Is drug neuroprotection after thrombectomy for acute stroke or other ischemic cerebral insults feasible: Future prospects

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Disclosures:
Co-inventor of patent on use of elovanoids for neuroprotection after ischemic stroke
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Stroke (>2400 yrs ago): Hippocrates
450 B.C.

Apothecary (Go: “Stuck down by violence”)
>2,000 years, no treatment for stroke

Medical risk factors for stroke prevention identified 1980

Used recently, little could be done for stroke therapy

Cerebral RCTs 1990

Carotid RCTs for the prevention of stroke (MASCET/ACAS)

New era in stroke 1996

Stroke is the first cause of death. If you were a few seconds faster, you would be alive today. What if we had had the knowledge before?
**New era in stroke: iv-rtPA**
1995
Reverse the course of stroke, if given within 3h from symptom onset.
Ability for some to survive a stroke with no or few disabilities if treated promptly.

**Stroke Centers + Telemedicine**
2005
- iv-rtPA (from 3h to 4.5h)
- Coordination of specialists treating stroke

**Endovascular thrombectomy of intracranial vessels (MCA, ACA)**
2015
- HERMES Trial (Lancet 2016): Proximal ICA, MCA occlusion, Moderate strokes (NIHSS > 6), Small infarct core (ASPECTS > 6)

**Extension Rx up to 24h (wake up strokes)**
2018
- DAWN trial (NEJM 2018)
  - However, only helps up to ~40% - 50% patients
- Pre-hospital CTA (Image:pre-hospital CTA showing an infarct)

**Future: Neoprotection delivery to the penumbra**
2023
- Neoprotection ensures (infarct, promotes neuron survival, and BBB disruption)
  - Preserve penumbra + progression of core infarct
Unique opportunity: MD now has a direct access to MCA / ACA acute occlusion

Catheter system to administer neuroprotection is already in place

- Following iv tPA + mechanical thrombectomy (now ‘standard treatment’), a catheter is in place in the reperfused penumbra to directly administer a potent neuroprotection agent
- This bypasses previous problems in human trials of neuroprotective medications
  - Delivered super-selectively via a microcatheter directly to the infarct core/penumbra:
    - Bioavailability is resolved
    - Systemic side effects ↓

Q: How can the penumbra be preserved further after mechanical thrombectomy?

Solution: Neuroprotection delivery to the penumbra after an acute ischemic stroke

Pre-clinical neuroprotection agents + thrombectomy (active trials)

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Elovanoids target key pathways in which neural injury and neuroprotection occur

 Ideal neuroprotection:

- Functional recovery/independence of stroke patients (improve mRS scores)
- Preserve penumbra and prevent progression of core infarct
- Treat remaining ~50% patients not helped by iv-tPA and thrombectomy alone
- Potentially offer thrombectomy + neuroprotection to patients currently denied (i.e.: those with small penumbra)

Q: How can the penumbra be preserved further after mechanical thrombectomy?

Penumbra: Tissue at risk, progressing towards infarction even after recanalization + reperfusion

‘Time is brain’ is really ‘collaterals are brain’ because collaterals form penumbra and preserve brain tissue for some time after a stroke

Imaging Penumbra: Multi-phase CTA quickly determines collateral flow and penumbra

May / not receive Rx

May help achieve better mRS / functional independence

Offered Rx

Denied Rx

Extend therapy to some of the remaining 50% patients who are otherwise denied treatment

‘I am a neural cell specific Knox necessary for active signaling for neuroprotection integrity’

Elovanoids are a novel class of homeostatic lipid mediators that protect neural cell integrity upon injury. Science Advances 2017.

Jun B…Bazan NG. Elovanoids are novel cell-specific lipid mediators necessary for neuroprotective signaling for photoreceptor cell integrity. Scientific Reports 2017.

Technology needed: Multiple modes of neuroprotection + molecules capable of being delivered to the penumbra

Elovanoids target key pathways in which neural injury and neuroprotection occur

Compiled from www.clinicaltrials.gov, Nov 2018 search: ‘neuroprotection and stroke’
Thank you, Frank and Jackie