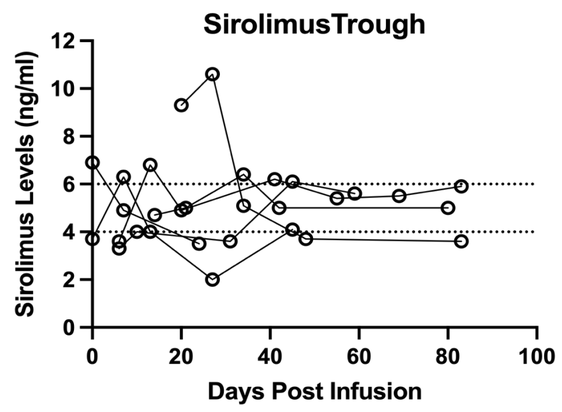

Figure 1: Sirolimus troughs over time

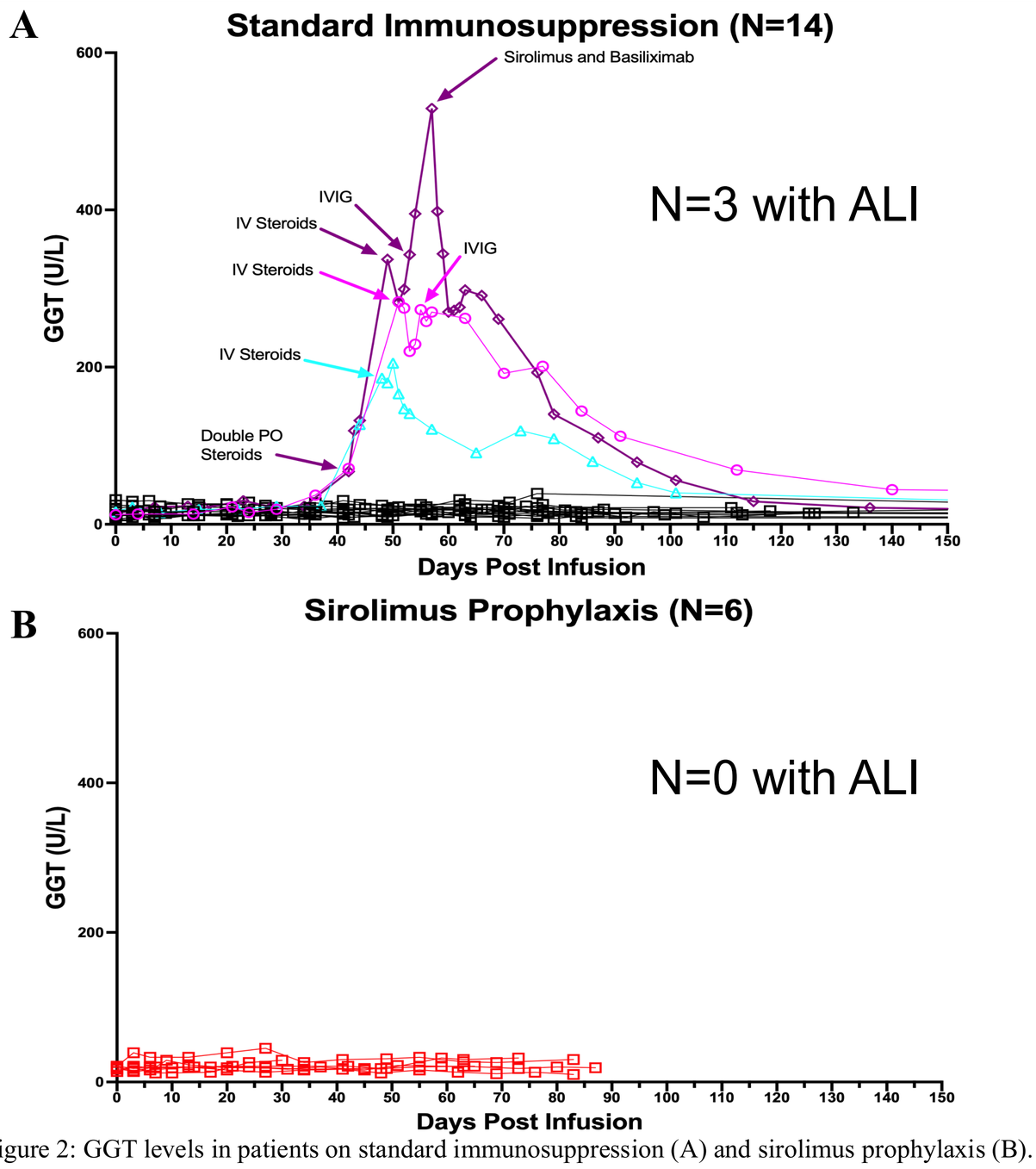

Figure 2: GGT levels in patients on standard immunosuppression (A) and sirolimus prophylaxis (B).

- No significant difference in rates of ALI between groups (p=0.53).

Conclusions

- Low-dose sirolimus prophylaxis appears to be safe and well-tolerated in DMD patients receiving DMR.
- While none of the 6 patients infused have had ALI, assessment of efficacy requires a larger sample size.

Disclosures: JHS and WBB have consulted with Sarepta. Sarepta played no role in the data collection or analysis of this abstract