Xanthine Oxidase Inhibition for Hyperuricemic Heart Failure Patients (EXACT-HF)

A Randomized Clinical Trial

Michael M. Givertz, MD,
on behalf of the NHLBI Heart Failure Clinical Research Network

No disclosures
Background

- Despite guideline-recommended therapy for patients with heart failure (HF) and reduced ejection fraction, morbidity and mortality remain high.
- Oxidative stress contributes to ventricular and vascular remodeling and disease progression in HF.
- Xanthine oxidase (XO) is a potential source of oxidative stress in HF, and therefore a logical target for therapy.
- Allopurinol is a potent XO inhibitor that may reverse several pathophysiological processes occurring in failing myocardium.
Background

- Acute studies in HF have shown that allopurinol can:
  - ↑ myocardial efficiency and reduce MVO$_2$
  - ↑ high-energy phosphates and ATP flux
- Chronic studies have shown improved endothelium-dependent vasodilation and regression of LVH
- OPT-CHF randomized patients with moderate-severe HF to 6 months of treatment with oxypurinol or placebo
  - No clinical benefit in overall study population
  - Signal of benefit in hyperuricemic (UA ≥ 9.5 mg/dl) patients
Hypothesis

- In patients with symptomatic HF due to left ventricular systolic dysfunction and elevated serum uric acid levels, treatment with allopurinol for 24 weeks will improve clinical outcomes compared to treatment with placebo.
Study Population

- NYHA Class II-IV
- HF symptoms for 3 months despite standard therapy
- LVEF ≤ 40%
- Serum UA level ≥ 9.5 mg/dl
- One additional marker of increased risk:
  - Hospitalization or ER visit for HF requiring IV diuretics within 12 months
  - LVEF ≤ 25%
  - BNP > 250 pg/ml or NT-pro-BNP level > 1500 pg/ml
Study Design

-7-14 days

Screen

Baseline

Follow-up visits

Double-blind
1:1 randomization
Stratified by site and creatinine

Allo 300 mg → Allo 600 mg

Placebo → Placebo

Day 0

Day 7-10

4 wk

12 wk

24 wk
Primary Endpoint

- Composite clinical endpoint (CCE)
- Classifies a subject’s clinical status as improved, worsened, or unchanged at 24 weeks based on hierarchical outcomes of:
  - Death
  - Hospitalization, emergency room or urgent clinic visit for worsening HF
  - Medication change for worsening HF
  - Patient Global Assessment
Study Endpoints

- Secondary endpoints at 12 and 24 weeks
  - Change in quality of life (KCCQ)
  - Change in submaximal exercise capacity (6-MWT)

- Other endpoints
  - Echocardiographic measures of LV remodeling
  - Biomarkers of HF (UA, NT-pro-BNP, cystatin C) and oxidative stress (myeloperoxidase)
  - Time to first HF hospitalization and to all-cause death and hospitalization
Statistical Methods

- All analyses conducted using intention to treat
- Row mean score statistic used to compare distributions of primary CCE
  - 250 patients (125 per group) needed to provide 83% power to detect statistically significant difference
- Changes from baseline between treatment groups
  - assessed at each time point with adjustment for baseline value
  - missing values handled using multiple imputation
- Cumulative event rates estimated using Kaplan-Meier method
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Allopurinol (N = 128)</th>
<th>Placebo (N = 125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>Male sex</td>
<td>86%</td>
<td>78%*</td>
</tr>
<tr>
<td>White race</td>
<td>71%</td>
<td>62%</td>
</tr>
<tr>
<td>Duration of heart failure (years)</td>
<td>5.1</td>
<td>5.5</td>
</tr>
<tr>
<td>NYHA class II / III / IV</td>
<td>46% / 52% / 2%</td>
<td>49% / 49% / 2%</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>25%</td>
<td>23%</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy</td>
<td>55%</td>
<td>51%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>57%</td>
<td>52%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>77%</td>
<td>79%</td>
</tr>
<tr>
<td>Atrial fibrillation or flutter</td>
<td>52%</td>
<td>46%</td>
</tr>
<tr>
<td>Gout</td>
<td>20%</td>
<td>25%</td>
</tr>
</tbody>
</table>

