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CASE REPORT

Is heart transplantation a real option in patients with Duchenne syndrome? Inferences from a case report

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Abstract

Duchenne muscular dystrophy (DMD) is the most frequent and severe form of MD. It firstly affects the skeletal muscles, causing severe disability, and subsequently the myocardium. The only two options to treat end-stage heart failure in these patients are either a left ventricular assist device (LVAD) implantation as destination therapy or a heart transplant. These hypotheses are still controversial, and data are very limited. We describe the case of an 18-year-old male patient, affected by DMD and in a wheelchair from the age of 11. He progressively developed dilated cardiomyopathy, and in 2016, at the age of 14 years, he underwent HeartWare LVAD implantation, as destination therapy, without post-operative complications. He has been followed up for 47 consecutive months; and 30 months after LVAD implantation, he developed an infection of the exit site, treated by antibiotics and surgical toilette. Following this event, on the basis of patient's good general conditions and willingness, we started to consider heart transplant as an option. Before the patient was listed, he underwent accurate workup, and we found higher values of forced vital capacity, forced expiratory volume in 1 s, and peak expiratory flow, compared with the predicted values of same-age DMD patients. The patient have neither scoliosis nor need for non-invasive mechanical ventilation, and finally, he was always treated with steroids with stable thoraco-abdominal function over the years. According to these considerations, the patient was listed for heart transplant. In 12 February 2020, at the age of 18 years, the patient underwent heart transplant with no post-operative complications. Cardiac transplantation is not considered a valid option for DMD patients, because of the shortage of donor availability and the systemic nature of DMD disease. Considering that this patient had already experienced an LVAD-related complication and he had better general condition than his DMD peers, we listed him for a heart transplant. We described the case of a DMD patient who underwent successful heart transplantation after 47 months of HeartWare LVAD assistance. Three months' follow-up is uneventful.

Keywords Duchenne syndrome; LVAD device; Heart transplant

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Introduction

Duchenne muscular dystrophy (DMD) is the most frequent and severe form of dystrophinopathies, and it is characterized by the complete absence of dystrophin, which forces most of the patients to use a wheelchair within the second decade.[1] Despite medical treatment, cardiac failure is common, and the only two options to treat end-stage heart failure in this kind of patients are left ventricular assist device (LVAD) implantation as destination therapy or heart transplant.[2]

Case report

We describe a case of 18-year-old male patient, affected by DMD and in a wheelchair from the age of 11, who has always been followed up by a multidisciplinary team in our Institution. Since the age of six, he was treated by oral medication with deflazacort. During these years, the patient was regularly followed up by pneumologists by using with spirometry and by neurologists who monitored the evolution of the neuromuscular disease in terms of thoraco-abdominal

function and scoliosis. Forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), and peak expiratory flow (PEF) were, respectively, 60%, 70%, and 70% of predicted values (FVC, 2.24 Lt; FEV1, 2.09 Lt; PEF, 4.07 Lt). The patient also underwent right-heart catheterization to monitor pulmonary vascular resistances with evidence of values within normal range. When he progressively developed dilated cardiomyopathy in 2016, at the age of 14, he underwent HeartWare LVAD implantation, because of acute refractory heart failure. The heart transplant option had not been considered by paediatric cardiac surgeons, (i) because of the emergency the patient was in and (ii) because of the common scepticism towards heart transplant in these DMD patients. Weaning from mechanical ventilation occurred as a routine, and no post-operative complications were encountered.

