Compare efficacy of the angiotensin converting enzyme inhibitor (ACEi) lisinopril with angiotensin II receptor antagonist (ARB) losartan for the cardiomyopathy of DMD

Rationale

A double-blind randomized clinical trial of lisinopril versus losartan is proposed. Both drugs are known to be effective for the treatment of dilated cardiomyopathy. ACEi have been reported to delay the onset and progression of left ventricle dysfunction in children with DMD[1,2]. Multiple studies show therapeutic efficacy of losartan in animals with cardiomyopathy related to muscular dystrophy and in patients with cardiomyopathy from diverse causes[3-8]. ARBs are often reserved for patients in whom heart failure is not adequately treated or where side effects preclude the use of an ACEi[9]. However, in DMD, losartan might be a better choice as a first line drug because of studies demonstrating a potential benefit for skeletal muscle in the mdx mouse[10]. Considering that both skeletal and cardiac muscles are major contributors of the disability of DMD, a drug that could improve both heart and skeletal muscles simultaneously would need consideration as the drug of choice for the cardiomyopathic DMD patient.

Inclusion Criteria

-Duchenne muscular dystrophy patients of all ages
-Null mutation of the dystrophin gene or muscle with <5% dystrophin
-Doppler echocardiogram with ejection fraction <55% within 30 days of enrollment
-Ability to cooperate for testing
-Glucocorticoid treatment acceptable including daily or weekend administration of prednisone or deflazacort

The following inclusion criteria are acceptable with regard to cardiac medications:

No prior treatment

Metoprolol or equivalent beta-blockers

Patients currently on lisinopril ≤5 mg, losartan ≤25 mg or enalapril ≤5 mg may be enrolled after a two-week washout if their repeat echocardiogram shows an EF >40% but does not exceed 55%. These patients would be enrolled in a washout cohort (see below).

Exclusion Criteria

-Patients with EF 55% or greater (even after washout)
-Patients with EF <40% after washout
-Patients taking >5 mg lisinopril, or >25 mg losartan or >5 mg enalapril
-Skeletal deformities or pulmonary anatomical variants that preclude consistent measures of Doppler echocardiography

Study Sample and Randomization

Patients will be randomized to receive lisinopril or losartan according to a randomization schedule provided by the bioinformatics core (randomization provided by statistician). There will be 75 patients in each group. Patients will be stratified according to prior exposure to ACEi or ARB; thus, naïve and washout patients will be randomized separately. The sample size provides a power of 0.9 to identify a treatment difference between the groups of 5% EF ($p = 0.05$ two-tailed test; power will be greater if a directional hypothesis is preferred). Power calculation is based on follow up studies of untreated DMD at NCH.

Subjects

DMD patients (n =150) will be enrolled in double-blind randomized (DBR) controlled trial of lisinopril (n= 75) vs losartan (n = 75) based in inclusion criteria as defined above (EF <55%). Seven collaborating centers will participate and include: Nationwide Children's Hospital, Boston

Children's, St. Louis Children's, University of Minnesota, UC Davis, Medical Center at Kansas University and Children's Mercy Hospital.
Up to 166 patients (~24 at each site) can be enrolled to include a 10% drop-out.

Siblings will be permitted to participate. When sibling participation arises, the randomization will apply to participating brothers so that they will be on the same blinded drug. It would be unacceptable to have siblings on different blinded drugs because of the potential for either inadvertently mixing medications which could compromise care or rarely for caregivers to perceive that one sibling has advantages over another related to the blinded medication and purposely making sure that both receive the same drug. For these reasons, it is highly appropriate for siblings to receive the same medications throughout the study.

This is a 2-year study. However, siblings may be enrolled on a different date; to avoid breaking the blind when the first brother enrolled completes the study, we recommend this patient to remain on blinded study drug for 1, 2, or 3 additional visits until his sibling completes the study. There is no additional risk since these drugs are commonly prescribed by cardiologists to treat heart failure in DMD patients. Patient will be monitored every 4 months and will be terminated from the protocol is EF drops > 10% (see below). If one brother needs to be terminated from the study because of adverse events or drop in EF, study drug will unblinded to the patient and cardiologist. It will be the cardiologist's decision as to whether sibling remains on the blinded study drug.

