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Eplerenone for early cardiomyopathy in Duchenne muscular dystrophy: a randomised, double-blind, placebo-controlled trial

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Summary

Background—Cardiomyopathy is a leading cause of death in patients with Duchenne muscular dystrophy and myocardial damage precedes decline in left ventricular systolic function. We tested the efficacy of eplerenone on top of background therapy in patients with Duchenne muscular dystrophy with early myocardial disease.

Methods—In this randomised, double-blind, placebo-controlled trial, boys from three centres in the USA aged 7 years or older with Duchenne muscular dystrophy, myocardial damage by late gadolinium enhancement cardiac MRI and preserved ejection fraction received either eplerenone 25 mg or placebo orally, every other day for the first month and once daily thereafter, in addition to background clinician-directed therapy with either angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB). Computer-generated randomisation was done centrally using block sizes of four and six, and only the study statistician and the investigational pharmacy had the preset randomisation assignments. The primary outcome was change in left ventricular circumferential strain (Ecc) at 12 months, a measure of contractile dysfunction. Safety was established through serial serum potassium levels and measurement of cystatin C, a non-creatinine measure of kidney function. This trial is registered with ClinicalTrials.gov, number NCT01521546.

Findings—Between Jan 26, 2012, and July 3, 2013, 188 boys were screened and 42 were enrolled. 20 were randomly assigned to receive eplerenone and 22 to receive placebo, of whom 20 in the eplerenone group and 20 in the placebo group completed baseline, 6-month, and 12-month visits. After 12 months, decline in left ventricular circumferential strain was less in those who received eplerenone than in those who received placebo (median ΔEcc 1.0 [IQR 0.3–2.2]*vs*2.2 [1.3–3.1]; p=0.020). Cystatin C concentrations remained normal in both groups, and all non-haemolysed blood samples showed normal potassium concentrations. One 23-year-old patient in the placebo group died of fat embolism, and another patient in the placebo group withdrew from the trial to address long-standing digestive issues. All other adverse events were mild: short-lived headaches coincident with seasonal allergies occurred in one patient given eplerenone, flushing occurred in one patient given placebo, and anxiety occurred in another patient given placebo.

Interpretation—In boys with Duchenne muscular dystrophy and preserved ejection fraction, addition of eplerenone to background ACEI or ARB therapy attenuates the progressive decline in left ventricular systolic function. Early use of available drugs warrants consideration in this population at high risk of cardiac death, but further studies are needed to determine the effect of combination cardioprotective therapy on event-free survival in Duchenne muscular dystrophy.

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Introduction

Duchenne muscular dystrophy, the most common severe form of muscular dystrophy, is an X-linked disorder in which the sarcolemmal protein dystrophin is effectively absent. Males with Duchenne muscular dystrophy typically die in the third or fourth decade of life; improved respiratory care has unmasked previously under-recognised cardiomyopathy as a leading cause of death.[1] Mouse models of Duchenne muscular dystrophy, autopsy data, and in-vivo human studies with cardiac MRI-based late gadolinium enhancement have all shown that progressive myocardial damage is well underway before left ventricular ejection fraction becomes abnormal.[2]

Exertional symptoms and signs of myocardial disease are typically absent because skeletal muscle disease progressively restricts functional capacity in these patients. Thus, without the use of more sensitive biomarkers, cardiac involvement can go undetected until left ventricular dysfunction and myocardial fibrosis are advanced. Although echocardiography remains a useful instrument to assess left ventricular dysfunction, cardiac MRI with gadolinium enhancement is advantageous for patients with Duchenne muscular dystrophy because it identifies myocardial damage before decline in ejection fraction is apparent by echocardiography.[3] Further, greater reproducibility allows lower sample sizes for clinical trials of cardiomyopathy in patients with rare diseases.[4] The increasing availability of cardiac MRI at major clinical centres for Duchenne muscular dystrophy has allowed earlier detection of cardiomyopathy, and has helped to refine current management typically to include drugs such as angiotensin-converting enzyme inhibitors (ACEI) once damage is evident. This strategy, however, might not be sufficient, because inexorable decline in systolic function has been shown with or without ACEI or angiotensin receptor blocker (ARB) therapy.[5]

Aldosterone acting via mineralocorticoid receptors serves as a common pathway leading to fibrosis across a broad range of myocardial disorders.[6] We previously tested mineralocorticoid receptor antagonism added to ACEI while ejection fraction was still normal in a mouse model that mimics the myocardial damage seen in patients with Duchenne muscular dystrophy.[7] This combination significantly reduced myocardial damage and improved (made more negative) midwall left ventricular circumferential strain (denoted as “Ecc”), a sensitive and early marker of left ventricular systolic dysfunction and adverse cardiac events.[8,9] Left ventricular circumferential strain is an appealing primary endpoint for clinical trials of Duchenne muscular dystrophy cardiomyopathy for several reasons. First, it is a sensitive measure of early myocardial disease in Duchenne muscular dystrophy, being abnormal compared with healthy controls even when ejection fraction is normal and late gadolinium enhancement shows no evident damage.[8] Second, the predominant myocardial fibre direction is circumferential, which makes circumferential strain a highly representative parameter of myocardial performance.[10] And third, strain acquisition is a simple addition to the cardiac MRI examination that also delivers high-precision myocardial characterisation and volumetric quantification. Early intervention is also motivated by the recognition that

