Significant Unmet Need in Infants with Mucopolysaccharidosis VII and Non-Immune Hydrops Fetalis: A Summary of Cases

Deborah Marsden, MBBS,1 Camille L. Bedrosian, MD,1 Tobin Chettiath, PharmD,2 J. Lawrence Merritt II, MD,1 Kirin Jamison, BS1

1Ultragenyx Pharmaceutical Inc., Novato, CA; 2Formerly Ultragenyx Pharmaceutical Inc., Novato, CA

BACKGROUND

Mucopolysaccharidosis VII (MPS VII): a Heterogeneous, Progressive, Neurometabolic Disorder
- MPS VII is an ultra-rare, autosomal recessive lysosomal storage disorder caused by inherited deficiency of β-glucuronidase1,2
- β-glucuronidase deficiency results in accumulation of glycosaminoglycans in lysosomes of many tissues, causing1,3
  - Multi-organ dysfunction
  - Cognitive impairment
  - Reduced life expectancy
- The first case of MPS VII was described in 1973 by Dr. William Sly4

Non-Immune Hydrops Fetalis (NIHF): A Life-Threatening Manifestation of MPS VII
- NIHF is a potentially life-threatening manifestation of MPS VII
  - Reported incidence in MPS VII: 41%1
  - Reported one-year survival rate in MPS VII: 58.7%5

METHODS

Real-World Analysis of NIHF Infant Cases
- Requests were received worldwide for vestronidase alfa as enzyme replacement therapy, including for fetuses diagnosed in utero or infants diagnosed <1 year of age
- Ultragenyx is committed to providing treatment for all patients (compassionate use, clinical trial, or commercially available drug)

ADA = anti-drug antibody; uGAG = urinary glycosaminoglycan.
### RESULTS

**Characteristics of MPS VII Patient Population to Be Treated with Vestronidase Alfa Upon Request**

- **Region**
  - United States: 13
  - Europe: 14
  - Latin America: 9
  - India: 1

- **Sex**
  - Female: 7
  - Male: 13
  - Not recorded: 17

- **NIHF Status**
  - Confirmed: 25
  - Unknown: 1
  - Untreated: 8

- **Treatment With Vestronidase Alfa**
  - Treated: 12 (76%)
  - Untreated: 4 (24%)

- **Mortality Was High for This Population of Patients with MPS VII and Severe NIHF**
  - Died during treatment: 15 (60%)
    - Untreated: 7 (37%)
  - Died before treatment: 3 (15%)
  - 1-Year Mortality by NIHF Status
    - Confirmed: 52% (9/18)
    - Unknown: 75% (3/4)

- **1-Year Survival**
  - Confirmed: 60% (12/20)
  - Untreated: 37.5% (7/19)

- **Potency for Improved Morbidities and Mortality**
  - Increased dose or frequency of vestronidase alfa®
  - In utero enzyme replacement therapy for prenatally diagnosed lysosomal storage disorders (Dr. Tippi MacKenzie, UCSF Fetal Treatment Center, NCT04532047)

- **Further research is needed**

**GUS Variant Prevalence and Location**

- **GUS Variant Locations**
  - Glycosyl hydrolysase family 2, sugar binding domain (Glyco_hydro_2_N)
  - Glycosyl hydrolysase family 2, TIM barrel domain (Glyco_hydro_2_C)

- **Variants and Classifications**
  - p.L176F: c.526G>T, Homo, 6 Pathogenic
  - p.P403S: c.1209C>T, Homo, 4 Pathogenic
  - p.H351Y: c.1053C>T, Hetero, 2 Pathogenic
  - p.R374C: c.1120C>T, Hetero, 2 Pathogenic
  - p.P415L: c.1244C>T, Homo, 2 Pathogenic
  - p.M430T: c.1289T>C, Hetero, 2 Pathogenic

- Among 17 patients with available data, 21 unique GUS variants were identified, most commonly occurring in the TIM barrel and sugar binding domains.
- Most variants were found to be pathogenic.
CONCLUSIONS

• There is an urgent unmet need in patients with MPS VII who have NIHF

• NIHF appears to be more common than previously reported and is associated with substantial morbidities

• Newborn screening could allow for earlier intervention

• Potential for in utero treatment

• Modeling data suggest higher or more frequent dosing in severely affected infants may reduce impact of morbidities

DISCLOSURES AND ACKNOWLEDGMENTS

• DM, CLB, JLM, and KJ are employees of and shareholders in Ultragenyx Pharmaceutical Inc. TC is a former employee of Ultragenyx Pharmaceutical Inc.

• Medical writing support was provided by Ben Scott (Scott Medical Communications, LLC) and was funded by Ultragenyx Pharmaceutical Inc.

• We wish to acknowledge the following collaborators and site investigators: Sun Lee, Brad Tinkle, Eric Culp, Angela Sun, Maria Descartes, Joy Dean, Catherine Dooch, Trent John, Hima Maramreddy, Tippie MacKenzie, Heather Lau, Jose Franco, Paul Harmatz, Chester B. Whiteley, Milsen S. Bauer, Guy Touati, Manuel Schiff, Benedicte Heron, Francois Feillet, Fiona Stewart, Ardeshir Monavari, Mar O’Callaghan, Maria Angeles Ruiz-Gomez, Simon Jones, Antonio Gonzalez-Meneses, Mahmul Coker, Hatice Serap Sivri, Faith Kardas, Fatih Ezgu, Esther Maier, Luz Roberto Silva, Diego Miguel, Helena Pimentel, Luz Maria Sanchez, Jaime Lopez, Jose Enrique Sanin, Gabriela Pacheco, Ana Posso, I.C. Verma

REFERENCES