Dystrophinopathy Gene Therapy

Diagnostic Harmonization

**BACKGROUND:** Gene therapy trials to date have largely focused cardiac evaluation on safety endpoints, although we eventually hope to understand the potential impact of these therapies on cardiac disease. Safety data are also limited by patient number, variable gene delivery methods, transgene, post-gene delivery medical therapy, and duration of follow-up. Given these limitations, this document will attempt to harmonize clinical monitoring based on expert recommendation.

A team-based approach to gene therapy delivery is necessary, including providers from multiple disciplines seeking to treat patients as well as mitigate and appropriately monitor side effects. These include representatives from Gene Therapy prescribers (currently, largely Neurology), Pharmacy, Cardiology, Hematology, Gastroenterology, and discussion with other services that may be involved on a case-by-case basis. **We strongly expect these recommendations to evolve as further data becomes available.** **The below approach is a general recommendation, that we hope will serve as a basis for discussion and generation of institution specific guidelines.**

**ACTION REVISED DATE:** 10.5.23

**OBJECTIVES:** To harmonize clinical practice of diagnostic cardiac evaluation in DMD patients who have received gene therapy based on expert consensus.

**BACKGROUND & POTENTIAL IMPACT OF GENE THERAPY**

Troponin leak and clinical myocarditis have been documented in multiple gene therapy trials to date. The severity of injury has been highly variable, up to and including mortality that has been attributed to cardiac dysfunction. The short- and long-term risk of clinical dysfunction and arrhythmia remains unclear. As long-term cardiac dysfunction and arrhythmia have been shown in other myocardial inflammation syndromes (e.g. viral myocarditis, immune checkpoint inhibitor myocarditis/pericarditis, etc) similar sequelae with DMD gene therapy is possible.

Myocarditis after gene therapy may occur due to multiple reasons:

1. Immediate viral vector associated myocarditis
2. Humoral/cellular response to vector leading to generalized inflammation with cardiac involvement
3. Humoral response to protein product expressed in cardiac tissue

The immunologic responses that may lead to myocarditis can be seen both immediately post-administration, as well as in the weeks and months post-administration depending on the cause.

While there are many unknowns, cases of mortality after gene therapy are known in the dystrophinopathy community. Furthermore, further data is needed to understand the risks of myocarditis across the phenotype, genotype, and product spectrum. Our understanding is likely to evolve over time as we move toward additional patients receiving the first approved products. Towards the goal of maximizing safety, we strongly advocate for the following guiding principles:

* A **team-based approach** is strongly recommended, with prespecified involvement from Gene Therapy prescribers (often, but not exclusively Neurology), and additional major stakeholders including at least Pharmacy, Cardiology, Hematology, Gastroenterology/Hepatology, and team members well-versed in immunomodulation (some sites use Immunology, Rheumatology, or others). Other teams have included Pulmonology, Nephrology and Infectious Disease. At a bare minimum, we encourage identifying the Cardiology team members to review labs and clinical questions.
* Our guidance for cardiac assessments is based on the initial, limited data. We encourage working with other team members to minimize extra blood draws over time. We anticipate multiple versions of this guidance as data evolves. Overtime minimizing the burden of care including diagnostic evaluation of all types will be an important step.
* **Informed consent detailing the possible cardiac complications is necessary.**

**ASSESSMENTS**

Troponin

Historically, troponin-I leak can be a sensitive and specific finding in myocarditis, when judged against the gold standard of endomyocardial biopsy.13 However, use of troponin-I to imply clinical course of myocarditis remains difficult.14 The association of elevated troponin in many patients with dystrophinopathies, as well as spontaneous episodes of elevation in troponin levels without infectious cause, makes the diagnosis of gene-therapy associated myocarditis more challenging.8 Of note, there is no current recommendation for use of standard troponin-I vs high-sensitivity assays, but the same platform should be used for comparison. **Troponin assessment prior to gene therapy, and serially at pre-specified timepoints, is prudent for detection of myocarditis.**