myocardial damage, irrespective of underlying cause, engages matricellular proteins such as osteopontin that promote ventricular remodelling before overt heart failure.[11] In recognition of the urgent need for effective cardioprotective regimens in this high-risk and understudied population, we sought to translate these preclinical findings with clinical evaluation of currently available drugs. We hypothesised that treatment with eplerenone in addition to background ACEI or ARB therapy for 12 months in boys with Duchenne muscular dystrophy and myocardial damage evident with late gadolinium enhancement, but preserved ejection fraction, would blunt decline in left ventricular circumferential strain compared with placebo.

Methods

Study design and participants

In this multicentre, randomised, double-blind, placebo-controlled trial, patients were enrolled from the following centres in the USA: The Ohio State University/Nationwide Children's Hospital, Columbus, OH; Cincinnati Children's Hospital Medical Center, Cincinnati, OH; and University of California Los Angeles, Los Angeles, CA. All enrolment and follow-up visits were completed between March 3, 2012, and July 1, 2014. Boys and young men aged 7 years or older with a diagnosis of Duchenne muscular dystrophy by mutation analysis, or by classic phenotypic features if genetics were not available, were screened; cardiac MRI examination with gadolinium-based contrast is part of the standard annual clinical evaluation for Duchenne muscular dystrophy at all three centres. Consecutive patients were screened for enrolment if they had all of the following: myocardial damage in one or more left ventricular segments[12] evident by late gadolinium enhancement; preserved left ventricular systolic function, defined as left ventricular ejection fraction 45% or greater by cine cardiac MRI; and background ACEI or ARB therapy, selection of which was dictated by clinical care. We excluded individuals with MRI-incompatible implants, severe claustrophobia, allergy to gadolinium contrast, previous use of eplerenone or spironolactone, use of potassium-sparing diuretics, use of another investigational agent within 4 weeks or five half-lives of the drug, whichever was longer, before screening, or scheduled surgery that would increase the risks of or potentially result in adverse events. Participants could not be taking or take for the duration of the study CYP3A4 strong inhibitors such as clarithromycin, telithromycin, itraconazole, ketoconazole, and protease inhibitors. Baseline serum potassium concentration less than 5.5 mmol/L was documented in all participants upon enrolment.

The institutional review board of each participating institution approved the study, which complies with the Declaration of Helsinki. Written informed consent was obtained before treatment in all cases. For participants aged 18 years and older, consent was obtained directly from the participant. For participants aged 14–17 years, both assent from the participant and permission from a parent or guardian were obtained. Parental permission alone was obtained for participants younger than 14 years old. An independent four-person data safety monitoring board provided continuous oversight from initial study design through study completion, and the data safety monitoring plan was approved by all

participating centres' institutional review boards. Study data were collected and managed with electronic data capture tools hosted at The Ohio State University.[13]

Randomisation and masking

Enrolled participants were randomly assigned (1:1) to receive either eplerenone 25 mg or placebo. Dosing was every other day for the first month, then once daily if potassium concentration at 1 month was within the accepted range of 5.5 mmol/L or less. Computer-generated randomisation was done centrally with block sizes of four and six, and only the study statistician and the investigational pharmacy had the randomisation assignments. The remaining study personnel were masked to randomisation. Both active drug and placebo were supplied by Pfizer (Sandwich, UK) as identical-appearing tablets. Approval for use of eplerenone outside its labelled indications for the purposes of this trial was obtained as a US Food and Drug Administration exemption from investigational new drug application.

Procedures

Cardiac MRI examinations were done with dedicated 3 T scanner facilities at each centre (Siemens Trio/Verio, Erlangen, Germany; Philips Achieva, Best, The Netherlands) for cardiac evaluation of Duchenne muscular dystrophy. Standardised acquisition protocols including contrast agent type and dose were implemented to insure consistent collection of imaging data across sites. The identical protocol was done at baseline, 6 months, and 1 year with clinically available techniques:[14] mid short axis grid tagged cine; long axis and contiguous short axis steady-state, free-precession cine imaging spanning the left ventricle; and late gadolinium enhancement with inversion-recovery gradient echo acquisitions in the identical long axis and short axis planes, with inversion time optimised to null normal myocardium.

