Recombinant human C1 esterase inhibitor (Conestat alfa) in the prevention of contrast-induced nephropathy in high-risk subjects (PROTECT): a randomized, placebo-controlled, double-blind single-center trial

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26th October 2019
Disclosures

- **Research grants**: Pharming Biotechnologies B.V., Fondation Machaon, University Basel
- **Travel grants**: MSD, Gilead, Pfizer, Pharming Biotechnologies B.V.
- **Lecture fee**: MSD, Mundipharma
- **Consultation fee**: Pharming Biotechnologies B.V.
Radiographic contrast media (CM)

- Essential tool in modern radiology and medicine
  - Diagnostic

- Therapeutic
Radiographic contrast media (CM)

- CM makes fluid visible by increasing absorbance (>10% compared to blood)
History

- **1910**: Barium sulphate for gastrointestinal contrast study

- **1920’s**: sodium iodide used to treat syphilis. Was found to be radio opaque on x-rays

- **Iodinated CM most commonly used today for**
  - CT scans
  - Angiographies
  - Arthrography
  - ..... 
  - Oral, rectal, intravenous.....

Conestat alfa and acute kidney injury
Physiology / Pathophysiology

Iodinated CM

- Majority water soluble, >90% renal elimination
- Does not enter the cells

Adverse events

- «Allergic» reaction
- Contrast-associated acute kidney injury
- Exacerbation of pre-existing hyperthyroidism
Contrast-associated acute kidney injury (CI-AKI)

- Third leading cause of acute kidney failure (ARF) in the hospital.¹

**Definition:**
- Exposure to iodinated CM
- Alternative major injuries are ruled out

**Consequences:**
- Prolonged hospitalization, significant morbidity and mortality and increased health care costs

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¹ Tublin ME et al., AJR 1998
Conestat alfa and acute kidney injury

Rudnick M et al., Clin J Am Soc Nephrol 2008;
Levy EM et al., JAMA 1996;
Giacoppo D, Circ Cardiovasc Interv 2015
McCullough PA, Am J Cardiolog 2006
## CI-AKI – risk factors

<table>
<thead>
<tr>
<th>Non-modifiable</th>
<th>Modifiable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal disease</td>
<td>Anemia</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Shock/Sepsis</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>CM &gt; 100ml</td>
</tr>
<tr>
<td>Age &gt; 75 years</td>
<td>Nephrotoxic drugs</td>
</tr>
<tr>
<td></td>
<td>Dehydration</td>
</tr>
<tr>
<td></td>
<td>Repeat administration of CM</td>
</tr>
</tbody>
</table>
CI-AKI – risk score

Risk of contrast media associated kidney injury

Multivariate Predictors

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>5</td>
</tr>
<tr>
<td>IABP use</td>
<td>5</td>
</tr>
<tr>
<td>CHF</td>
<td>5</td>
</tr>
<tr>
<td>SCr &gt;1.5 mg/dL</td>
<td>4</td>
</tr>
<tr>
<td>(SCr &gt;132 μmol/L)</td>
<td></td>
</tr>
<tr>
<td>Age &gt;75 y</td>
<td>4</td>
</tr>
<tr>
<td>Anemia</td>
<td>3</td>
</tr>
<tr>
<td>DM</td>
<td>3</td>
</tr>
<tr>
<td>Contrast volume</td>
<td>1 point/100 mL</td>
</tr>
</tbody>
</table>

Risk group: Low ≤5, Moderate 6 to 10, High 11 to 15, Very High ≥16

CIN, contrast-induced nephropathy; DM, diabetes mellitus; IABP, Intra-aortic balloon pump

Mehran R, J Am Coll Cardiol 2004
CI-AKI – Prevention

- Hydration with 0.9% sodium chloride
- Low-osmolar/iso-osmolar CM
- Lowest amount of CM possible
- Stop of nephrotoxic drugs (e.g. certain pain killer and antibiotics)

??