Other Biomarkers

Other biomarkers, such as markers of inflammation, white cell counts, platelet counts, BNP are not typically part of the myocarditis diagnosis, have not been predictive of outcomes of classical myocarditis, and there is not yet enough publicly available data regarding gene therapy-associated myocarditis to fully assess their importance or timeline of change. **Thus other biomarkers would be exploratory, and are not advocated for or against at this time, but may help understand the totality of the myocarditis risk.**

Arrhythmia

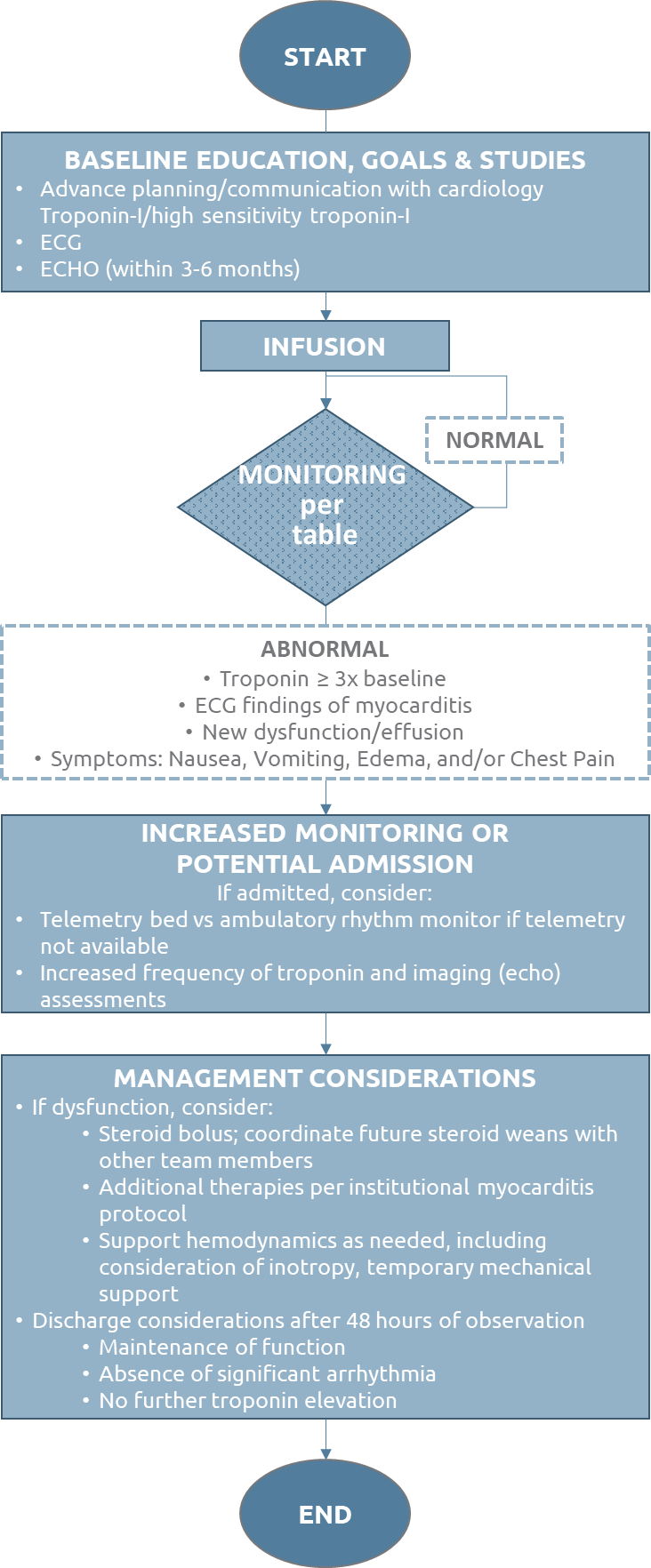
Atrial and ventricular ectopy have been described in DMD, including in patients across the spectrum of cardiomyopathy (including prior to onset of systolic dysfunction). The frequency and severity of each generally correlates with the severity of cardiomyopathy, although individual cases of symptomatic arrhythmia including sudden cardiac death have been reported early in the disease process.1-3 The substrate is generally thought to be areas of myocardial inflammation due to cell injury or fibrofatty replacement of the myocardium.

