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EDITORIAL COMMENT

Steroid Therapy Effectively Delays Duchenne's Cardiomyopathy*

G. William Dec, MD

Boston, Massachusetts

Duchenne muscular dystrophy (DMD), the most common form of muscular dystrophy, is caused by a defective gene located on the X chromosome responsible for dystrophin production. The vast majority (70% to 85%) of dystrophin mutations are deletions; point mutations in the coding sequence or the splicing site account for the remainder (1). Significant associations between dilated cardiomyopathy and dystrophin mutations in exons 12 and 14 and possible protection against dilated cardiomyopathy by exon 51 and 52 mutations have been reported (2).

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Cardiac involvement is universally present in the disorder and typically manifests itself in the form of dilated cardiomyopathy or arrhythmias. Dystrophin normally provides mechanical reinforcement to the sarcolemma and stabilizes the glycoprotein complex by linking actin at the amino-terminus to the dystrophin-associated protein complex and sarcolemma at the carboxyl-terminus. Its absence results in a fragile cellular membrane that is more easily damaged during repetitive muscle contractions. This results in the development of myocyte necrosis and subsequent fibrosis leading to progressive ventricular dilation and failure (1). Dystrophin is also an important component of the membrane in Purkinje fibers; thus, conduction disease and arrhythmias are not uncommon in the condition (1). Although progressive respiratory failure is the most common cause of mortality in DMD, heart failure accounts for ~25% of all deaths (1). DMD cardiomyopathy is characterized by extensive fibrosis and thinning of the ventricular wall. Disproportionate scarring occurs early in the posterolateral left ventricular wall. As the disease progresses, myocardial fibrosis also spreads to the remaining walls.

Left ventricular dysfunction is usually present by 10 to 12 years of age and nearly universal by the late teenage years. Echocardiography, particularly using tissue characterization, and cardiac magnetic resonance imaging have both been shown to detect structural changes in the myocardium well before the onset of systolic dysfunction or overt cardiomyopathy (3). The ability to detect early disease has led to the development of therapeutic interventions designed to slow its rate of progression.

Inhibition of the renin-angiotensin-aldosterone system, either alone or combined with beta-blockade, can delay progressive left ventricular dysfunction (1–3). The majority of the data come from observational studies because few clinical trials enroll children. At least 1 observational study suggests that the early diagnosis and treatment of dilated cardiomyopathy may lead to improved ventricular remodeling (2). Among a cohort of 27 affected boys, an angiotensin-conversing enzyme inhibitor was started after their first abnormal echocardiogram (left ventricular ejection fraction <55% or evidence of left ventricular enlargement). A beta-blocker (either carvedilol or metoprolol) was added after 3 months if repeat echocardiography showed no improvement. After >3 years of follow-up, left ventricular size and function showed normalization, improvement, or stabilization in 66%, 26%, and 8%, respectively. The mean ejection fraction increased from 36% to 53% and ventricular geometry improved. Data on the use of beta-blockers as sole therapy in this population are lacking.

Schram et al. (4) report in this issue of the *Journal* on the impact of steroid therapy on the development of dilated cardiomyopathy and mortality in DMD patients. In this retrospective observational study, 87 patients (mean age, 9.1 ± 3.5 years) were followed for more than a decade. Patients were already receiving a renin-angiotensin aldosterone antagonist; steroid therapy was initiated based on the treating clinicians' decision. The principal findings of this study were as follows. 1) Steroid treatment was associated with an 85% reduction in all-cause mortality in multivariate analysis (hazard ratio: 0.15; 95% confidence interval: 0.40 to 0.56; $p = 0.0046$). This striking mortality reduction was entirely due to fewer heart failure–related deaths (0% vs. 22%; $p = 0.001$). 2) Steroid use was associated with an 86% lower rate of new-onset cardiomyopathy. 3) The annual rates of decline in left ventricular ejection fraction (−0.43% vs. −1.09%; $p = 0.01$) and fractional shortening (−0.32% vs. +0.65%; $p = 0.0025$) were less pronounced in steroid-treated patients. Beneficial effects were observed in patients with normal or impaired left ventricular ejection fraction at baseline. Ventricular remodeling also demonstrated a benefit with a smaller observed increase in left ventricular end-diastolic dimension (+0.47 mm/year vs. +0.92 mm/year; $p = 0.01$) in steroid-treated patients. The mechanism(s) by which steroids slow the cardiomyopathic process is not yet fully understood.