Treatment Protocol
This is a double-blind randomized controlled trial comparing lisinopril with losartan. Both medications will be concealed in gelatin capsules with microcrystalline cellulose as filler prepared at Nationwide Children's and distributed to all participating Centers upon enrollment of a patient. Each patient will be provided with a 4-month (16-week) supply of medication. Patients will be enrolled for a period of 2 years. Specific criteria for administering the blinded capsules are as follows:

1) Patients fulfilling entry criteria will be enrolled in the study and receive blinded medications at entry level dosing. Either they receive lisinopril 5 mg or losartan 25 mg. Patients 70 kg and heavier may be prescribed twice the entry dose (lisinopril 10 mg and losartan 50 mg [=2 blinded capsules], based on recommendations of initial dose of 0.07 mg/kg for lisinopril and 0.7 mg/kg for losartan. In this case, patients will be asked to take 1 capsule for the first two weeks of treatment and increase to 2 capsules if they do not experience any side effects (dizziness, cough, lightheadedness, or other side effects). Case report forms will be submitted at entry and all follow up visits.

2) If patients experience side effects and report them within the first weeks of starting the treatment, the cardiologist may recommend cutting the dose in half. If necessary, a new kit will be provided to patients with blinded capsules containing either 2.5 mg of lisinopril or 12.5 mg of losartan.

3) Patients will return at 4-month (16-week) intervals (4, 8, 12, 16, 20 and 24 months) and compliance will be addressed by counting the pills. A +/- 8-day window is acceptable (drug will be delivered accordingly).

4) EF (Doppler-echo) will be determined at each of the 4-month return visits and **compared with baseline EF**. If the EF improves or stays the same the dosing will not change. If there is a >5% drop in EF the dose of lisinopril will increase by 5 mg (1 pill) or losartan

will increase by 25 mg (1 pill). The Cardiologist will remain blinded as to which drug is increased. The schedule of Doppler-echocardiograms and dose increases will continue throughout the duration of the study.

5) At any visit if the drop in EF is >10% **from baseline**, the patient will be terminated from the blinded study. The medication dosing schedule at termination will be provided to the cardiologist/primary care physician of their liking by the safety monitor and the PI will remain blinded.

6) Dr. Allen will be provided with echocardiogram images for all subjects enrolled and will review the results for the entire study. He will communicate with the site PI if he considers that the dose should be increased based on his review. After patients are terminated from this protocol, they will be asked to enroll in the Natural History Study (a protocol that collects echocardiogram and EKG – NCH IRB09-00066), and long-term follow-up will be possible if patients accept this option.

7) Treatment for hypertension (beta-blockers) is acceptable prior to enrollment and may be necessary during the duration of the study. New medications added to the regimen of the patient **must** be recorded on the Medications CRF.

Washout cohort

Study will be offered to patients currently on lisinopril ≤5 mg, losartan ≤25 mg, or enalapril ≤5 mg. Patients on lisinopril >5 mg, losartan >25 mg or enalapril >5 mg will not be considered for enrollment in this washout cohort. Patients who agree to participate will stop taking their current heart medications for a period of 2 weeks. They will return to the hospital for a repeat echocardiogram (covered by the grant) at the end of the two-week washout.

- If EF is >55% after the two-week washout, patients will not be enrolled but will be referred to their cardiologist to decide to keep them off medications and watch them, or to put them back on prophylaxis.
- If EF is <40% after the two-week washout, patients will not be enrolled but put back on the same drug they were previously on before washout or at the discretion of their cardiologists. Cardiologist will provide care.
- If EF is between 40 and 55%, they will be randomized in the trial and receive a kit of blinded capsule at entry dose. They will have baseline muscle testing done and safety labs drawn (see below).

Physical Therapy Protocol

A series of tests of tests will be completed by the physical therapist at the 1st (month 0), 4th (month 12) and 7th (month 24) visits:

A. <u>Strength testing:</u> using a hand held dynamometer on the following muscle groups:

Shoulder abductors
Elbow flexors
Elbow extensors
Hip flexors
Knee extensors
Ankle dorsiflexors
Hand grip
Finger pinch
Key grip

B. Functional tests including the following:

1. Brooke Upper Extremity Functional Rating Scale: a functional scale that determines upper extremity function.

2. Nine-Hole-Peg test: This is a timed test that determines finger dexterity and function.

3. 6-minute walk test (6MWT): Patients will be asked to walk on a measured pathway for 6 minutes and the distance they will be able to walk without assistance will be recorded. At the beginning and end of the test, the patient's pulse, blood pressure and respiratory rate will be recorded. Heart rate and distance will be recorded at each minute. Patients will be carefully supervised and have a walking companion to assist in preventing falls. Any falls will be recorded.