Experienced investigators and core laboratory staff masked to clinical data undertook all image analysis. Midwall left ventricular circumferential systolic strain (Ecc) was computed from each mid left ventricular short axis tagged cine acquisition (HARP, Diagnosoft; Durham, NC, USA). Measurements of left ventricular circumferential strain were repeated by two operators for 106 tagged cine acquisitions; mean interobserver difference was −0.4% (SD 2.2). Left ventricular mass, volumes, and ejection fraction were measured with a scanner (Argus, Siemens Healthcare, Erlangen, Germany) from short axis cines (ejection fraction=[end-diastolic volume − end-systolic volume]/end-diastolic volume), and extent of myocardial damage by late gadolinium enhancement was calculated as a percentage of left ventricular myocardium with the full-width half-maximum technique (CMR42, Circle Cardiovascular Imaging; Calgary, AL, Canada).

Blood was drawn for potassium measurement at baseline and again at 1, 3, 6, 9, and 12 months; the study drug was withheld or discontinued for potassium at concentrations greater than 5.5 mmol/L. At baseline, 6-month, and 12-month visits, concentrations of troponin-I, creatine kinase total, creatine kinase isoenzymes, and haematocrit were measured. Iso-enzymes of creatine kinase includes the MB fraction, mostly located in the myocardium, and the MM fraction, mostly located in the skeletal muscle. Blood concentrations of cystatin C, a reliable measure of renal function in boys with Duchenne muscular dystrophy,[15] were

measured in baseline and 12-month blood samples (Mayo Medical Laboratories; Rochester, MN, USA). Concentrations of troponin-I were measured with an ultrasensitive assay (ADVIA Centaur TroponinI Ultra, Siemens), and creatine kinase and isoenzyme concentrations were similarly assayed from serum samples (Mayo Medical Laboratories). Concentrations of osteopontin in peripheral plasma samples, which were collected at baseline and 12 months with EDTA and stored at −80°C, were measured with sandwich ELISA able to detect human osteopontin with assay range of 0.312–20 ng/mL and sensitivity of 0.024 ng/mL (DOST00, R&D Systems; Minneapolis, MN, USA).

Outcomes

The primary outcome was 12-month change in left ventricular circumferential strain. The secondary endpoints were 6-month change in strain; 6-month, 12-month, and 6-month to 12-month changes in left ventricular ejection fraction and volumes (end-diastolic volume and end-systolic volume); left ventricular myocardial extent of late gadolinium enhancement; the blood biomarkers creatine kinase, creatine kinase MB fraction, troponin-I, and osteopontin. Adverse events and any admissions to hospital because of heart failure, documented arrhythmias, death, or hyperkalaemia (potassium concentration ≥5.5 mmol/L) were also recorded via telephone interviews and at clinic visits.

Statistical analysis

An absolute difference of 1% in strain units at 12 months, the primary outcome, was considered clinically significant. On the basis of strain data in patients with Duchenne muscular dystrophy with varying degrees of myocardial damage,[8] we expected a mean change in strain over 12 months of 1% (SD 1) for the eplerenone group and 2% (1) for the placebo group. Using a sample size of 40 (20 in both groups) and a type I error rate of 5%, we estimated that we would have 88% power to detect a significant difference in the strain change between the eplerenone and placebo groups. Baseline characteristics of the study patients were summarised as appropriate to the type of data. The comparisons of baseline to 6-month and 12-month changes in imaging and blood biomarkers between treatment groups were done with independent two-sample *t* tests or Wilcoxon rank-sum test (if the normality assumption was violated). The correlation between continuous variables was computed with the Pearson's correlation coefficient. Linear regression models were used to examine the associations between treatment and change in left ventricular circumferential strain and ejection fraction over 12-month follow-up. Natural log-transformation was applied when necessary. Potential treatment effect modification was assessed using interaction terms. Data were analysed with Stata 13.1.

This trial is registered with ClinicalTrials.gov, number NCT01521546.

Role of the funding source

The funding sources had no role in the design of the study, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all of the study data, and the corresponding author had final responsibility for the decision to submit the report for publication.

Results

Between Jan 26, 2012, and July 3, 2013, 188 boys were screened and 42 were enrolled across three sites. 20 were randomly assigned to receive eplerenone and 22 to receive placebo, of whom 20 in the eplerenone group and 20 in the placebo group completed baseline, 6-month, and 12-month visits (figure 1). Baseline characteristics of the enrolled cohort were similar between the two groups (table 1). Use of ACEI predominated over ARB as background therapy, with similar duration of ACEI or ARB therapy before enrolment in both groups. A smaller proportion in each group was on a β-blocker at enrolment, and duration of use was similar between the groups. Additional drugs taken by participants in both groups included multivitamins, coenzyme Q10, vitamin D, calcium, alendronate, and proton pump inhibitors (data not shown). Two participants were also taking furosemide. Most participants were on background corticosteroid therapy, and had a similar mean number of years of prednisone (around 30 mg per day) or deflazacort (around 25 mg per day) therapy before enrolment in both groups. Two participants, one in each treatment group, who were not on ventilator support at the beginning of the study, had been started on nocturnal ventilator support by the end of the study. No participants had received any other experimental drug. All participants were non-smokers. One participant in the placebo group requested withdrawal from the study at the 3-month blood draw to deal with long-standing digestive issues.

