

Therapeutic Strategy for Heart Failure in Becker Muscular Dystrophy

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Becker muscular dystrophy (BMD) and Duchenne muscular dystrophy (DMD) are clinical variants of “dystrophinopathy” which is caused by an X-linked mutation in the *dystrophin* gene. An out-of-frame mutation results in an absence of a functional dystrophin protein, causing the more severe variant DMD characterized by progressive muscle weakness and premature death. An in-frame-mutation results in a partially functional dystrophin protein, causing the milder variant BMD characterized by the slowly progressive muscle disorder and mild clinical symptoms.

Recently developed gene therapy such as antisense oligonucleotide-mediated exon skipping is one of the promising treatment options for DMD patients.¹⁾ However, the gene therapy could produce incomplete dystrophin protein and the therapy may transform the phenotype of the patients from severe DMD into mild BMD (Figure). Myocardial involvement in BMD has wide variability which is unrelated to skeletal muscular involvement severity, and the relatively preserved daily activity can even cause unexpectedly severe heart failure in BMD. Moreover, the effect of novel gene therapies on cardiac function has not been well substantiated. Although respiratory failure was previously the major cause of death, heart failure and life threatening arrhythmia have now emerged as the leading causes of death in dystrophic patients.^{2,3)} Nevertheless, it seems that cardiac managements remain highly variable and generally undertreated.⁴⁻⁶⁾ Further understanding and optimization of treatment strategies for heart failure are of critical importance to improve prognosis and quality of life in patients with BMD.

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Nakamura, *et al* report that corticosteroids can be a treatment option for severely advanced stages of refractory heart failure in BMD.⁷⁾ This report includes useful suggestions about multiple treatment options; medications such as glucocorticoids, angiotensin converting enzyme (ACE) inhibitors, beta-adrenergic blockers, anti-arrhythmic amiodarone, diuretics, intravenous inotropic agents, and cardiac resynchronization therapy (CRT) with an implantable cardioverter defibrillator (CRT-D).

As is often the case with BMD, mild symptoms delay

hospital visits for neurological diagnosis. Subsequently, the first cardiac evaluation may reveal advanced heart failure and is often too late for initial treatment. The latest Japanese guideline for Duchenne muscular dystrophy in 2014 recommended ACE inhibitor initiation as a first-line medication once left ventricular (LV) dysfunction had been identified.⁸⁾ However, concealed pathological abnormality with fibrosis can be present in the heart at an age earlier than that with overt LV dysfunction.^{5,9-11)} Medical therapy initiation at an earlier stage without obvious LV dysfunction may be a choice to delay the onset of heart failure.¹²⁾ Early cardiac screening should be strongly recommended and each patient must be more informed of the importance of constant hospital visits for evaluations.

Arrhythmias, tachycardia, and sudden cardiac death with autonomic dysregulation are often identified in dystrophic patients.¹³⁻¹⁵⁾ Although the association between *dystrophin* gene and neurological phenotype has not been well investigated, the autonomic dysregulation per se can be a primary result from dystrophin abnormality. The sinus tachycardia in dystrophic patients is associated with poor prognosis which is also the case with general chronic heart failure.^{9,16,17)} The prolonged sinus tachycardia with cardiac overwork leads to progressive cardiomyopathy.¹³⁾ A treatment option using beta blockers should be more preferred, particularly in dystrophic patients with an elevated heart rate. As discussed by Nakamura, *et al*, an earlier or initial treatment with beta-blockers could ameliorate tachycardia and arrhythmia, possibly reversing the LV remodeling.⁷⁾ Further research focusing on efficacy of initial treatment with high-dose beta-blocker for dystrophic patients with tachycardia is needed.

