MRI-guided thrombolysis with alteplase at 0.6mg/kg for stroke with unknown time of onset: THAWS randomized controlled trial

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Purpose

• To test whether alteplase at 0.6mg/kg is effective and safe in patients with wake-up stroke or stroke with unknown onset time who had DWI-FLAIR mismatch

Trial design

• Investigator-initiated, Phase III, multicenter, randomized, open label, blinded endpoint trial
• Standard indication for intravenous thrombolysis otherwise time window more than 4.5 hours since last-known-well (e.g., wake-up stroke)
• DWI-FLAIR mismatch: acute ischemic lesion on DWI and no remarkable corresponding hyperintensity on FLAIR
• Randomly assigned (1:1) to receive alteplase at 0.6mg/kg (rt-PA group) or standard medical treatment (control group)
• Sample size=300 (assumption of positive results of WAKE-UP trial)

Following the early termination and positive results of the WAKE-UP trial, steering committee decided to stop recruitment with 131 patients on 10th July 2018
# Primary and Safety Outcomes

<table>
<thead>
<tr>
<th>Primary outcome</th>
<th>rt-PA Group</th>
<th>Control Group</th>
<th>Relative risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>mRS 0-1 at 90 days, no./total no. (%)</strong></td>
<td>32/68 (47)</td>
<td>28/58 (48)</td>
<td>0.97 (0.68, 1.41)</td>
<td>0.892</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Safety outcomes</th>
<th>rt-PA Group</th>
<th>Control Group</th>
<th>Relative risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic ICH at 36 hours†, no./total no. (%)</td>
<td>1/71 (1.4)</td>
<td>0/60 (0)</td>
<td>Infinity (0.06, infinity)</td>
<td>1.0</td>
</tr>
<tr>
<td>Major extracranial bleeding‡, no./total no. (%)</td>
<td>0/71 (0)</td>
<td>0/60 (0)</td>
<td>N.A.</td>
<td>N.A.</td>
</tr>
<tr>
<td>Death at 90 days, no./total no. (%)</td>
<td>2/71 (2.8)</td>
<td>2/60 (3.3)</td>
<td>0.85 (0.06, 12.58)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

†symptomatic ICH: SITS-MOST criteria (a type 2 parenchymal hemorrhage with deterioration in NIHSS score of ≥4 points)
‡major extracranial bleeding: ISTH major bleeding definition
Conclusions

• There was no difference in favorable outcome (mRS 0-1 at 90 days) between the rt-PA and control groups in ischemic stroke patients with unknown time of onset from our relatively small data set.

• The safety of alteplase at 0.6mg/kg was comparable to that of standard treatment.

• Early study termination precludes any definitive conclusions, and additional research may be warranted.