One participant in the placebo group died from fat embolism, a sporadic and potentially lethal complication of Duchenne muscular dystrophy,[16] 1 month after enrolment. No other deaths and no symptomatic heart failure or arrhythmias were reported. Cystatin C concentrations indicated normal renal function at the beginning and end of the study in both the eplerenone group (median 0.71 mg/L [IQR 0.59–0.86] *vs* 0.70 mg/L [0.54–0.89], p>0.999) and the placebo group (0.74 mg/L [0.62–0.84] *vs* 0.78 mg/L [0.62–0.89], p=0.675). Serum potassium did not exceed 5.5 mmol/L at any timepoint in either group. A concentration of 5.5 mmol/L was obtained in a haemolysed blood sample from one participant in the eplerenone group 1 month after study drug initiation. The 3-month value in this participant was 4.8 mmol/L, and it remained below the safety threshold for the remainder of the study. One participant in the placebo group who was on supplemental oral potassium at the time of enrolment had a baseline potassium concentration of 5.1 mmol/L; potassium supplementation was discontinued upon enrolment, and serum potassium remained 5.0 mmol/L or less for the remainder of the study.

In the placebo group, one participant reported flushing after the first two doses and another reported an anxiety attack after starting study drug. One participant in the eplerenone group experienced an increase in frequency of headaches that accompanied long-standing seasonal allergies that ceased with initiation of fexofenadine by his physician.

Left ventricular systolic circumferential strain magnitude decreased between baseline and 12 months in both groups, but this decline was significantly less in participants randomly assigned to receive eplerenone compared with those assigned to placebo (table 2, figures 2, 3). Similarly, decline in left ventricular ejection fraction was attenuated in the eplerenone group versus the placebo group (table 2, figures 2, 3). This change occurred in the setting of

a significant change in end-systolic volume rather than end-diastolic volume. Measurements of volume, ejection fraction, and strain changes between baseline and 6 months versus 6 months and 12 months indicated that at least 6 months of therapy were needed to achieve significant attenuation in the decline of cardiac structure and function (tables 3, 4).

All participants had at least one left ventricular segment with evident myocardial damage by late gadolinium enhancement, as required for enrolment. Only 18 (50%) of 36 baseline creatine kinase MB values were non-zero, and an even smaller proportion of baseline troponin-I measurements were >0.1 ng/mL (7 [17%] of 41). The extent of abnormal left ventricular myocardium by late gadolinium enhancement over the first 6 months of treatment was reduced with eplerenone versus placebo; this difference diminished between 6 months and 12 months, and was not significant when comparing baseline with 12-month change. Troponin-I, total creatine kinase, and creatine kinase MB fraction did not change significantly during the study period (table 2).

Greater extent of baseline myocardial damage by late gadolinium enhancement predicted greater left ventricular strain decline across all participants ($p_{interaction}$=0.014 for the strain change from baseline to 6-month follow-up and $p_{interaction}$=0.035 from baseline to 12-month follow-up). For example, a shift of 1 SD in baseline late gadolinium enhancement (around 0.1 unit) would result in 2.60 unit change in the estimated adjusted treatment differences for the strain change from baseline to 6-month follow-up and 1.89 unit change from baseline to 12-month follow-up. Baseline late gadolinium enhancement extent similarly affected change in ejection fraction from baseline to 6-month follow-up ($p_{interaction}$=0.001) and baseline to 12-month follow-up ($p_{interaction}$=0.050), but not for ejection fraction change between 6 months and 12 months ($P_{interaction}$=0.329). For example, a shift of 1 SD in baseline late gadolinium enhancement (around 0.1 unit) would result in 6.70 unit change in the estimated adjusted treatment differences for the ejection fraction change from baseline to 6-month follow-up and in 4.95 unit change from baseline to 12-month follow-up. Baseline strain was not a significant effect modifier for strain or ejection fraction change at any time interval (data not shown).

Concentrations of osteopontin did not change significantly during the course of the study (tables 2–4). However, 12-month change in this cytokine-like protein was associated with change in myocardial damage by late gadolinium enhancement (r=0.440, p=0.019).

Discussion

Treatment with eplerenone in boys with Duchenne muscular dystrophy and early cardiomyopathy significantly reduced 12-month decline in left ventricular strain and ejection fraction compared with placebo when added to background ACEI or ARB therapy (panel). This effect was preceded by a reduction in myocardial damage as shown by late gadolinium enhancement cardiac MRI in the first 6 months of therapy, and was smaller in participants with a greater extent of myocardial damage at baseline. Blood concentrations of cardiac enzymes are widely used to show acute ischaemic or inflammatory injury. That enzyme levels were insensitive to the extent of late gadolinium enhancement abnormality suggests that the latter better demonstrates cumulative damage in this disease. Although

significant changes in late gadolinium enhancement or blood biomarkers of myocardial damage were not noted in 12 months of treatment, 12-month change in plasma concentrations of osteopontin, a cytokine-like protein with a central role in tissue injury, were associated with change in late gadolinium enhancement during this period.

