Review of: "Prognostic indicators of disease progression in Duchenne muscular dystrophy: A literature review and evidence synthesis"

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First, we thank for the opportunity to comment on such a valuable paper.

In rare and intractable diseases such as Duchenne muscular dystrophy (DMD), high levels evidence is rare and limited, therefore we often need to pool patient-level data from different studies to indirectly assess treatment efficacy. Identifying and adjusting for factors influencing clinical courses is crucial to minimize bias. Ferizovic et al. conducted a systematic review of the evidence for DMD and integrated 23 prognostic indicators with significant differences for each of eight clinically meaningful outcomes categories. They consequently designated two endogenous and two exogenous core indicators. This study covers the available evidence, and the prognostic indicators identified will form the essential adjustment factors for future clinical research in DMD. It is also interesting that the results also reflected the changes and progress in medical treatments for DMD. We should pay specific consideration when using them, as the authors mentioned in ‘Discussion’.

1. Clinically meaningful indicators might lack statistical significance

We have introduced drugs such as angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker (ACEI/ARB)

and beta-blocker as a treatment for DMD since they have established evidence in non-DMD patients who suffered from heart failure. Randomized controlled studies are often unacceptable in DMD, as the authors mentioned in 'Introduction,' making it hard to obtain high levels of evidence. We should consider adjustment using evidence in other diseases, if necessary.

In the history of medical care for DMD, mechanical ventilation has had the most significant impact on the survival of the patients. Mechanical ventilation improved systemic conditions including heart failure as well as respiratory status, however it is not easy to standardize procedures compared to drug therapy, and evidence is limited except for their survival.

Rehabilitation is another area where evidence-building from clinical research findings is complex, but its impact on the clinical course is significant. For example, prevention of lower limb contracture through a joint range of motion exercise and orthosis is critical in maintaining independent ambulation. Preservation of airway clearance and lung compliance through respiratory physiotherapy is crucial for excellent respiratory outcomes and improved survival. Data generation for such fundamental treatment techniques is often complicated, since randomization and blinding are hard to conduct, however there are sometimes considerable differences in such techniques among facilities and regions.

2. The relationship between skeletal muscle and myocardial impairment

Among eight outcome categories, loss of independent ambulation, lower extremity and motor function, muscle strength, respiratory function, upper extremity function, and scoliosis are firmly related. We should consider factors that have a significant impact on any of these eight outcomes to have the potential to affect other outcomes.

In contrast, cardiac function is highly independent, as the authors mentioned in 'Discussion.' We must be aware that factors beneficial for skeletal muscle are not always favorable for the myocardium. For example, in BMD, female cases, and X-linked dilated cardiomyopathy, there are cases in which cardiomyopathy is more prominent than skeletal muscle impairment. Currently available antisense oligonucleotides are not permeable into the myocardium. We should carefully monitor their effects on cardiac function during long-term therapy.

3. The impact of new therapeutic drugs

Among 23 prognostic indicators identified in this study, ten were therapeutic agents. The fact that many novel therapeutic agents besides glucocorticoids have evidence acknowledges that muscular dystrophy therapy is entering a new era.

Clinical trials focus on particular subjects and outcomes, therefore we must wait to know the extent and magnitude of the impact of new drugs on the entire DMD clinical course until the drugs are released and accumulate sufficient data. We are eager to emerge a treatment that will remedy all outcomes.

Finally, we hope that the appropriate use of these factors will promote evidence-building and enhance the development of treatments.