C. Pulmonary function testing to determine forced vital capacity (FVC) using a spirometer. The patient is asked to blow into a tube as fast and hard as possible in order to determine their forced vital capacity.

D. Activities of daily living will be measured using the Egen Klassification Scale. This questionnaire consists of 10 questions about activities that patients perform in their daily life which is scored from 0-3. Patients may be both asked to answer questions and at times demonstrate the task.

E. Health related quality of life will be measured using the PedsQL. This questionnaire includes 25 questions and will be filled out both by the patient and a parent (ideally the same one at first, 1-year and 2-year visit).

To provide homogeneity beyond the timeline of the study, the DMD patient will continue to be followed in the MDA Clinic. A case report form will be submitted by the muscular dystrophy treating doctor on these follow up visits through the Natural History Study, if patient agrees to participate.

Evaluation for Side Effects

History and physical examination for side effects will be done by cardiologist at 4-month follow-up visits. The side effect exams are coincident with the return for cardiac assessment at 4-month intervals. History of Intercurrent illness will be recorded including: episodes of light headedness, dizziness, syncope/ pre-syncope, chronic cough. Changes in medications will be noted. Exam includes height, weight, blood pressure, pulse, cardiac exam, pulmonary exam, and check of extremities for edema.

Laboratory Examination

GGT (best choice to monitor liver)[11], cystatin c (best choice to monitor renal function because usual measures such as creatinine are too low in DMD)[12], electrolytes (potassium is most important because it can effect cardiac function and may be affected by ACEi). This will be done at baseline, month 4, month 12, month 16 and month 24 (end-of-study).
If one of the tests value is out of the range and clinically significant, the test will be repeated. If still out of the range and clinically significant, patient will be terminated from the study.

Test	Units	Reference Range	Clinically Significant Range
GGT	U/L	8 - 78	120
Cystatin C	mg/mL	0.5 – 1.3	≥ 1.6
Electrolytes:			
Sodium	mmol/L	135 – 145	≤ 123 – ≥ 155
Potassium	mmol/L	3.7 – 5.6	≤ 2.9 – ≥ 6.1
Chloride	mmol/L	95 – 106	≤ 79 – ≥ 126
CO_2	mmol/L	18 – 35	≤ 12 – ≥ 39

Goals and Expectations

The hypothesis for this controlled trial is that losartan and lisinopril are equal in efficacy in maintaining cardiac function The study is designed to also obtain information on skeletal muscle function (based on studies in mdx mice showing improved skeletal muscle function taking losartan[10]). Thus, one outcome is that both drugs demonstrate equal efficacy in cardiac function and losartan improves skeletal muscle as well. This would have implications for potentially establishing losartan as the drug of choice for the cardiomyopathy. If lisinopril is more effective than losartan in maintaining (improving) cardiac function, then lisinopril would be the treatment choice for cardiac disease and the use of losartan as a supplement to treat the skeletal muscle would most likely require further study. A less likely outcome is that losartan is more effective in maintaining cardiac function compared to lisinopril. .

Statistical Evaluation

A paired t test with repeated measures analysis of variance will be used to compare differences in EF and muscle strength between lisinopril and losartan. For muscle testing, forced vital capacity (FVC) will be considered as the primary outcome and hand-held myometry (hand grip, key grip, finger pinch, elbow flexor, elbow extensor, shoulder abductor) as the secondary outcome. A p value of ≤ 0.05 will be considered significant between the groups.

Open-label study

If a patient meets the inclusion criteria for the double blind study, but declines to participate, he will be offered to participate in the open-label study. In this study, we will enroll patients who were prescribed either losartan or lisinopril. These patients will be followed-up on a regular basis by their cardiologist, and will have echoes done. If they enroll in the study, patients will have their muscle function tested by a clinical evaluator. The physical therapy protocol is the same as in the double blind study (see above) as well as the schedule (visit 1 the day the patient is prescribed either losartan or lisinopril; visit 4 at the end of year 1; visit 7 at the end of year 2). It will be recommended that cardiologist prescribes laboratory examination for safety. (following the blinded protocol). Patient's insurance will cover for laboratory echocardiogram charges as part of regular standard of care.

Separate consent and assent forms entitled "Compare efficacy of the angiotensin converting enzyme inhibitor (ACEi) lisinopril with angiotensin II receptor antagonist (ARB) losartan for the cardiomyopathy of Duchenne muscular dystrophy – OPEN LABEL STUDY" will be used to enroll patients who agree to participate.

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