Future applications of recombinant human C1 esterase inhibitor (conestat alfa) in the setting of ischemia/reperfusion injury

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Disclosures

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- **Consultation fee**: Pharming Biotechnologies B.V.
The complement system and cascade

- Group of approximately 20 plasma proteins
- Essential part of the innate immune/defense system
- Many complement proteins are produced in the liver
- Activation
  - Antibodies
  - Bacteria/viruses
  - Sugars on dying cells or microorganisms
  - ....
- Common terminal pathway: membrane attack complex
The complement system and cascade

The complement system and cascade plays a crucial role in many diseases by regulating inflammation, immunity, and blood coagulation. Dysregulation of the complement system can lead to various pathologies, including:

- **Dysregulation**
  - PNH
  - aHUS and TTP
  - Transplant rejection

- **Autoimmune**
  - Lupus nephritis
  - Guillain-Barré Syndrome
  - IgA nephropathy

- **Inflammatory**
  - Macular degeneration
  - ANCA-associated vasculitis
  - Atherosclerosis
  - Sepsis

- **Ischemia-reperfusion**
  - Myocardial infarction
  - Stroke

- **Acute injuries**
  - Trauma
  - Hemodialysis

The complement system is activated through three pathways:

- **Classical pathway**
  - C1r → C1s → C1q
  - C4, C2

- **Lectin pathway**
  - MASP1 → MASP2
  - C3, C3(H2O), Properdin

- **Alternative pathway**
  - Spontaneous hydrolysis
  - C4, C2

Complement activation results in the formation of convertases that lead to:

- **Opsonization**
  - Enhanced phagocytosis by immune cells

- **Cell lysis**
  - Destruction of pathogenic organisms

**Eculizumab** (Pexelizumab) is a monoclonal antibody that inhibits C5 convertase, effectively blocking the terminal complement pathway and reducing inflammation.

The complement system and cascade

Eculizumab (Pexelizumab)

Alexion Provides Update On Phase 2 Clinical Trial With Eculizumab In Antibody Mediated Rejection (AMR) In Living-Donor Kidney Transplant Recipients

“….we are disappointed that this trial did not meet its primary composite endpoint,”....

Pexelizumab for Acute ST-Elevation Myocardial Infarction in Patients Undergoing Primary Percutaneous Coronary Intervention. A Randomized Controlled Trial

Mortality

JAMA 2007

Universitätsspital Basel

The complement system and cascade

- Platelet activation
- Inflammation
- Vascular permeability
- Clot formation
- Complement activation

Dobo J et al., Immunol Rev 2016
The complement system – a hot topic

C1 esterase inhibitor (C1INH)
- Licensed for replacement therapy in patients with C1INH deficiency (hereditary angioedema)

Morgan BP, Harris CL, Nat Rev Drug Discovery 2015
C1 esterase inhibitor (C1INH)

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

Panagiotou A, Frontiers Immunol 2018
C1INH is a potent MASP-1/-2 inhibitor

- Platelet activation
- Inflammation
- Vascular permeability
- Clot formation
- Complement activation

Dobo J et al., Immunol Rev 2016

Ischemia/reperfusion injury (IRI)

- Ischemia
  - Hypoxic injury
    - Cell death
  - O$_2$ decrease
- Reperfusion injury
  - Tissue damage

Reperfusion: spontaneous, angioplasty, thrombolysis

Yellon DM, NEJM. 2007

Conestat alfa and IRI

www.msdmanuals.com
Examples of IRI

IRI injury is a feature of many diseases

- Thromboembolic diseases (stroke, myocardial infarction)
- Major (cardiac) surgery
- Sepsis (DIC)
- Autoimmune diseases
- Transplantation
- Trauma / major bleeding
- .......
Mechanisms of IRI

Inflammation

- Macrophages
- T cells
- B-cells
- Neutrophiles
- Free oxygen radicals
- Coagulation system
- Complement system
- Cytokines
- Endothelial cells
- Kinin system

Tissue damage
Cell death

Conestat alfa and IRI
Mechanisms of IRI

- Inflammation
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- B-cells
- Neutrophiles
- Free oxygen radicals
- Tissue damage
- Cell death

Conestat alfa and IRI
IRI and the lectin pathway of complement

Lectin pathway deficiency attenuates IRI in animal models (cardiac, cerebral, renal, muscle, gut ischemia)

Gesuete R et al., Ann Neurol. 2009

Schwaeble WJ et al., PNAS. 2011
IRI and lectin pathway inhibition

Inhibition of the lectin pathway limits ischemic damage in animal models (cerebral, renal, intestinal ischemia)

Van der Pol et al., Am J Transplant 2012
Orsini F, Circulation 2012
Of mice and humans....