N-acetylcysteine  RenalGuard Therapy®

Sodium bicarbonate  Mannitol

Statins  Forced diuresis
CI-AKI - Pathophysiology

**Predisposing factors**
- Renal disease
- Diabetes
- Age >75
- Sepsis
- Shock
- CM > 100ml
- Hypotension
- Nephrotoxic drugs
- Anemia
- EF <40%

**Direct kidney injury**

**Medullary ischemia**

**Oxidative stress**

**Reperfusion injury**

**CI-AKI**

**Inflammation**

**Complement system**

**C1 esterase inhibitor**

**Other factors**
- Nephrotoxic drugs
- Bleeding/hypotension
- Cholesterol embolism
- ...

Osthoff M et al., Biomed Res Int 2013
www.msdmanuals.com

Conestat alfa and acute kidney injury
C1 esterase inhibitor (C1INH)

- Human plasma protein – multiple-action-multiple-target inhibitor (complement, coagulation and contact (kinin) system, fibrinolysis)

Panagiotou A, Frontiers Immunol 2018

Conestat alfa and acute kidney injury

26.10.2019
C1 esterase inhibitor (C1INH)

- Human plasma protein – *multiple-action-multiple-target inhibitor* (complement, coagulation and contact (kinin) system, fibrinolysis)
- Approved for hereditary angioedema
- Plasma-derived or recombinant version *(rhC1INH/conestat alfa)*

- Ameliorates experimental renal ischemia/reperfusion injury

Huang H, Scientific Reports 2018

Conestat alfa and acute kidney injury
C1 esterase inhibitor (C1INH)

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- Plasma-derived or recombinant version *(rhC1INH/conestat alfa)*

- Ameliorates experimental renal ischemia/reperfusion injury

*Complement deposition in the kidneys*  
*Serum creatinine increase*

Van der Pol et al., Am J Transplant 2012; Danobeitia JS et al., PLOS one 2017

Conestat alfa and acute kidney injury
Study rationale

- Ischemia/reperfusion injury contributes to CI-AKI
- rhC1INH reduces experimental renal ischemia/reperfusion injury

Is prophylactic rhC1INH treatment associated with a reduced risk of CI-AKI in high-risk patients?
Study design – PROTECT study
Recombinant Human C1 Esterase Inhibitor in the Prevention of Contrast-induced Nephropathy in High-risk Subjects

<table>
<thead>
<tr>
<th>Study type</th>
<th>Randomized, double-blind, placebo-controlled, exploratory (phase 2) study</th>
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<td>Study population</td>
<td>Individuals with chronic kidney disease scheduled for elective coronary angiography (+/- angioplasty)</td>
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Pilot study
- small study often done to assist the preparation of a larger, more comprehensive study
- to demonstrate feasibility of key components
- to estimate key parameters for a larger trial
- to identify a target population for a larger trial

«Some signal» of efficacy
- «Good results»: to demonstrate
- No safety concern

Conestat alfa and acute kidney injury
Study design – elective coronary angiography

Chest pain (worsening)
Progressive shortness of breath
Positive cardiac stress test
Before major surgery

Conestat alfa and acute kidney injury
Study design – elective coronary angiography

- 30 - 90 minutes
- 50 - 400 ml contrast media
- Usually safe, most common side effect: bleeding

Conestat alfa and acute kidney injury
Study design

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<td>≥18a, eGFR ≤ 50ml/min/1.73m² plus ≥ 1 of the following: Age ≥ 75y, congestive heart failure NYHA III/IV, diabetes mellitus, anemia (hematocrit ≤ 39% for men and ≤ 36% for women), history of pulmonary edema</td>
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**Multivariate Predictors**
- Hypotension
- IABP use
- CHF
- SCr > 1.5 mg/dL
- (>132 μmol/L)
- Age > 75 y
- Anemia
- DM
- Contrast volume 1 point/100 mL

**Risk group:**
- Low ≤ 5
- Moderate 6 to 10
- High 11 to 15
- Very High ≥ 16

**Development dataset N=5571**
**Prediction dataset N=2786**
## Study design

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</tr>
<tr>
<td>Exclusion criteria</td>
<td>Allergy to rabbits, recent (≤ 2wk) pulmonary edema or myocardial infarction, dialysis, multiple myeloma, recent (≤ 7d) exposure to contrast media, pregnancy/lactation, treatment with N-acetylcysteine or sodium bicarbonate</td>
</tr>
</tbody>
</table>
Biomarker of acute kidney injury

Malyszko J, Scientific Reports 2015; Briguori C, J Biomedicine Biotechnology 2014
Fähling M, Nature Rev Nephrology 2017
Intervention