Morbidity and mortality due to cardiomyopathy in a disease in which myocytes are genetically programmed for progressive damage are significant, but not unexpected. Cardiac MRI affords earlier detection of myocardial damage, with well-established diagnostic and prognostic value across a broad range of non-ischaemic cardiomyopathies.[21] With increasing recognition of the effect of cardiomyopathy on morbidity and mortality in Duchenne muscular dystrophy, improved strategies are needed to change the natural history of declining left ventricular systolic function and to attenuate its sequelae. ACEIs, ARBs, β blockers,[22] and corticosteroids all affect cardiac function to varying degrees, but are not sufficient to halt disease progression.[5] And although gene therapy-based approaches hold promise, the anticipated regulatory timeline, challenges facing myocardial delivery, and need for genotype-specific therapies support the investigation of more readily available interventions for currently affected individuals.

We noted that a drug with established effectiveness in other cardiac diseases seems to provide benefit at an early stage of cardiac involvement in Duchenne muscular dystrophy. The combination of eplerenone and ACEI or ARB therapy significantly slowed the decline in systolic function known to precede symptoms of cardiomyopathy in Duchenne muscular dystrophy compared with ACEI or ARB therapy alone. Future longer-term studies should assess the effect on decompensated heart failure, arrhythmias, and death in Duchenne muscular dystrophy; clinical trials have shown that this type of combination therapy reduces such events in patients with heart failure with reduced ejection fraction[23,24] and patients with ischaemic myocardial injury and left ventricular systolic dysfunction, even without evident heart failure.[25] Because heart failure in patients with Duchenne muscular dystrophy typically occurs only after ejection fraction has dropped significantly, the positive effect of mineralocorticoid receptor antagonists in previous trials in patients with symptomatic heart failure with reduced ejection fraction and in patients with acute myocardial infarction and reduced ejection fraction is encouraging and relevant for Duchenne muscular dystrophy cardiomyopathy. No previous trial of mineralocorticoid receptor antagonism has taken into account baseline extent of myocardial damage,[26] which significantly modified therapeutic response in our study. This finding parallels the results of our preclinical studies in which earlier treatment in a dystrophic mouse model resulted in significantly more attenuation of cardiac pathology compared with later treatment.[7]

Few histopathological data exist for what myocardial enhancement by late gadolinium enhancement represents in Duchenne muscular dystrophy.[27] In other non-ischaemic cardiomyopathies, mid-myocardial enhancement by late gadolinium enhancement corresponds to fibrosis,[28] whereas epicardial enhancement in myocarditis represents inflammatory infiltrate.[28,29] The consistent lateral wall epicardial enhancement seen in early Duchenne muscular dystrophy cardiomyopathy,[2] identical to the myocarditis pattern, suggests that myocardial damage detected by late gadolinium enhancement might include an inflammatory component. This suggestion is supported by preclinical data showing

increased cardiac damage in mice without both dystrophin and the anti-inflammatory cytokine interleukin 10, compared with those without only dystrophin.[30]

Myocardial damage can occur via oxidative stress, inflammatory cytokines, and extracellular matrix remodelling.[31] Our data, which associate change in osteopontin with change in late gadolinium enhancement over 12 months, might support an anti-inflammatory response. Osteopontin is a key mediator of tissue injury, particularly inflammatory myocardial damage.[32,33] Further studies are needed to explore whether polymorphisms in the osteopontin gene or other genetic modifiers contribute to severity of cardiac disease in Duchenne muscular dystrophy and response to mineralocorticoid receptor antagonist treatment. We noted clinical cardiac benefit in Duchenne muscular dystrophy, which was consistent with the cardiac benefit predicted by our preclinical studies that also showed skeletal muscle improvement;[7] the results of this work should inform subsequent trials that focus on skeletal outcomes.

A large multicentre observational study recently endorsed the strong prognostic value of left ventricular circumferential strain for incident heart failure events in a multiethnic cohort of asymptomatic individuals free of known cardiovascular disease.[9] Accruing data in boys with Duchenne muscular dystrophy are needed to insure that left ventricular circumferential strain provides an equally high prognostic value for this population. Use of background corticosteroids was common in this cohort, and half were also receiving β-blocker therapy. Murine data suggest that prednisolone might attenuate the benefit of combination therapy;[34] whether or not this is relevant in human disease in which corticosteroids are widely used to delay loss of ambulation is unknown. Although the distributions of use of β-blockers and corticosteroids were similar in both treatment groups, further studies are needed in a larger cohort to understand how each affects treatment response. Randomised trials assessing both prednisone and deflazacort in Duchenne muscular dystrophy would be especially relevant. While this study endorsed the safety of our treatment strategy, safety in a more diverse set of boys in more diverse settings warrants evaluation. Concentrations of cardiac enzymes were not informative in this study; recognition that regenerating skeletal muscle can express creatine kinase MB should temper interpretation of these results. Similarly, the muscle source of osteopontin changes in the blood cannot be known without further investigation. The study duration was only 12 months, noting that the primary outcome measure of left ventricular strain measurably declines during this period. Many patients and their families would have been reluctant to take the chance of being assigned placebo and forgo participation in other investigational treatment studies for a longer period. Although the fundamental goal of this study was to test the use of early intervention with available drugs in a disorder in which patients are likely to have progressive cardiomyopathy, the need for long-term clinical follow-up is apparent when recognising that hard events, such as cardiac failure and death, are unlikely to occur for many more years.