Huang H, Scientific Reports 2018
IRI and the lectin pathway in humans

Cerebral ischemia

Lectin pathway deficiency seems to be associated with less severe IRI in humans

Infarct volume in ml (MRI)

MBL <100 ng/ml

MBL >100 ng/ml

p=0.004

Lectin pathway deficient

MBL >100 ng/ml

Osthoff M et al., PLoS One. 2011

Conestat alfa and IRI

26.10.2019
IRI is a complex phenomenon
C1 esterase inhibitor (C1INH)

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

Panagiotou A, Frontiers Immunol 2018
Future applications of rhC1INH in IRI

Renal ischemia

- A reduction in renal perfusion is the consequence of many diseases
  - Infections
  - Heart failure
  - Kidney transplantation
  - Trauma
  - Major surgeries
  - ...
- Associated with a worse prognosis
- Very little interventions available

Petäjä L, J Cardiothorac Vasc Anesth 2017
rhC1INH as potential treatment for renal IRI

**Survival**

- Sham + PBS
- Sham + C1INH
- IRI + PBS
- IRI + C1INH

**Complement deposition in the kidneys**

- placebo
- rhC1-INH

Castellano G, Am J Patholog 2010; Danobeitia JS et al., PLOS one 2017
rhC1INH as potential treatment for renal IRI

Survival

Glomerular complement deposition

Renal transplantation
Nephroprotection (infarct, sepsis, surgery, trauma...)

Castellano G, Am J Patholog 2010; Danobeitia JS et al., PLOS one 2017
Future applications of rhC1INH in IRI
Ischemic stroke

• Third leading cause of death
• Leading cause of disability in adults

Treatment
• Intravenous fibrinolysis (clot lysis)
• Conservative management (70-80%!)

Good outcome up to 4.5 hours after onset of symptoms

Future treatment
• Intravenous fibrinolysis +/- endovascular thrombectomy
• Only endovascular thrombectomy

Good outcome up to 6 (-24h) hours after onset of symptoms

Emberson J et al., Lancet 2014
rhC1INH as potential treatment for cerebral IRI

Is rhC1INH superior to plasma-derived products?

Gesuete R et al., Ann Neurol. 2009

Infarction volume

Ischemic stroke = blood clot in the brain
Same, same but different

Human plasma derived C1INH

99%

oligomannose-type glycans
<1%

Half-life
30h

Conestat alfa (rhC1INH)

N-glycans

3%

Mannose

5%

Mannose

9%

Half-life
3h

<table>
<thead>
<tr>
<th></th>
<th>C1s</th>
<th>Factor XIa</th>
<th>Factor XIIa</th>
<th>Kallikrein</th>
</tr>
</thead>
<tbody>
<tr>
<td>rhC1INH\textsuperscript{a}</td>
<td>$6.1 \pm 0.3 \times 10^4$</td>
<td>$9.8 \pm 0.5 \times 10^2$</td>
<td>$6.9 \pm 0.5 \times 10^3$</td>
<td>$9.1 \pm 0.1 \times 10^3$</td>
</tr>
<tr>
<td>H-C1INH\textsuperscript{a}</td>
<td>$5.1 \pm 0.3 \times 10^4$</td>
<td>$9.0 \pm 0.2 \times 10^2$</td>
<td>$5.7 \pm 0.4 \times 10^3$</td>
<td>$7.6 \pm 0.3 \times 10^3$</td>
</tr>
</tbody>
</table>
Lectin pathway inhibition

Binding to lectin pathway proteins

Gesuete R et al., Ann Neurol. 2009
US patent information 2006
Future applications of rhC1INH in IRI
Ischemic stroke

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Good outcome up to 6 (-24h) hours after onset of symptoms

![Graph showing infarction volume changes over time](image)

*Infarction volume, mm³*

- Good outcome up to 4.5 hours after onset of symptoms

Emerson J et al., Lancet 2014
Gesuete R et al., Ann Neurol. 2009
Future applications of rhC1INH in IRI
Myocardial infarction

- Major cause of death worldwide
- Effect of current treatment has reached a plateau.

Treatment
- Coronary angiography
- «Blood thinner»

Puymirat E, Circulation 2017
Future applications of rhC1INH in cardiac IRI

Buerke M, Circulation 1995
Future applications of rhC1INH in IRI
Myocardial infarction

Fattouch K et al., Eur J Cardiothorac Surg 2007
Thielmann M et al., Eur J Cardiothorac Surg 2006
De Zwaan C et al., Eur Heart J 2002
Various other potential future applications

- **Traumatic brain injury**
- **Transplantation**
- **Sepsis**
  - Severe infections

- **Cardiac surgery**
- **Transcatheter aortic valve replacement**

Conestat alfa and IRI

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Conclusion

Ischemia/reperfusion injury is common!

Pharmacological interventions have not yet been successful

rhC1INH is a promising compound for the treatment of IRI

- Multiple-target, multiple-action inhibitor of important IRI perpetrators
- Successful intervention in animal models of IRI
- Safety is excellent
- Superior to pdC1INH

Future trials in patients with myocardial infarction or stroke warranted
Thank you very much for your attention

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