During the following 47 months the patient was regularly followed up, and we only report an infection of the exit site, treated by antibiotics and surgical toilette, 30 months after LVAD implantation. The debridement of the drive line consisted of incision of the skin following the path of the cable, exteriorization of the cable more proximally, cleaning of the fistulous path, and re-suturing of the skin. Although the recovery was excellent, seeing that the drive line exit was very close to the sternal wound, the patient became psychologically stressed enough to spontaneously ask for a radical solution to the problem. FVC, FEV1, and PEF were, respectively, 1.66 Lt, 1.62 Lt, and PEF 4.41 Lt. Based on the patient's good general conditions and patient personal motivation, our multidisciplinary team started to consider heart transplant as an option. Thus, in 12 February 2020, at the age of 18, the patient underwent heart transplant with no post-operative complications. Weaning from mechanical ventilation occurred as a routine once more. In the first post-transplant day, it was possible to extubate the patient. The discharge from the ICU was possible on the third post-operative day. As far as mobilization is concerned, in our Unit, the patients are followed up by a specialized team of physiotherapists. The patient was trained by them from the first days; and as soon as he was transferred from the ICU to the ward, mobilization was started as soon as possible. As regards sternal stabilization, as we usually do, we suggested to use a tissue sternal band. Mobilization in a wheelchair was possible on the fifth post-operative day. The total hospital stay was 3 weeks, the time needed to perform the three canonical biopsies for the evaluation of any myocardial rejection. A standard triple-agent immunosuppressive therapy was administered (cyclosporine, mycophenolate mofetil, and steroid). At 3 months, FVC, FEV1, and PEF were unchanged than at the pre-transplant.

Discussion

Muscular dystrophies or dystrophinopathies are a group of inherited muscle disorders. X-linked, with recessive trait, is caused by a mutation of gene of dystrophin, a protein that connects membrane proteins and intracellular actin filaments of the muscle cells. The result is a group of neuromuscular disorders characterized by muscle weakness firstly affecting the skeletal muscles, causing different degrees of disability, and subsequently involving also the myocardium. In most cases, patients die because of respiratory or cardiac failure due to muscle degeneration during the second or third decade. Cardiomyopathy in DMD occurs in $>$50% of patients by the age of 15.[1] Even though it is the most frequent cause of death in these patients, its natural history and effective treatments are still poorly understood.[2,3] While medical treatment is based on the actual guidelines for heart failure,[4] more advanced therapies such as ventricular assist device (LVAD) implantation or cardiac transplantation are still controversial.[5] Considering the prognosis of DMD disease, and the rapid general worsening of patients affected after 20 years of age, LVADs are usually used as destination therapy and the decision to implant an LVAD is extremely complex.[2,5–7] The largest series reported in the literature included seven children who underwent Jarvik 2000 implantation, with a median follow-up of 21 months.[6] In 2017, Stoller *et al.*[8] described the case of an 18-year-old patient with DMD who underwent LVAD implantation as destination therapy, with a follow-up of 38 months. This represents the longest survival after LVAD implantation ever reported in the literature. On the other hand, heart transplantation, as a solution for DMD patients with heart failure, has always been viewed with scepticism for the following reasons. First is the shortage of donors. Following the concept of the 'transplant benefit', the few hearts available are for the recipients with the greatest chance of long-term survival. Second is the reduced life expectancy of DMD patients, especially if older than 20 years. The systemic nature of DMD disease always raised concerns about the poor prognosis. On these grounds, heart transplant option has been always considered only in a selected group of patients with preserved pulmonary function and less advanced skeletal muscle disease.[2] The literature reports only few cases of patients with DMD who underwent cardiac transplantation. In 1993, Rees *et al.*[9] described the cases of three patients who underwent heart transplantation, with a mean follow-up of 40 months. Wu *et al.*[10] reported other three cases of adult DMD patients who had cardiac transplantations and were still alive after 5.4 years of follow-up. Another case of heart transplantation, 10 months after the implantation of HeartMate II LVAD, was reported by Wittlieb-Weber *et al.*[11] Papa *et al.*[5] described the case of a 14-year-old boy who underwent cardiac transplantation and was alive after 4 years of follow-up. Two further articles that addressed the same topic were published by Ruiz-Cano *et al.*[12] and Wells *et al.*[13] Wells *et al.*,[13] by studying the UNOS data and performing a propensity-matching analysis, concluded that patients with MDs, where the majority were affected by Becker MD, undergoing heart transplant have shown similar long-term post-transplant outcomes as compared with matched cardiomyopathy-related heart transplant recipients.

According to their conclusions, heart transplantation is an effective treatment for a selected group of patients with MD only when skeletal muscle involvement has been previously carefully assessed by a multidisciplinary team. On the other hand, the effect of this strategy on quality of life will need further investigation.