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Panel: Research in context

Systematic review

We searched PubMed on Oct 10, 2014, for clinical trials with the terms “randomised”, “double blind”, “placebo”, “cardiac”, and “Duchenne,” with no language restrictions. We identified four reports that met these criteria, and focused on growth hormone,[17] perindopril,[18] idebenone,[19] and sildenafil.[20]

Interpretation

We know of no other randomised, double-blind, placebo-controlled clinical trials of eplerenone in patients with Duchenne muscular dystrophy. Our trial is also, to the best of our knowledge, the first that assessed baseline extent of myocardial damage as a predictor of response. Our findings suggest that early treatment with eplerenone attenuates decline in cardiac function, which is a leading cause of death in Duchenne muscular dystrophy. Subsequent trials should compare various mineralocorticoid receptor antagonists and dosing regimens with differing background therapies. Future studies should also examine the clinical effect on skeletal muscle as well as genetic and other modifiers that might affect skeletal versus myocardial response to treatment.

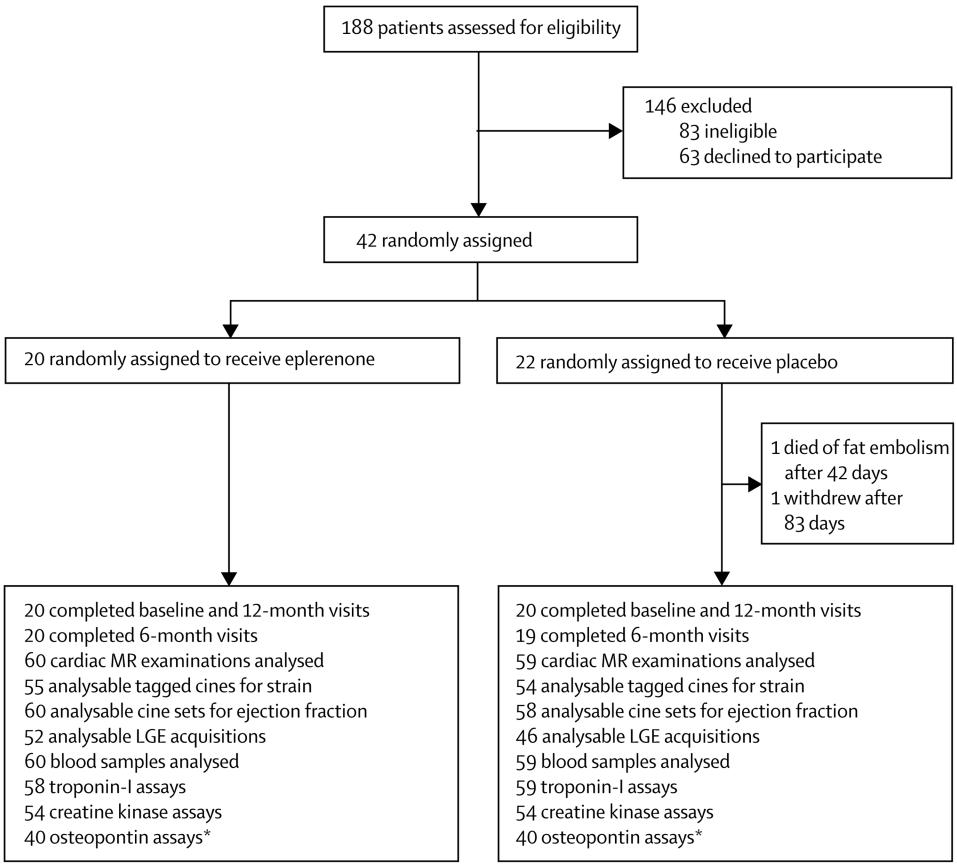

Figure 1. Trial profile

LGE=late gadolinium enhancement. *Measured at baseline and 12 months.

