Eplerenone for early cardiomyopathy in DMD

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Today’s agenda

1) Background eplerenone
2) Cardiac MRI-important trial endpoint
3) Pre-clinical mouse data
4) Results from the trial
5) What’s next
Eplerenone

- Aldosterone antagonist
- Potassium sparing diuretic – meaning it helps the body get rid of water but keep potassium
- Used in the management of chronic heart failure in children and adults
- Marketed by Pfizer under the trade name **Inspra**
- Similar to spironolactone (common)
- More selective for the mineralocorticoid receptor than spironolactone
  - Less undesirable side effects (gynecomastia in boys)
  - Does not possess any anti-androgen or estrogenic effects
What is aldosterone?

- **Steroid hormone** *(mineralocorticoid family)* produced by the outer section of the **adrenal cortex** in the **adrenal gland**.
- Plays a central role in the regulation of blood pressure
  - Acts by increasing reabsorption of electrolytes and water in the **kidney**
  - Results in the conservation of **sodium**, secretion of **potassium**, increase in water retention, and increase in **blood pressure** and blood volume.
- When dys-regulated, aldosterone becomes disease causing and contributes to the development and progression of cardiovascular and renal disease
Negative Effects of Aldosterone

- Cardiac fibrosis and remodeling
- Vascular injury and fibrosis
- Progressive renal disease
- Thrombogenesis "clot formation"
- edema
- Cardiac rhythm abnormalities
Aldosterone receptor antagonists

- Prevent negative effects by blocking the aldosterone receptor
  - Receptors are overexpressed in the failing heart
  - Mineralocorticoid-receptor antagonists likely affect other important HF pathways
  - Two commonly used aldosterone blocking drugs:
    - Spironolactone
      - A nonselective aldosterone receptor antagonist
      - Use associated with side effects due to its binding to other steroid receptors
    - Eplerenone
      - The first agent in a class of drugs known as the selective aldosterone receptor antagonists (SARAs)
      - These drugs have a relatively long history of use

Aldosterone Antagonists:
Long Track Record of Success in Heart Disease

1953
- Isolation and Purification of Aldosterone from Adrenal Glands

1957-59
- Kagawa Assay and Spironolactone Compound Invented

1960
- Spironolactone Launched
- Aldosterone Discovered

1961
- The Relationship Between Renin, Angiotensin II and Aldosterone Discovered

1973-1979
- Non-selectivity of Spironolactone Characterized and Published

1987
- Selectivity of Eplerenone Published

1990
- Aldosterone Involved in Cardiac Fibrosis

1993
- Searle Acquired Worldwide Rights to Eplerenone

1998
- RALES Results

2002
- Eplerenone

2003
- Inspra® (Eplerenone) Approved for Hypertension in U.S.
- EPHESUS Results

Nationwide Children’s
When your child needs a hospital, everything matters."
Treatment with Mild Heart Failure Symptoms

Hazard ratio, 0.76 (95% CI, 0.62–0.93)  
P=0.008

Hazard ratio, 0.58 (95% CI, 0.47–0.70)  
P<0.001

>90% also on ACEI or ARB

Zannad F et al. NEJM 2011.
Safety

• Increased potassium levels
  – Especially if kidney function is abnormal

• Safety in both pediatric and adult patients has been established
How does MRI work?

- Body consists of water (hydrogen and oxygen atoms) which consist of protons.
- Protons are like tiny magnets and are sensitive to magnetic fields.
- In the powerful scanner magnet, the protons line up in the same direction, in the same way a magnet can pull the needle of a compass.
- Short bursts of radio waves are then sent to certain areas of the body, knocking the protons out of alignment. When the radio waves are turned off, the protons realign and in doing so send out radio signals, which are picked up by receivers.
- Signals distinguish between the various types of tissue because the protons in different types of tissue realign at different speeds and produce distinct signals.
- In the same way that millions of pixels on a computer screen can create complex pictures, the signals from the millions of protons in the body are combined to create a detailed image of the inside of the body.
- So MRI is like a big radio tuned to hydrogen (water)
MRI findings in DMD

- Few histo-pathological studies exist for what myocardial enhancement by late gadolinium enhancement (LGE) represents in DMD
  - In other non-ischemic cardiomyopathies mid-myocardial enhancement by LGE corresponds to fibrosis
  - Epi-cardial enhancement in myocarditis represents inflammatory infiltrate
  - The consistent lateral wall epicardial enhancement seen in early DMD cardiomyopathy is identical to the myocarditis pattern suggest that myocardial damage detected by LGE might include an inflammatory component
  - Supported by preclinical data in mice
Can See Heart Muscle Damage with Cardiac MRI, Before EF Falls