A few reports including Nakamura, *et al* to date showed that device treatments such as a pacemaker or CRT device implantation have insufficient outcome in patients with muscular dystrophy.^{7,18-20)} Poor echocardiographic imaging due to scoliosis may cause errors in the determination of device indications. Thoracic deformation with organic malposition can increase technical difficulty and inadequate positioning at the time of device implantation. Progressive diseases can cause advanced thoracic deformation which can result in late lead failure complications. The risk of device intervention in dystrophic pa-

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Received for publication July 4, 2016. Accepted July 4, 2016.

Released in advance online on J-STAGE September 5, 2016.

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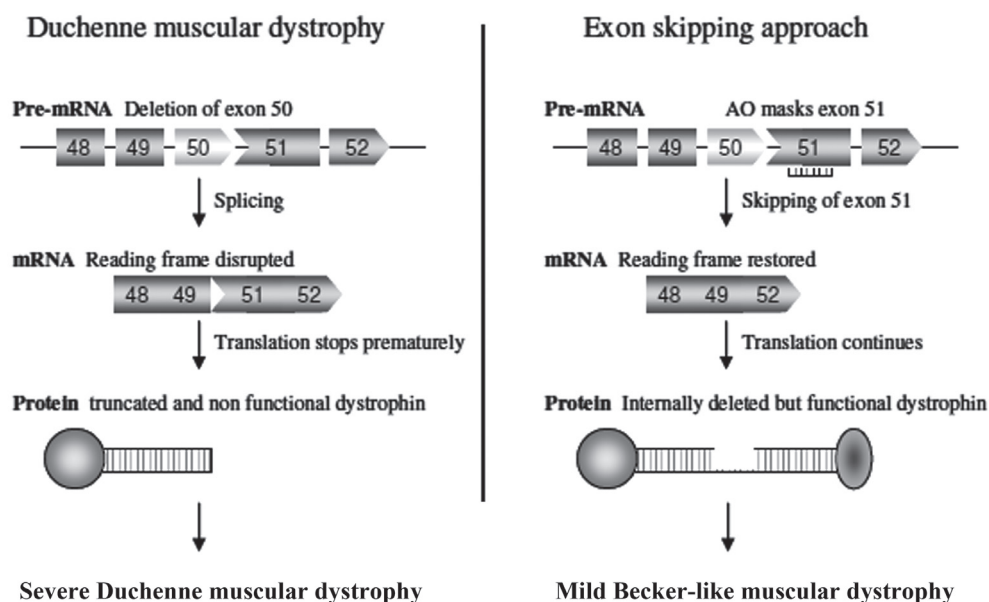


Figure. Figure of exon skipping gene therapy arranged from that presented by Goyenvall and Davies.¹⁾ In this example, a deletion of exon 50 disrupts the open-reading frame of the dystrophin pre-mRNA. The out-of-frame mRNA leads to production of the truncated and non-functional dystrophin protein (left). An antisense oligonucleotide directed against exon 51 can induce effective exon skipping and restore the open reading frame, leading to generation of the partially functional dystrophin protein. The gene therapy can change a clinical phenotype from a severe Duchenne muscular dystrophy to a mild Becker-like muscular dystrophy (right).

tients is quite high, and careful consideration and individualized discussion are needed when determining the indication.

Corticosteroids are one of the key drugs for treatment of dystrophic patients and seem to improve not only muscle strength but also cardiac function.²¹⁻²³⁾ However, most studies to date showed therapeutic effects only in chronic and milder phenotypic patients with DMD. It should be noted that a report by Nakamura, *et al* indicated that corticosteroids can be a treatment option even in the advanced refractory heart failure in BMD.⁷⁾ In terms of the corticosteroid treatment, associations with 1) glucocorticoid description, timing of initiation, and dosage, 2) genetic background of *dystrophine* gene mutation, 3) left ventricular noncompaction, 4) renal function, and 5) respiratory function or nocturnal ventilation are remaining issues that need to be addressed.^{3,7,24-26)} Further studies to optimize treatment for improving prognosis and quality of life in patients with BMD are necessary in the near future.

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