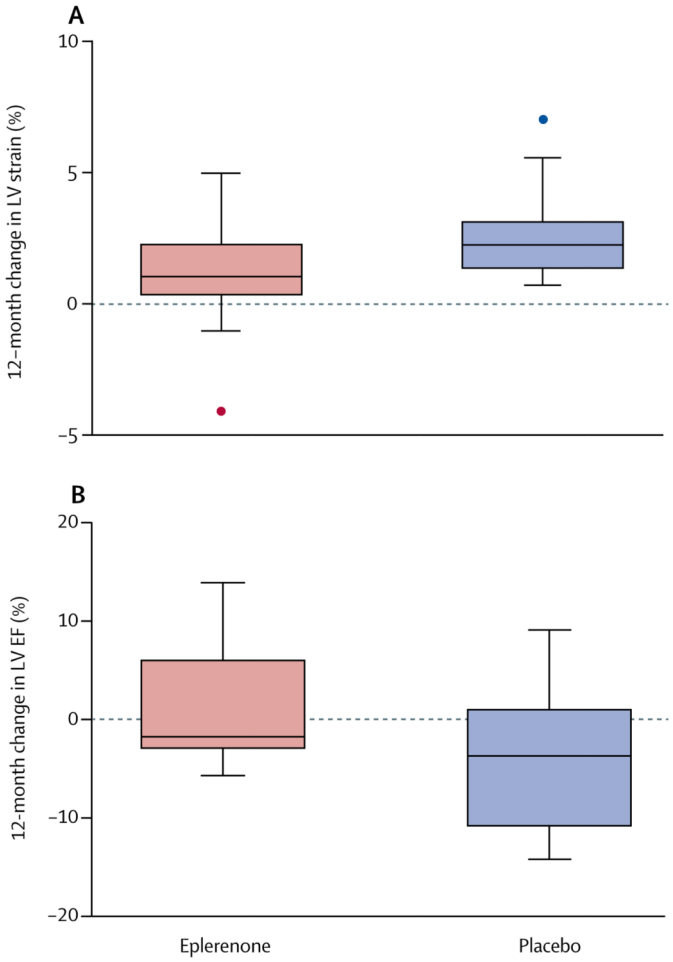

Figure 2. Ventricular systolic function measured by strain (A) or ejection fraction (B) over 12 months

Note that a more negative strain value indicates better contractility. The horizontal lines (from top to bottom) represent the upper adjacent value (the largest observation less than or equal to the upper quartile plus 1.5 times the IQR), upper quartile (75th percentile), median, lower quartile (25th percentile), and lower adjacent value (the smallest observation that is greater than or equal to the lower quartile minus 1.5 times the IQR). All values including those outside these ranges (dots) were included in the analytic sample. LV=left ventricular. LV EF=left ventricular ejection fraction.

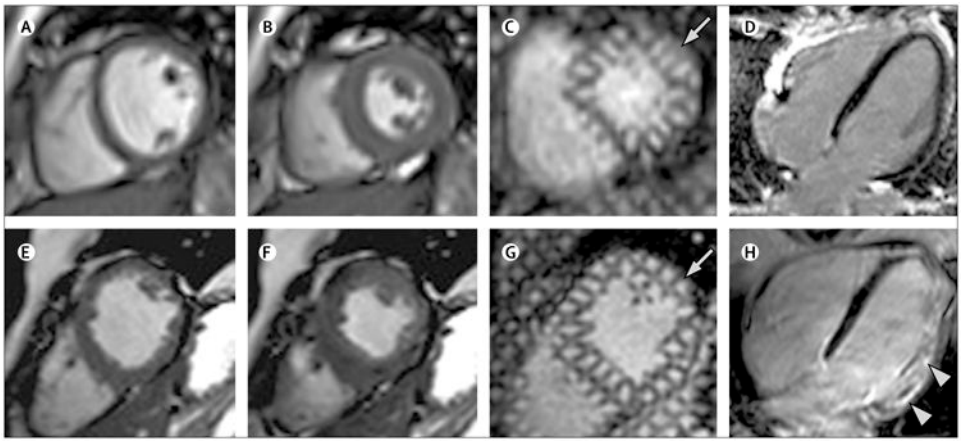

Figure 3. Representative cardiac magnetic resonance images at 12-month follow-up

Images are from two participants with similar baseline left ventricular ejection fraction (47% and 48%, respectively) assigned to eplerenone (top row) versus placebo (bottom row). After 12 months, end-diastolic (A, E), and end-systolic (B, F) frames show improvement in ejection fraction to 57% in the first participant versus decline to 35% in the second participant. End-systolic frames from tagged cine imaging (C, G) show preserved systolic deformation of grids—ie, preserved systolic strain in the eplerenone-treated participant versus reduced systolic deformation, most evident in the lateral wall (arrow), of the placebo-treated participant. Follow-up myocardial damage by late gadolinium enhancement was minimal in the former (D), while more extensive in the latter (H, arrowheads).