However, these are small and anecdotal patient series, and precise guidelines are still not well defined.

In DMD patients, the cardiac condition is strongly linked to respiratory involvement. In 2018, LoMauro *et al.*[14] analysed a series of 115 patients, trying to identify specific timepoints of respiratory impairment during disease progression. They found that in these patients, parameters such as FVC, FEV1, and PEF, expressed as percentage of predicted values, linearly declined progressively over the years since childhood. Additionally, they identified that the presence of scoliosis, the absence of diaphragm in breathing participation, and nocturnal non-invasive mechanical ventilation (NIMV) can have an impact on the prognosis, based on the evidence of lower values of FVC. Scoliosis usually gets worse over years, and it influences directly both the restrictive lung pattern and the action of the diaphragm by determining a compression of the abdomen, especially starting at the age of 14. On the other hand, patients under steroids therapy were credited with better spirometric values than were not-treated patients.

Based on the patterns identified by LoMauro *et al.*,[14] we tried to compare our patient's respiratory data with the trends of respiratory function identified in that paper. We found that our patient had higher values of FVC, FEV1, and PEF as compared with the predicted values by Lo Mauro *et al.*[14] (*Figures 1–3*), even though the values observed in our case slavishly followed those of the graph curves. Over the years, our patient has always been treated with steroid with stable thoraco-abdominal function and have neither scoliosis nor need for NIMV. Having verified the same respiratory conditions towards peers affected by the same disease, we infer that it was decided correctly the first time when we used an LVAD as a system to overtake the emergency. This strategy is commonly used in these cases. Additionally, listing the patient for a heart transplant proved to be a proper way to overcome the related LVAD complications. However, only at the time of the heart transplant did we have a table concerning the spirometric tests to infer on, as the Lo Mauro publication was published in 2018.

By analysing this case report retrospectively, there are some important issues that deserve to be discussed. Considering the importance of the diaphragm muscle and skeletal condition, as a contribution to breathing, both the type of device and the type of surgical approach need to be evaluated. Surely, the best device is the one that offers the possibility of an intra-pericardial implant. Furthermore, the surgical approach that alters the thoracic ventilatory mechanics to a lesser extent must be chosen. In our case, we used a HeartWare LVAD device, the centrifugal pump with the lowest profile on the market, which offered the chance of an intra-pericardial device implant.[15] Additionally, we implanted the LVAD through a full-sternotomy, avoiding the thoracotomic approach in order to not damage the function of the intercostal muscles. The values of the spirometric tests, performed after the first intervention, showed that no further exceptional decay had occurred. Additionally, the current case represents the longest surviving DMD patient assisted with a HeartWare LVAD (47 months).

As far as the decision to list the patient for heart transplantation is concerned, we must first of all consider that it had not been taken from the beginning. Primarily, the patient was implanted with a destination therapy strategy. He was implanted in an emergency by a team other than the one who then performed the heart transplant. We were subsequently 'forced' to move to heart transplant,

Figure 1 Evolution with age of mean forced vital capacity (FVC) of our patient (red dots) in comparison with mean values reported by LoMauro *et al.* Blue line: absolute values (A) and percentage of predicted values.

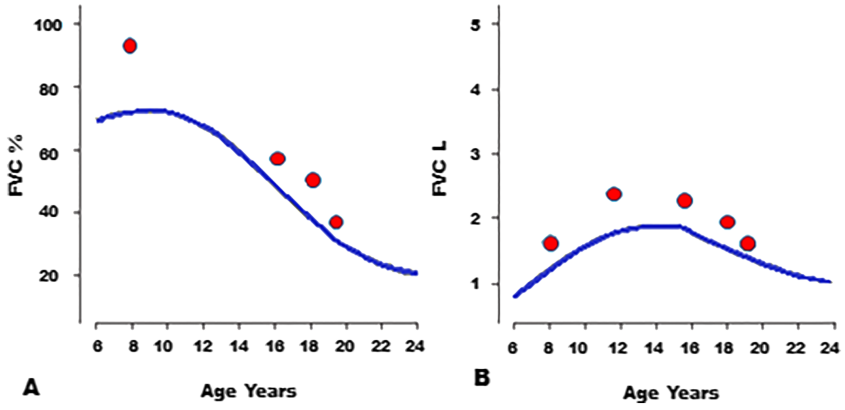

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Figure 2 Evolution with age of mean forced expiratory volume in 1 s (FEV1) of our patient (red dots) in comparison with mean values reported by LoMauro *et al*. Blue line: absolute values (A) and percentage of predicted values.