**ECG findings can be non-specific in myocarditis, but classical changes in assessment of myocarditis should still be present, and should be considered as part of myocarditis screening**. Sub-clinical myocarditis could also be missed early on, and secondarily, arrhythmia burden may be further increased. **This could be detected on later ambulatory rhythm monitor which should be undertaken within the first 6 months post-gene therapy.**

Imaging

Cardiac magnetic resonance (CMR) is the gold standard for assessment of ventricular function and has become a critical tool in the diagnosis of acute myocarditis. CMR studies suggest that the progression of DMD systolic dysfunction typically begins after the development of late gadolinium enhancement (LGE).5 DMD patients have a classic pattern of LGE that begins in the subepicardium of the free wall at the base/mid-LV;6, 7 of note, this pattern is identical to that seen in patients with acute myocarditis. In addition, data suggest that there can be patches of elevated T2 times in “healthy” DMD patients (i.e. asymptomatic patients at routine clinic visits), supporting the hypothesis that inflammation is part of the pathway of cardiomyopathy progression. Further complicating the picture, there have been multiple descriptions of dystrophinitis, a myocarditis-like picture that can develop in DMD patients and leads to classic findings of myocarditis including elevated troponin and CMR findings supportive of myocarditis based on the modified Lake-Louise Criteria.8-10 While CMR is also the gold standard imaging method for the diagnosis of myocarditis and is currently an integral part of diagnostic criteria published by the CDC,12  it may also be overly sensitive for the diagnosis of myocarditis.13 There are also not insignificant risk for younger children requiring sedation for a diagnostic study, typically required in those less than 8 years of age at many institutions. **Based on these considerations and the current younger age group of 4-to 6-year-olds FDA approved to receive DMD Gene Therapy (Elevidys), we do not recommend CMRI for baseline or post-infusion screening at this time.**

As echocardiography has the advantage of availability, lower cost, and shorter duration without need for sedation,  **we do recommend that echocardiography be undertaken at baseline and at pre-specified timepoints.** Although DMD echocardiographic images are suboptimal compared with CMR, echocardiography is generally adequate for assessment of clinical changes, and images are generally better at the younger ages.11 **Echocardiographic assessment would include function, effusion, and valvar regurgitation.**

**PROTOCOL**

Baseline Communication and Studies

We encourage pre-gene therapy discussions with families as related to goals of care, including willingness to receive inotropic medications and temporary mechanical circulatory support in case of serious hemodynamic complications. Gene Therapy providers (or primary neurologists) are likely most appropriate to have this conversation with patients/families, although with some aid from Cardiologists as needed. Similarly, we encourage communication by Cardiology team members with Cardiac ICU / Surgery teams of the (low) potential of these patients to require advanced cardiac therapies and to assess emergent care strategies preemptively.

We recommend **baseline troponin, ECG and echocardiogram within 3-6 months prior to gene therapy** infusion. At this age, these studies are likely to be normal, although troponin elevation in an asymptomatic DMD patient may be found, and thus serve as a baseline.

Post Gene Therapy Minimum Assessments

* Clinical assessment of any patient with nausea, vomiting, chest pain, palpitations, abdominal pain, severe fatigue, rapid breathing should always be obtained in person by gene therapy team with cardiology consultation as needed for clinical concerns. (GI symptoms are common post gene therapy infusion)
* Assessment of **troponin** **at** **3 days** **post-infusion** is recommended to capture early virally-mediated cardiac inflammation
* At **one week** post-infusion, an assessment of **troponin, ECG and echocardiogram** is recommended.
* **Further troponin checks are to be undertaken at 2 weeks and 3 weeks post infusion.**
* If all normal studies, next assessment would be at **1 month** post-infusion with repeat troponin, ECG and echocardiogram.
* If all normal studies, next assessment would be at **3 months** post-infusion with repeat troponin, ECG, echocardiogram, and an ambulatory rhythm monitor