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From Massachusetts General Hospital, Boston, Massachusetts. The author has reported that he has no relationships relevant to the contents of this paper to disclose.

This study extends findings from previous smaller studies investigating the effects of corticosteroids (either prednisone or deflazacort) on ventricular function. Markham et al. (5) demonstrated that steroid treatment was cardioprotective for freedom from the development of left ventricular dysfunction in 93% of steroid-treated patients versus 53% of untreated patients. Houde et al. (6) found that left ventricular ejection fraction was higher in steroid-treated patients compared with those who did not receive steroid treatment. These earlier studies did not report concomitant medical therapy or examine the effects of steroids on all-cause mortality. Perhaps most importantly, the present study enrolled >75% of patients with normal ejection fraction at the time of steroid initiation. Thus, this study is the largest series to examine the effects of steroid treatment on cardiac size and function in DMD patients already receiving standard pharmacological therapy.

Limitations of the present study include its nonrandomized, observational methodology, the relatively small number of patients available for multivariate modeling, and the inclusion of patients with varied degrees of left ventricular dysfunction. Several questions also arise from this study. 1) When is the optimum timing for steroid initiation to limit the development of dilated cardiomyopathy? 2) Is a regimen of prednisone or deflazacort more likely to produce benefit? 3) Can alternate-day steroid dosing (which is associated with fewer side effects) produce similar cardiac benefits? 4) Should serial cardiac assessment using tissue Doppler parameters or cardiac MRI be used to determine the optimum time to initial steroid treatment or to monitor response to therapy? Because it is unlikely that randomized, controlled studies will examine these specific questions, empirical therapy is likely to remain the standard of care for the foreseeable future.

The identification of the specific gene responsible for DMD led to initial enthusiasm that transfer of a functioning dystrophin protein (either by myoblast transfer or by direct genetic manipulation) might provide substantial clinical benefit. Unfortunately, initial clinical results of myoblast transfer have been disappointing (7). Oligonucleotide-induced exon skipping has been shown in a murine model to induce dystrophin expression in skeletal muscle but has not been shown efficacious in the myocardium. Preliminary results of a placebo-controlled trial demonstrated a statistically significant improvement in 6-min walk distance among patients who received the exon 51 skipping–drug eteplirsen (8). A second approach has focused on stop codon–based therapy. Ataluren, an investigational orally administered drug, promotes ribosomal read-through of stop codon mutations, thereby allowing continuation of the translational process to produce a functional protein (9). Although encouraging results had been reported in preclinical efficacy studies, the drug's effects on cardiac dysfunction have not been systematically examined. Finally, gene replacement strategies have been explored using adenoviruses and adeno-associated viruses (9). To date, this approach has been limited primarily by the inability of available viral vectors to carry very large molecules such as dystrophin. Unfortunately, truncated dystrophin molecules have proven ineffective.

What are the therapeutic implications of this study because the majority of DMD patients currently receive corticosteroid therapy? The striking cardiac benefit suggests that initiation of treatment either at a younger age or prompted by detection of subclinical cardiac dysfunction by echocardiographic or cardiac magnetic resonance imaging might further improve the cardiovascular morbidity and prolong survival. Despite recent progress, the prognosis with DMD remains poor, with virtually all patients dying of worsening skeletal muscle dysfunction and respiratory failure in their third decade. Additional therapies designed to improve the fundamental molecular abnormality in dystrophin production are urgently needed to treat this inexorably progressive disease of children and young adults.

Reprint requests and correspondence: Dr. G. William Dec, Massachusetts General Hospital, Bigelow 810, 55 Fruit Street, Boston, Massachusetts 02114. E-mail: gdec@partners.org.

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