- Screening
- Informed consent
- Randomization
- Baseline samples
- Hydration

Blood/urine sampling
- Discharge

Outpatient visit
- Blood/urine sampling

Telephone interview

Group 1: rhC1INH
- <84kg: 50 U/kg
- >84kg: 4200 U

Group 2: placebo
- Sodium chloride

Blood/urine sampling
Trial profile and baseline characteristics

1566 patients screened (01/2017-5/2018)

1486 not randomised
Protocol exclusion criteria
1360 eGFR>=50ml/min
25 acute heart failure
7 STEMI/NSTEMI
39 contrast media exposure
13 dialysis
12 no additional risk factor
2 other
Other reasons
29 patient not willing
2 other

80 randomized

40 assigned placebo
1 angiography not performed
39 included in mITT
1 protocol violation
38 included in PP

40 assigned rhC1INH
2 angiography not performed
38 included in mITT
2 protocol violation
36 included in PP

Abbreviation: rhC1INH, recombinant human C1 inhibitor; eGFR, estimated glomerular filtration rate; mITT = modified intention-to-treat analysis (participants who have received at least one dose of study medication and have undergone the planned elective angiography); PP = per protocol analysis (two doses of study medication)
## Baseline characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo N=39</th>
<th>rhC1INH N=38</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>11 (28.2)</td>
<td>12 (31.6)</td>
<td>0.8</td>
</tr>
<tr>
<td>Age in years, mean (SD)</td>
<td>77.7 (9.4)</td>
<td>76.2 (7.0)</td>
<td>0.4</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>23 (59.0)</td>
<td>25 (65.8)</td>
<td>0.5</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>14 (35.9)</td>
<td>18 (47.4)</td>
<td>0.3</td>
</tr>
<tr>
<td>Heart failure, n (%)</td>
<td>21 (53.8)</td>
<td>16 (42.1)</td>
<td>0.3</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>20 (51.3)</td>
<td>24 (63.2)</td>
<td>0.3</td>
</tr>
<tr>
<td>Previous MI, n (%)</td>
<td>12 (30.8)</td>
<td>13 (34.2)</td>
<td>0.8</td>
</tr>
<tr>
<td>ACE-I or ATII-RA, n (%)</td>
<td>29 (74.4)</td>
<td>33 (86.8)</td>
<td>0.2</td>
</tr>
<tr>
<td>Loop diuretic, n (%)</td>
<td>19 (48.7)</td>
<td>16 (42.1)</td>
<td>0.6</td>
</tr>
<tr>
<td>Metformin, n (%)</td>
<td>8 (20.5)</td>
<td>8 (21.1)</td>
<td>1</td>
</tr>
<tr>
<td>Aspirin, n (%)</td>
<td>21 (53.8)</td>
<td>24 (63.2)</td>
<td>0.5</td>
</tr>
<tr>
<td>Statin, n (%)</td>
<td>21 (53.8)</td>
<td>29 (76.3)</td>
<td>0.06</td>
</tr>
<tr>
<td>Betablocker, n (%)</td>
<td>20 (51.3)</td>
<td>28 (73.7)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Abbreviation: RAAS, renin-angiotension-aldosterone system; CAD, coronary artery disease; MI, myocardial infarction;
## Intervention characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo N=39</th>
<th>rhC1INH N=38</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine (µmol/l)</td>
<td>128 (52)</td>
<td>133 (36)</td>
<td>0.9</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>41 (15)</td>
<td>44 (10)</td>
<td>0.8</td>
</tr>
<tr>
<td>Urinary NGAL (ng/ml)</td>
<td>17.7 (39.9)</td>
<td>21.1 (46.8)</td>
<td>0.6</td>
</tr>
<tr>
<td>Cystatin C (mg/l)</td>
<td>1.58 (0.4)</td>
<td>1.55 (0.5)</td>
<td>0.8</td>
</tr>
<tr>
<td>Reason for angiography</td>
<td></td>
<td></td>
<td>0.7</td>
</tr>
<tr>
<td>Angina</td>
<td>13 (33.3)</td>
<td>17 (44.7)</td>
<td></td>
</tr>
<tr>
<td>Before surgery or TAVR</td>
<td>8 (20.5)</td>
<td>9 (23.7)</td>
<td></td>
</tr>
<tr>
<td>Positive stress test</td>
<td>9 (23.1)</td>
<td>7 (18.4)</td>
<td></td>
</tr>
<tr>
<td>Coronary artery stenosis</td>
<td>4 (10.3)</td>
<td>4 (10.5)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5 (12.8)</td>
<td>1 (2.6)</td>
<td></td>
</tr>
<tr>
<td>Contrast media (ml)</td>
<td>112 (94)</td>
<td>110 (83)</td>
<td>0.5</td>
</tr>
<tr>
<td>PCI</td>
<td>15 (38.5)</td>
<td>15 (39.5)</td>
<td>0.7</td>
</tr>
</tbody>
</table>