Cine (Function) Image

Post-Contrast (Gadolinium Enhancement) Image
Myocardial Strain-abnormal before change in EF

Hor KN et al. JACC 2009.
**Preclinical Mouse Study: Spironolactone + Lisinopril**

- Het mouse: dystrophin-deficient and missing 1 copy of utrophin
- Severe skeletal muscle fibrosis
- Cardiomyopathy progression similar to DMD patients

**Treatment w/ACEI and aldosterone antagonist:**
Het – untreated
Het treated (8) – treatment started at 8 weeks-of-age
Het treated (4) – treatment started at 4 weeks-of-age

**Analysis at 20 weeks-of-age:**
*in vivo* cardiac MRI
*in vitro* muscle force measurements (heart, EDL, diaphragm)
heart and skeletal muscle histological analysis
• At 20 weeks there was preserved EF despite extensive myocardial fibrosis and injury
• Myocardial strain was abnormal
• Strain improved with treatment initiated at 8 weeks
• Improvement was more marked at 4 weeks

Rafael-Fortney Circulation 2011
Drug treatment improves histological parameters of heart and skeletal muscles.

Drugs Also Improves Skeletal Muscle

The eplerenone trial-methods

• Multicenter, randomized, double-blind placebo controlled trial
  – The Ohio State University/Nationwide Children’s Hospital
  – Cincinnati Children’s Hospital Medical Center
  – University of California Los Angeles
• All visits occurred between 3/12-7/14
## Methods

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Methods

- Enrollment criteria
  - Age 7 years or older
  - Evidence of fibrosis by cardiac MRI
  - Ejection fraction <45% by cMRI
  - On an ACEI or ARB
  - Randomly assigned to receive either eplerenone (25 mg) or placebo
- 42 patients entered the study
  - 20 eplerenone/22 placebo
Safety and Adverse Events

- No significant hyperkalemia
- Stable kidney function throughout
- No deaths in those randomized to eplerenone; 1 death in placebo arm due to a fall and fat embolism
Outcomes-what did we measure

• Primary outcome measure
  – 12 month change in LV circumferential strain (1% change in strain units was considered clinically significant)

• Secondary endpoints
  – change in LVEF and LV systolic and diastolic volumes
  – LV myocardial extent of late gadolinium enhancement
  – Blood biomarkers creatine kinase, creatine kinase MB fraction, troponin I and osteopontin
    • a cytokine-like protein with a central role in tissue injury particularly inflammatory myocardial damage
Results—at 12 months

- No significant changes in late gadolinium enhancement
- No significant change in blood biomarkers of myocardial damage
Results-at 12 months

– Did see
  • Statistical difference in 12 month change in plasma concentration of osteopontin
  • This was associated with change in LGE during this period
    – Might support an anti-inflammatory response to eplerenone
  • Significant change in myocardial strain
  • Significant attenuation in the decline of ejection fraction
Eplerenone Attenuated Decline in Strain & Ejection Fraction
Conclusions

• Eplerenone seems to provide benefit at an early stage of cardiac involvement in DMD
• Eplerenone (+ACE/ARB) slowed the decline of function compared with ACEI or ARB therapy alone
• No previous trial of mineralocorticoid receptor antagonism has taken into account baseline extent of myocardial damage which significantly modified therapeutic response.
• This study parallels the results of our preclinical studies in which the dystrophic mouse model resulted in significantly more attenuation of cardiac pathology compared with later treatments.
Open-Label Extension Phase

• No risks identified, potential benefit
• Other trials showed increased benefit after 1-2 years
• Subset of first study subjects enrolled
• Results will be available later this year
Next Clinical Trial Underway Comparing Spironolactone to Eplerenone

• Non-inferiority trial – participants randomized to get one or the other
• Non-inferiority trials test whether a new product is not unacceptably worse than a product already in use.
• Primary outcome: cardiac function
• Secondary outcomes: lung & arm function

https://www.duchenneconnect.org/news/
clinical-trial-news/
Thank You

• Study participants and their families
• Research teams at NCH, OSU and collaborators across the country
• Our sponsors