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Glucocorticoid Therapy for Duchenne Cardiomyopathy: A Hobson's Choice?

Subha V. Raman, MD, MSEE; Linda H. Cripe, MD

> Doubt is not a pleasant condition, but certainty is an absurd one.[1]

As if receiving a diagnosis of Duchenne muscular dystrophy (DMD) were not terrible enough, consider the impact when a parent learns of the disease's progressive and inexorable effects on their son's heart.[2] A relentless search for effective therapies against relentless cardiomyopathy ensues. Those with access to well-informed teams at centers dedicated to interdisciplinary DMD care may get timely and sensitive screening for cardiac involvement, with institution of agents such as angiotensin-converting enzyme inhibitors and β-blockers that benefit a broad spectrum of myocardial diseases.[3,4] Those without access to such centers may themselves have to educate less-experienced clinicians on appropriate diagnostic testing and medical therapy, armed with evidence collected from advocacy organizations or their own web-based searches. Crucial to decision-making are published data from high-quality clinical trials, ideally based on mechanistically insightful preclinical investigations, that provide evidence in favor of or against a particular treatment.

In this issue of *JAHA*, Tandon and colleagues describe their analysis of clinically-acquired cardiac magnetic resonance scans in conjunction with steroid use recorded from the medical record in a large, single-center DMD patient cohort.[5] Two major findings are reported. First, they confirm prior results showing that increasing age is a risk factor for worsening left ventricular systolic function. As more damaged myocardium is less likely to function properly, increasing late gadolinium enhancement (LGE) abnormality in parallel with declining left ventricular ejection fraction should not come as a surprise. Their second finding describes an association between steroid use and change over time in number of LGE-positive myocardial segments. When considering the sequelae of chronic corticosteroid therapy, the conclusion that longer steroid treatment duration confers lower age-related increase in myocardial damage warrants closer examination. In particular, what evidence does the scientific literature offer on glucocorticoid therapy for DMD cardiomyopathy?

Randomized controlled trials over the last several decades have established glucocorticoids as *the* therapy to prolong ambulatory function[6]; unfortunately, none included any cardiac end points. Evidence from a number of studies associate prednisone and deflazacort use with better cardiac function and outcomes in boys with DMD.[7–9] However, the designs of these retrospective observational studies incur inherent biases that make interpretation of even a large amount of data potentially erroneous.[10] Data of similar caliber suggesting that one may retard scoliosis[11] and preserve pulmonary function have been used to justify continued prescription of high-dose glucocorticoids even after loss of ambulation. What is not uncertain are the well-documented adverse effects of chronic, high-dose prednisone and, to a lesser extent, deflazacort therapy in DMD: personality changes, weight gain, cataracts, growth hormone and testosterone deficiencies, diabetes, gastrointestinal complications, and bone fractures.[12,13] Notably, glucocorticoid use remains outside of the realm of both pediatric and adult guidelines for heart failure management.[14,15] Even in conditions such as viral myocarditis and cardiac sarcoidosis, the scrutiny of systematic review has exposed the limitations of data generated from observational and retrospective studies, precluding endorsement of efficacy.[16,17]

Given the authors' implication that longer steroid use is beneficial to the heart in this vulnerable patient population, it is important to carefully consider the limitations of the current study. It is well established that there exists extreme variability in steroid dosing regimens for the treatment of DMD. In addition, many patients elect to be treated with deflazacort, a glucocorticoid not yet available in the United

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From the Division of Cardiovascular Medicine, Ohio State University, Columbus, OH (S.V.R.); Nationwide Children's Hospital Heart Center, Coloumbus, OH (L.H.C).

Correspondence to: Subha V. Raman, MD, MSEE, Davis Heart and Lung Research Institute, The Ohio State University, 473 W. 12th Ave, Suite 200, Columbus, OH 43210. E-mail: raman.1@osu.edu

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States. Even if we assume similar cardiac effects of prednisone and deflazacort (which may not be the case), the long-term cardiac impact is likely different for one patient on 15 mg qd for 4 years versus another who receives a weekend pulse regimen of 500 mg for 4 years. The analysis does not distinguish between the 2, yet one has received a cumulative dose nearly 5 times greater than the other. An even more significant limitation of the study is the lack of a formal control group. As only 3 of 98 patients in this cohort were steroid naïve, it is difficult to speculate that the data support a protective effect of glucocorticoid therapy. Some patients were as old as 22.5 years at time of first cardiac magnetic resonance, and some as young as 9.4 years at time of last cardiac magnetic resonance: This implies a wide variation in age span between first and last scans that, in turn, suggests caution in drawing conclusions from data associations in a heterogeneous group of individuals at various stages of cardiac and neuromuscular disease. Finally, the 4% event rate in a multiyear retrospective study of a disease where nearly all patients will die of cardiopulmonary causes suggests that implications regarding prognosis be tempered.

LGE positivity is equated with myocardial fibrosis in this article. While this may certainly be valid in more advanced disease, we simply do not have the histopathological corroboration for LGE in early stage Duchenne cardiomyopathy that has been established in other conditions affecting the myocardium. It is likely that some of the LGE positivity represents inflammation as it does in myocarditis, a condition with a nearly identical pattern of epicardial enhancement to that seen in the early myocardial damage of DMD. The label ascribed to LGE has implications beyond nosology: Instead of simply being a marker of disease progression, early LGE positivity may be asking us to more precisely target inflammation with refined therapy.

While the authors state that the study was not powered to measure the confounding effect on their findings of angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, and β-blocker therapies, it would be useful to know the prevalence of use in this cohort. We recently showed in a randomized, controlled trial that combining eplerenone with background angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy attenuates decline in left ventricular systolic function, noting that evident myocardial damage by late gadolinium enhancement was a requirement for enrollment.[18] The present study's finding that LGE-negative patients did not show a significant ejection fraction decline may be used to justify a strategy of deferring combination therapy if myocardial damage is not evident by LGE. Deferring any cardioprotective treatment based on these results may be ill informed when one recognizes the absence of left ventricular strain data. Hor et al have shown greater sensitivity for early myocardial disease in DMD using tagged cine cardiac magnetic resonance–derived strain, which was abnormal in boys as young as 7 years even in the face of LGE-negative myocardium with preserved ejection fraction.[19]

This is a medically complex patient population where cardiomyopathy cannot be studied or treated in isolation. A multitude of factors clearly impact the course of both skeletal and cardiac disease from the time of diagnosis. Omission of confounding variables that impact cardiac disease progression, particularly respiratory status and use of ventilatory support devices, clouds data interpretation. Cardiorespiratory interactions are well known to impact both right and left ventricular function. In addition, therapies not infrequently encountered in this patient population include growth hormone, testosterone, vitamin D, as well as a variety of approved and unapproved nutritional supplements—all with the potential to impact myocardial performance and modulate the effects of glucocorticoid therapy.

We conclude with 3 observations. First, amidst the daily burden of living with this disease, patients and families searching for useful information may stop with publication titles. Second, some of the variability in glucocorticoid therapy, particularly outside of the United States,[20] reflects different perceptions of risk versus benefits by providers and families. And third, retrospective data from a diverse though large cohort must be interpreted with the limitations that such data present. If there is a link between steroid use and preservation of myocardial function in DMD, the truth lies in a carefully controlled prospective clinical trial. We must offer something better than simply "take or leave" glucocorticoids, particularly with increasing longevity for those with DMD. With a number of well-designed clinical trials under way, better choices for more effective cardioprotection with less attendant morbidity are within reach.

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Disclosures

None.

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