Abnormal findings

* An increased **troponin value of > 3 times that of the baseline warrants further investigation, at a minimum a follow-up troponin and ECG within the following day**, and may include imaging, physical exam, and cardiology consultation.
* **Troponin elevation > 3 times baseline paired with significant clinical symptoms or ECG changes, warrants an echocardiogram and hospital admission**
* **Any decrement in function on echocardiogram warrants an admission**
* **Troponin elevation > 10x baseline warrants admission for observation**
* **In patients with abnormalities to minimum screening studies not meeting above thresholds, it is reasonable to consider more frequent assessments**, including ECG or echo alongside the troponin at 2 weeks and 3 weeks post-infusion, or an extra troponin, ECG, and/or echo at 2 months post-infusion, or other interval at the discretion of the treating Cardiologists.

**ADMISSION WITH CLINICAL CONCERN FOR MYOCARDITIS**

Acute myocarditis of any etiology has a highly variable course without standardized clinical care protocols across institutions. We recommend continuing your institutional practices with some other considerations:

* If patients are admitted for monitoring, telemetry to assess for arrhythmias and frequent repeat troponins is appropriate. **If patient troponins do not increase, function remains normal, and no arrhythmias are seen after 48 hours of close observation, it may be reasonable to discharge without further therapies.**
* **Increased steroids to help attenuate the inflammatory response are often part of the treatment of gene therapy associated liver injury and may be helpful for gene therapy associated myocarditis.** Steroid bolus and tapers should be prescribed in collaboration with Neuromuscular/Gastroenterology/Hepatology colleagues in whom there may be other considerations.
* Later onset of myocarditis may indicate a humoral response, and discussion with Immunology/Rheumatology colleagues may be helpful.
* Preventing acute decompensation and supporting hemodynamics is always the goal which may require inotropes and temporary mechanical support. **Anticipatory discussions with patient, family, and critical care providers are important for best outcomes.**

**AUTHORS**

Deipanjan Nandi, MD, Chet Villa, MD, Jonathan Soslow, MD, Beth Kaufman, MD, Aravindhan Veerapandiyan, MD, Carol Wittlieb-Weber, MD, Paul Esteso, MD, Jennifer Conway, MD, Aaron Olson, MD, Kan Hor, MD, Hugo Martinez, MD

**CONTRIBUTING CENTERS**

Nationwide Children’s Hospital, Cincinnati Children’s Hospital Medical Center, Monroe Carell Jr. Children’s Hospital at Vanderbilt, Lucile Packard Children’s Hospital, Arkansas Children's Hospital, Children’s Hospital of Philadelphia, Boston Children's Hospital, Stollery Children’s Hospital, Seattle Children's Hospital, & Le Bonheur Children's Hospital

***Disclaimer:*** *The ACTION network is focused on quality improvement efforts such as harmonizing best practice protocols, disseminating them among institutions, and helping centers to improve care practices at the local level. This protocol was developed as a consensus tool for pediatric VAD programs. The information in the protocols are based on center practices, individual opinions, experiences, and, where available, published literature. Centers may choose to adapt this protocol to include in their center-specific protocols with reference to ACTION with the understanding that these are meant as guidelines and not standard of care. (Revised 10/3/2023)*

**REFERENCES**

* 1. Chiang DY, Allen HD, Kim JJ, Valdes SO, Wang Y, Pignatelli RH, Lotze TE and Miyake CY. Relation of Cardiac Dysfunction to Rhythm Abnormalities in Patients With Duchenne or Becker Muscular Dystrophies. *Am J Cardiol*. 2016;117:1349-54.