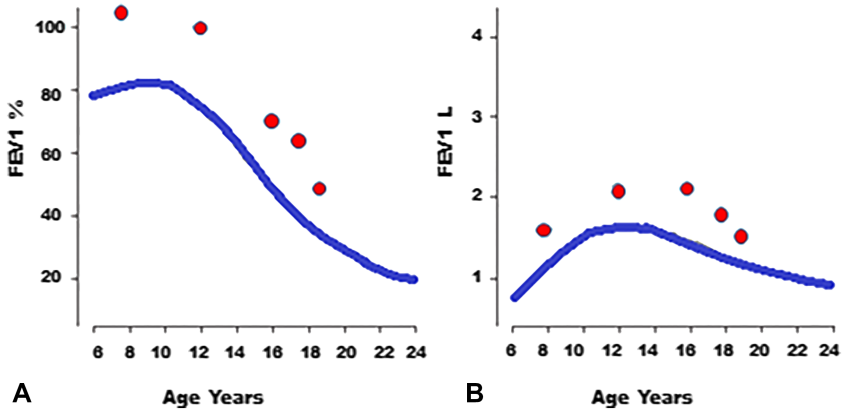
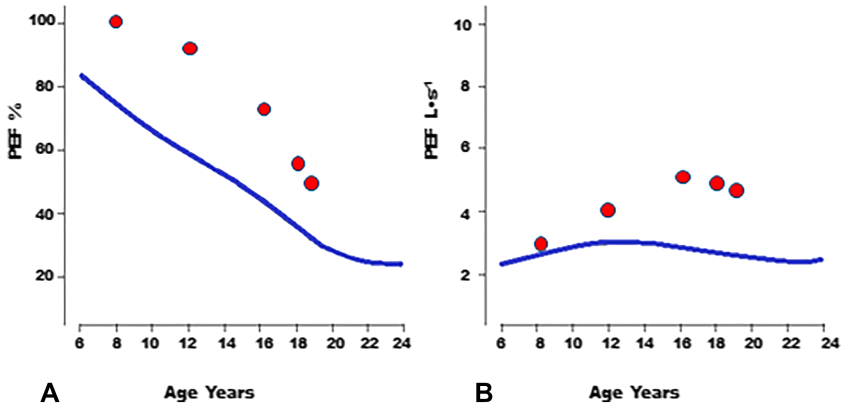


Figure 3 Evolution with age of mean peak expiratory flow (PEF) of our patient (red dots) in comparison with mean values reported by LoMauro *et al*. Blue line: absolute values (A) and percentage of predicted values.



guided above all by the desire of the patient, who has now come of age. Once the first complication occurred, which was infection of the drive line, although successfully treated with a surgical revision of the exit site, this determined a different patient psychological behaviour, such as to push him towards further therapies. By observing the curves of LoMauro paper,[14] and analysing the results of our patient's spirometric tests, with higher values of FEV1, FVC, and having no scoliosis or other negative characteristics such as NIMV, we concluded that there was a feasibility for heart transplantation. The problem that remains unsolved is the following: Is it the new heart that survives the patient, or is it the patient who survives the new heart? According to the International Society for Heart and Lung Transplantation database, we know that median survival of a heart transplant at a young age is around 13 years.[16] The median survival of a DMD patient aged 18 years probably does not exceed the survival of a transplant recipient. Considering the concept of 'transplant benefit', we conclude that even though the patient had better general condition than peers when he was heart transplanted, it would have been much more reasonable to transplant him years earlier, thus also avoiding VAD-related complications.

Conflict of interest

Tomaso Bottio has no conflict of interest to declare.

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