Critical Limb Ischemia Progression is associated with an Inflammatory Profile

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Hendrik Gremmels
University Medical Center Utrecht
Presenter Disclosure

Hendrik Gremmels, MD

“CLI progression is associated with an inflammatory profile”

FINANCIAL DISCLOSURE
No relevant financial relationship exists
Introduction

• Critical Limb Ischemia (CLI) is the most severe manifestation of peripheral arterial disease, presenting with ischemic rest pain and/or ulceration.
• Treatment options are often limited, leading to major amputation in 20-40% of cases.
• Decision to amputate is often subjective: need for objective predictors of disease progression.
• Existing prediction models perform poorly (AUC ca. 60%).
Study population: JUVENTAS Cohort

• 112 patients were followed for 6 months after inclusion in a RCT investigating bone-marrow mononuclear cells as therapy for CLI
  
  – Inclusion criteria were severe infrapopliteal occlusion (Fontaine IIb, III or IV)
  – ABI < 0.6

• Recorded primary outcomes: major amputation and death

• 34 control patients
<table>
<thead>
<tr>
<th>Juventas Baseline</th>
<th>Total Cohort (n=112)</th>
<th>Primary Endpoint (n=27)</th>
<th>No Primary Endpoint (n=85)</th>
<th>P-Value</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>77/35 (31%)</td>
<td>18/9 (33%)</td>
<td>59/26 (31%)</td>
<td>0.98</td>
<td>21/13</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>66 [58-74]</td>
<td>71 [62-78]</td>
<td>65 [55-72]</td>
<td>0.03</td>
<td>65 [60-72]</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>26.6 (4.54)</td>
<td>25.9 (5.45)</td>
<td>26.8 (4.24)</td>
<td>0.43</td>
<td>23.2 (2.32)</td>
</tr>
<tr>
<td>Smoking (Current/Past/Never)</td>
<td>27/72/13</td>
<td>6/15/6</td>
<td>21/57/7</td>
<td>0.09</td>
<td>0/7/27</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>4.29 (1.10)</td>
<td>4.16 (1.06)</td>
<td>4.33 (1.11)</td>
<td>0.47</td>
<td>4.91 (0.96)</td>
</tr>
<tr>
<td>HDL (mmol/l)</td>
<td>1.20 (0.44)</td>
<td>1.22 [0.54)</td>
<td>1.20 (0.41)</td>
<td>0.92</td>
<td>1.41 (0.53)</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.45 [0.9-2.0]</td>
<td>1.2 [0.9-1.7]</td>
<td>1.6 [0.9-2.0]</td>
<td>0.38</td>
<td>0.6 [0.6-0.8]</td>
</tr>
<tr>
<td>Hemoglobin (mmol/l)</td>
<td>8.17 (1.08)</td>
<td>7.66 (0.84)</td>
<td>8.32 (1.11)</td>
<td>0.0016</td>
<td>8.9 (0.81)</td>
</tr>
<tr>
<td>History of CVA</td>
<td>8 (7.1%)</td>
<td>5 (18.5%)</td>
<td>3 (3.5%)</td>
<td>0.019</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>History of MI or Angina</td>
<td>43 (38.4%)</td>
<td>12 (44.4%)</td>
<td>31 (36.4%)</td>
<td>0.5</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>History of Major Amputation</td>
<td>9 (8.0%)</td>
<td>4 (14.8%)</td>
<td>5 (5.9%)</td>
<td>0.22</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>History of Dialysis</td>
<td>4 (3.6%)</td>
<td>0 (0.0%)</td>
<td>4 (4.7%)</td>
<td>0.57</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Rutherford class (2/3/4/5/6)</td>
<td>1/7/39/62/3</td>
<td>0/0/7/19/1</td>
<td>1/7/32/43/2</td>
<td>0.27</td>
<td>0</td>
</tr>
<tr>
<td>Fontaine class (IIB,III,IV)</td>
<td>8/39/65</td>
<td>0/7/20</td>
<td>8/32/45</td>
<td>0.09</td>
<td>0</td>
</tr>
<tr>
<td>Ulcer</td>
<td>65 (58.0%)</td>
<td>20 (74%)</td>
<td>46 (54%)</td>
<td>0.013</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Ulcer Area (cm²)</td>
<td>1.88 [1.0-4.0]</td>
<td>2.38 [1.0-5.0]</td>
<td>1.62 [0.99-3.5]</td>
<td>0.43</td>
<td>0</td>
</tr>
</tbody>
</table>
Sub-Study design and methods

• Peripheral blood plasma at inclusion

• Cytokine panel by multiplex ELISA
  – GROα, HGF, LIF, SCF, SCGFβ, SDF1α, TRAIL, IL6, IL8, FGFβ, GCSF, GMCSF, IP10, MCP1, PDGFβb, RANTES, TNFα and VEGF

• Plasma values of cytokines were related to major outcomes
  – Compound outcome: Amputation or death
  – Amputation-free survival

• Univariate and multivariate prediction models were created to predict amputation and death
Results

- Pro-inflammatory cytokines markers show the greatest potential for identifying patients that are likely to undergo amputation.

- Particularly Interleukin 6 (IL-6) is highly abundant in patients at-risk.
IL6 predicts amputation

- Kaplan Meier analysis shows IL-6 levels are associated with amputation-free survival (p=0.009)
Prediction of outcomes

- IL-6 is the best predictor for amputation or death at 6 months (AUC = 73%)
- Additional parameters (Hb and ABI) further increase sensitivity and specificity (AUC = 78%)
Comparison to existing models

- Models using IL-6 perform well compared to existing prediction scores
  - Prevent 3
  - Finnvasc
  - BASIL

<table>
<thead>
<tr>
<th>Model</th>
<th>C-Statistic</th>
<th>AUC + 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevent 3</td>
<td></td>
<td>61.70 [ 50.30 , 73.10 ]</td>
</tr>
<tr>
<td>Finnvasc</td>
<td></td>
<td>62.20 [ 50.20 , 74.20 ]</td>
</tr>
<tr>
<td>BASIL</td>
<td></td>
<td>72.40 [ 60.10 , 84.70 ]</td>
</tr>
<tr>
<td>IL6 Alone</td>
<td></td>
<td>73.50 [ 63.90 , 83.10 ]</td>
</tr>
<tr>
<td>IL6, Hb and ABI</td>
<td></td>
<td>78.20 [ 66.90 , 89.50 ]</td>
</tr>
</tbody>
</table>
Amputation vs Death

In contrast to traditional risk factors, IL-6 levels are primarily associated with amputation, less with mortality.
Example Optimal Decision Rule
Conclusions

• Critical Limb Ischemia is associated with high morbidity and reduced quality of life
• Levels of pro-inflammatory cytokines are markedly increased in patients with Critical Limb Ischemia
• IL-6 levels predict amputation within 6 months

• Utilization of IL-6 as biomarker may add in the development of tailored treatment plans for CLI patients
• Further research may elucidate which factors are causally involved in disease progression
Acknowledgements

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Frans Moll, MD, PhD
Marianne C. Verhaar, MD, PhD
JUVENTAS Results

Amputation at 6 Months

- Placebo: 10 / 79
- BM-MNC: 15 / 81

Death at 6 months

- Placebo: 5 / 79
- BM-MNC: 4 / 81
ABI progression versus Time

[Graph showing ABI progression over time for different tertiles of IL6]
IL-6 ROC

AUC: 77.4% (61.0%–93.7%)