1. Villa CR, Czosek RJ, Ahmed H, Khoury PR, Anderson JB, Knilans TK, Jefferies JL, Wong B and Spar DS. Ambulatory Monitoring and Arrhythmic Outcomes in Pediatric and Adolescent Patients With Duchenne Muscular Dystrophy. *J Am Heart Assoc*. 2015;5.
2. Menon SC, Etheridge SP, Liesemer KN, Williams RV, Bardsley T, Heywood MC and Puchalski MD. Predictive value of myocardial delayed enhancement in Duchenne muscular dystrophy. *Pediatric cardiology*. 2014;35:1279-85.
3. Gupta N, Yang J, Reynolds K, Lenane J, Garcia E, Sung SH, Harrison TN, Solomon MD and Go AS. Diagnostic Yield, Outcomes, and Resource Utilization With Different Ambulatory Electrocardiographic Monitoring Strategies. *Am J Cardiol*. 2022;166:38-44.
4. Tandon A, Villa CR, Hor KN, Jefferies JL, Gao Z, Towbin JA, Wong BL, Mazur W, Fleck RJ, Sticka JJ, Benson DW and Taylor MD. Myocardial fibrosis burden predicts left ventricular ejection fraction and is associated with age and steroid treatment duration in duchenne muscular dystrophy. *J Am Heart Assoc*. 2015;4.
5. Silva MC, Meira ZM, Gurgel Giannetti J, da Silva MM, Campos AF, Barbosa Mde M, Starling Filho GM, Ferreira Rde A, Zatz M and Rochitte CE. Myocardial delayed enhancement by magnetic resonance imaging in patients with muscular dystrophy. *J Am Coll Cardiol*. 2007;49:1874-9.
6. Puchalski MD, Williams RV, Askovich B, Sower CT, Hor KH, Su JT, Pack N, Dibella E and Gottliebson WM. Late gadolinium enhancement: precursor to cardiomyopathy in Duchenne muscular dystrophy? *Int J Cardiovasc Imaging*. 2009;25:57-63.
7. Hor KN, Johnston P, Kinnett K, Mah ML, Stiver C, Markham L and Cripe L. Progression of Duchenne Cardiomyopathy Presenting with Chest Pain and Troponin Elevation. *J Neuromuscul Dis*. 2017;4:307-314.
8. Abutaleb ARA, McNally EM, Khan SS, Anderson AS, Carr JC and Wilcox JE. Myocarditis in Duchenne Muscular Dystrophy After Changing Steroids. *JAMA Cardiol*. 2018;3:1006-1010.
9. Ferreira VM, Schulz-Menger J, Holmvang G, Kramer CM, Carbone I, Sechtem U, Kindermann I, Gutberlet M, Cooper LT, Liu P and Friedrich MG. Cardiovascular Magnetic Resonance in Nonischemic Myocardial Inflammation: Expert Recommendations. *J Am Coll Cardiol*. 2018;72:3158-3176.
10. Soslow JH, Xu M, Slaughter JC, Stanley M, Crum K, Markham LW and Parra DA. Evaluation of Echocardiographic Measures of Left Ventricular Function in Patients with Duchenne Muscular Dystrophy: Assessment of Reproducibility and Comparison to Cardiac Magnetic Resonance Imaging. *J Am Soc Echocardiogr*. 2016.
11. Gargano JW, Wallace M, Hadler SC, Langley G, Su JR, Oster ME, Broder KR, Gee J, Weintraub E, Shimabukuro T, Scobie HM, Moulia D, Markowitz LE, Wharton M, McNally VV, Romero JR, Talbot HK, Lee GM, Daley MF and Oliver SE. Use of mRNA COVID-19 Vaccine After Reports of Myocarditis Among Vaccine Recipients: Update from the Advisory Committee on Immunization Practices - United States, June 2021. *MMWR Morb Mortal Wkly Rep*. 2021;70:977-982.
12. Smith SC, Ladenson JH, Mason JW, et al. Elevations of cardiac troponin I associated with myocarditis. Experimental and clinical correlates. Circulation 1997;95:163-8.
13. Butto, Arene, Joseph W. Rossano, Deipanjan Nandi, Chitra Ravishankar, Kimberly Y. Lin, Matthew J. O’Connor, Robert E. Shaddy, and Pirouz Shamszad. “Elevated Troponin in the First 72 h of Hospitalization for Pediatric Viral Myocarditis Is Associated with ECMO: An Analysis of the PHIS+ Database.” Pediatric Cardiology 39, no. 6 (August 2018): 1139–43. https://doi.org/10.1007/s00246-018-1871-2.