Median values or % shown

*p-value < 0.05*
## Baseline Characteristics

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<th>Characteristic</th>
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</thead>
<tbody>
<tr>
<td>Medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor/ARB</td>
<td>84%</td>
<td>86%</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>96%</td>
<td>94%</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>55%</td>
<td>50%</td>
</tr>
<tr>
<td>Digoxin</td>
<td>39%</td>
<td>46%*</td>
</tr>
<tr>
<td>ICD</td>
<td>67%</td>
<td>69%</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>108</td>
<td>108</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>72</td>
<td>74</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.8</td>
<td>31.6</td>
</tr>
<tr>
<td>Cystatin C (mg/dL)</td>
<td>1.44</td>
<td>1.34</td>
</tr>
<tr>
<td>NT-pro-BNP (pg/mL)</td>
<td>2708</td>
<td>2283</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>11.0</td>
<td>11.1</td>
</tr>
</tbody>
</table>

*Median values or % shown

*p-value < 0.05
Uric Acid Levels

Baseline | 12 weeks | 24 weeks
---|---|---
Allopurinol | P<0.0001 | P<0.0001
Placebo
Primary Endpoint

Overall P=0.25

Percent

Worsened

Unchanged

Improved

Allopurinol
Placebo
Secondary Endpoints

**Quality of Life**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>12 Weeks</th>
<th>24 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall summary score</td>
<td>Allopurinol</td>
<td>Placebo</td>
<td>P=0.41</td>
</tr>
</tbody>
</table>

**Submaximal Exercise**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>12 Weeks</th>
<th>24 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distance walked (m)</td>
<td>Allopurinol</td>
<td>Placebo</td>
<td>P=0.75</td>
</tr>
</tbody>
</table>
Other Endpoints

- No differences in LV volumes, mass or ejection fraction
- No differences in cystatin C, NT-pro-BNP or myeloperoxidase
- No difference in proportion of patients who died (6%), had an unscheduled outpatient visit (30%), or were hospitalized (38%) for any reason
- No difference in proportion of patients who were moderately or markedly better on Patient Global Assessment
Risk of Death or Hospitalization

Allopurinol vs Placebo

P-Value: 0.6240
Hazard Ratio: 0.91
95% CI: 0.61, 1.34

Number at Risk:
- Placebo: 125, 122, 115, 110, 106, 101, 97, 91, 88, 81, 78, 74, 40
- Allopurinol: 128, 125, 112, 108, 104, 103, 102, 96, 92, 90, 87, 82, 50

Weeks Post Randomization: 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24
Risk of HF Hospitalization

Allopurinol vs Placebo

P-Value 0.1480
Hazard Ratio 0.67
95% CI 0.38, 1.16

Weeks Post Randomization

Number at Risk:

<table>
<thead>
<tr>
<th></th>
<th>Baseline (0)</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 6</th>
<th>Week 8</th>
<th>Week 10</th>
<th>Week 12</th>
<th>Week 14</th>
<th>Week 16</th>
<th>Week 18</th>
<th>Week 20</th>
<th>Week 22</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>125</td>
<td>123</td>
<td>117</td>
<td>113</td>
<td>111</td>
<td>108</td>
<td>103</td>
<td>98</td>
<td>98</td>
<td>95</td>
<td>93</td>
<td>91</td>
<td>54</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>128</td>
<td>125</td>
<td>120</td>
<td>118</td>
<td>116</td>
<td>115</td>
<td>114</td>
<td>110</td>
<td>109</td>
<td>108</td>
<td>106</td>
<td>101</td>
<td>65</td>
</tr>
</tbody>
</table>
## Adverse Events

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Allopurinol (N = 128)</th>
<th>Placebo (N = 125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>63</td>
<td>58</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>Cardiac</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>Infection</td>
<td>19</td>
<td>13</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Nervous system</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Renal and urinary</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Respiratory</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue</td>
<td>15*</td>
<td>6</td>
</tr>
<tr>
<td>Rash</td>
<td>10*</td>
<td>2</td>
</tr>
</tbody>
</table>

% shown

*p-value < 0.05
Conclusions

● In HF patients with reduced ejection fraction and hyperuricemia, XO inhibition with allopurinol:
  ● safely lowers uric acid levels, but
  ● has no beneficial effects on clinical status, exercise capacity, quality of life, or LV structure and function

● Other adjunctive therapies for high-risk HF patients are needed
Thank You