Table 1

Baseline characteristics

	Eplerenone (N=20)	Placebo (N=22)
Age, years	14.5 (12.0–18.5)	15.0 (11.0–19.0)
White ethnic background	18 (90%)	20 (91%)
Ambulatory	10 (50%)	8 (36%)
Ventilatory support	7 (35%)	6 (27%)
Dystrophin mutation type*		
Exon deletion	17 (85%)	14 (64%)
Exon duplication	1 (5%)	3 (14%)
Point mutation	2 (10%)	3 (14%)
Intron splice mutation	0	1 (4%)
Left ventricular ejection fraction	56.1% (5.6)	57.9 (7.1)
Left ventricular strain	−16.3% (2.3)	−16.9 (2.1)
LGE	0.30 (0.09)	0.27 (0.10)
Blood pressure, mm Hg		
Systolic	107.1 (12.2)	107.5 (15.0)
Diastolic	64.4 (10.6)	68.2 (12.6)
Heart rate, beats per min	91.2 (14.0)	91.3 (12.3)
Weight, kg	53.5 (15.6)	52.1 (19.0)
Serum potassium, mmol/L	4.0 (0.3)	4.0 (0.5)
Background medical therapy at enrolment		
ACEI	18 (90%)	20 (91)
ARB	2 (10%)	2 (9)
ACEI or ARB duration, years	1.7 (17)	1.5 (1.5)
β-blocker	8 (40%)	9 (41%)
β-blocker duration, years	1.9 (0.9)	1.2 (0.4)
Steroid	17 (85%)	18 (82%)
Prednisone	10 (59%)	13 (72%)
Deflazacort	7 (41%)	5 (28%)
Steroid duration, years	5.5 (2.8)	5.4 (2.9)

Data are median (IQR), n (%), or mean (SD). LGE=late gadolinium enhancement. ACEI=angiotensin-converting enzyme inhibitor. ARB=angiotensin receptor blocker.

*One patient in the placebo group did not have mutation analysis, but was deemed to have Duchenne muscular dystrophy by a neuromuscular specialist on the basis of classic clinical phenotype and skeletal muscle biopsy.

Table 2

Baseline to 12-month changes in imaging and blood biomarkers by treatment group

	Eplerenone	Placebo	p value
Imaging			
Left ventricular strain, %	1.0% (0.3 to -2.2)	2.2% (1.3 to –3.1)	0.020
Left ventricular ejection fraction, %	−1.8% (-2.9 to 6.0)	−37% (−10.8 to 1.0)	0.032
EDV, mL	−2.44 (9.82)	0.07 (17.32)	0.584
ESV, mL	−1.64 (7.89)	4.07 (8.25)	0.034
LGE, % of left ventricular mass	−1% (−6 to 3)	−3% (−5 to 4)	>0.999
Blood			
Troponin-I, ng/mL	0 (−0.01 to 0.03)	0 (−0.01–0.03)	0.463
Total creatine kinase, U/L	−2238 (3320)	−2784 (3649)	0.727
Creatine kinase MB, %	0	0 (−1 to 0)	0.504
Osteopontin, ng/mL	4.35 (44.24)	2.58 (37.20)	0.893

Data are mean (SD) or median (IQR). EDV=end-diastolic volume. ESV=end-systolic volume. LGE=late gadolinium enhancement

Table 3

Baseline to 6-month changes in imaging and blood biomarkers by treatment group

	Eplerenone	Placebo	p value
Imaging			
Left ventricular strain, %	0.84% (2.68)	0.38% (2.56)	0.602
Left ventricular ejection fraction, %	0 (−3.8 to 4.0)	1.0% (−5.0 to 2.1)	0.474
EDV, mL	1.50 (14.35)	0.87 (13.70)	0.893
ESV, mL	1.4 (−4.5 to 6.6)	1.7 (−2.9 to 3.6)	0.915
LGE, % of left ventricular mass	−2% (6)	4% (6)	0.034
Blood			
Troponin-I, ng/mL	0 (−0.01 to 0.01)	0 (−0.02 to 0.01)	0.840
Total creatine kinase, U/L	−590 (−1868 to 4)	−520 (−3156 to 1205)	0.589
Creatine kinase MB, %	0.19% (1.52)	0.13% (1.68)	0.616
Osteopontin, ng/mL	−13.25 (42.12)	−11.06 (33.56)	0.859

Data are mean (SD) or median (IQR). LGE=late gadolinium enhancement. EDV=end-diastolic volume. ESV=end-systolic volume.

Table 4
6-month to 12-month changes in imaging and blood biomarkers by treatment group

	Eplerenone	Placebo	p value
Imaging			
Left ventricular strain, %	0.97 (3.32)	1.98 (273)	0379
Left ventricular ejection fraction, %	1.6 (−0.8 to 2.9)	−2.8 (−5.7 to −1.8)	0.036
EDV, mL	−1.6 (−10.5 to 4.7)	−0.1 (−8.2 to 6.8)	0.426
ESV, mL	−2.9 (−6.6 to 0.3)	2.9 (−2.0 to 6.4)	0.033
LGE, % of left ventricular mass	0 (7)	−4 (5)	0.063
Blood			
Troponin-I, ng/mL	0.01 (0–0.05)	0 (−0.04 to 0.01)	0.153
Total creatine kinase, U/L	−124 (−1307 to 110)	−578 (−1819 to 9)	0.432
Creatine kinase MB, %	0 (−1 to 0)	0 (−1 to 0)	0.532
Osteopontin, ng/mL	17.60 (41.27)	16.18 (41.01)	0.917

Data are mean (SD) or median (IQR). LV=left ventricle. LGE=late gadolinium enhancement. EDV=end-diastolic volume. ESV=end-systolic volume.