Abbreviations; eGFR, estimated glomerular filtration rate (calculated with the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-Epi)); PCI, percutaneous coronary intervention; TAVR, transcatheter aortic valve replacement
Change in C1INH concentration

- Placebo
- rhC1INH

% change of C1INH levels

<table>
<thead>
<tr>
<th>Time</th>
<th>Placebo</th>
<th>rhC1INH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>after 1st dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>after 2nd dose</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

p < 0.0001
Results – peak urinary NGAL increase within 48 h

<table>
<thead>
<tr>
<th>Median (IQR)</th>
<th>Placebo</th>
<th>rhC1INH</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Entire population</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute (ng/ml)</td>
<td>22.5 (80.3)</td>
<td>4.7 (51.4)</td>
<td>0.038</td>
</tr>
<tr>
<td>Relative (%)</td>
<td>121 (277)</td>
<td>29 (152)</td>
<td>0.052</td>
</tr>
<tr>
<td><strong>Percutaneous coronary intervention (PCI)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute (ng/ml)</td>
<td>26.2 (117.8)</td>
<td>1.8 (15.2)</td>
<td>0.039</td>
</tr>
<tr>
<td>Relative (%)</td>
<td>205 (385)</td>
<td>11 (79)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Relative peak increase (%)
Results – course of urinary NGAL

Absolute concentration (ng/ml, medians)  

Relative concentration (%, medians)

Conestat alfa and acute kidney injury
## Results – secondary endpoints / safety

### Secondary endpoint

<table>
<thead>
<tr>
<th>Secondary endpoint</th>
<th>Placebo</th>
<th>rhC1INH</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystatin C increase &gt; 10% within 24h</td>
<td>13 (33.3)</td>
<td>6 (15.8)</td>
<td>0.045</td>
</tr>
<tr>
<td>Acute kidney injury&lt;sup&gt;1&lt;/sup&gt;</td>
<td>7 (17.9)</td>
<td>6 (15.8)</td>
<td>0.7</td>
</tr>
<tr>
<td>Troponin T peak increase within 24h (ng/l)</td>
<td>8 (33.0)</td>
<td>10.5 (56.0)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

<sup>1</sup> increase in serum creatinine of ≥26 µmol/l or ≥50% within 48h

### Safety (within 3 months)

<table>
<thead>
<tr>
<th>Safety (within 3 months)</th>
<th>Placebo</th>
<th>rhC1INH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite cardiovascular/renal outcome&lt;sup&gt;1&lt;/sup&gt;, n (%)</td>
<td>3 (8)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Any adverse event, n (%)</td>
<td>16 (41)</td>
<td>14 (37)</td>
</tr>
<tr>
<td>Any possible drug-related adverse event, n (%)</td>
<td>2 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Serious adverse event, n (%)</td>
<td>8 (21)</td>
<td>8 (21)</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>3 (8)</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>1</sup> death, unstable angina/acute coronary syndrome, hospitalization for heart or renal failure or hemodialysis
Conclusion

1st human trial of rhC1INH in ischemia/reperfusion injury setting

Administration of rhC1INH before and 4 hours after coronary angiography
  • was associated with less renal injury (as reflected by urinary NGAL and cystatin C)
  • in particular in patients undergoing more invasive procedures

The safety profile was favorable in a patient population with multiple comorbidities and polypharmacy

Future studies are warranted to investigate the nephroprotection by rhC1INH in more detail
To be continued....
Myocardial infarction and kidney injury
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Department of Clinical Research
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Thank you very much for your attention

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