Pharmacological Treatment of Ischemic Stroke

Alicia Molinero Pérez, Degree on Biomedical Science,
Universitat Autònoma de Barcelona, Spain

UAB Universitat Autònoma de Barcelona

Introduction

A **ischemic stroke (IS)** is caused by the transient or permanent disruption of the Cerebral Blood Flow (CBF) to a single or several brain areas, during ≥24h, due to the **blockade of a vessel**.

The importance of stroke relies on its **high impact worldwide** since it has been estimated that around 11,569,538 of IS events took place worldwide during 2010, resulting in the loss of 39,389,408 Disability-Adjusted Life Years (DALYs)[1]. **(Figures 1 & 2)**

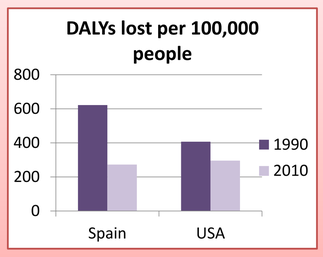

Figure 1[1]

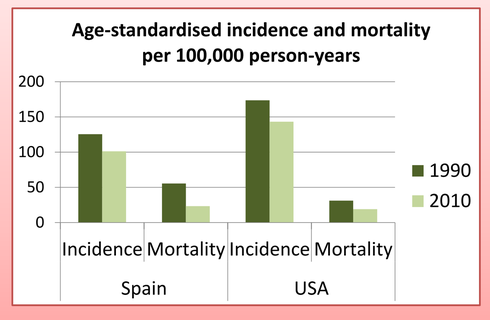

Figure 2[1]

Objectives

- To show the current state of the ischemic stroke pharmacological treatment combining the Spanish and the USA's guidelines.
- To highlight the importance of the combination of rt-PA with mechanical devices.
- To approach the new studies which are being carried out just now in research laboratories.

Clinical Situation

First Steps:

The ***Stroke Code*** (Código Ictus) has been created in order to coordinate the journey of the patient to and within the hospital section known as ***Stroke Unit*** (Unidad de Ictus).

The **objective** is to uncover the main cause of IS taking ≤60min, thus provide a suitable acute treatment.

Initial emergency evaluation:

- Analysis of a stroke ranting scales e.g. NIHSS
- Blood Glucose measurement
- Baseline electrocardiogram
- Haematological study
- Chest radiography (only in Spain)
- Non-Contrast CT scan evaluation (≤45min)

Information addapted from:

- Guía para el diagnostic y tratamiento del ictus from the Sociedad Española de Neurologia (**SEN**. 2006) used in the Spanish hospitals and its review published on 2011 (published online on 2014)
- Guidelines for the Early Management of Patients with Acute Ischemic Stroke from the American Heart Association/American Stroke Association (**AHA/ASA**) used by the American doctors. (2013)

Two approaches proposed by SEN:

1- Measures intended to improve or re-establish the Cerebral Blood Flow (CBF)

TREATMENT OF CHOICE:

Intravenous Recombinant Tissue Plasminogen (IV rtPA)

FDA approval 1996
Dose: 9mg/kg with a maximum dose of 90mg
Viability assessed by CT scan evaluation
Triggers the fibrinolysis of the thrombus.

Weaknesses:

- It is a highly time-dependent treatment:
- Only displays effect on 50% of patients, with a rapid action in 21% of the cases[2]
- Exhibits a later arterial re-occlusion in, at least, 1/3 of patients
- 50% of non-responder patients might suffer side-effects of the administration.

However, **no other treatments have shown a higher potency or effectiveness than rt-PA.**

NEXT STEP: Intra-arterial (IA) administration of rt-PA using Mechanical Thromberectomy devices.

Benefits:

- Reduction of the systemic concentration of the compound
- Direct infusion into the thrombus

Risks:

- The technique: catheter manipulation
- Delayed administration (additional imaging techniques)

Table 1: The mechanical Thromberectomy devices[2]

Retrievers	**Coil Retriever**	Merci	1st approved by FDA (2004)
		Catch	Symptomatic haemorrhage
	Stent Retriever	Solitaire FR	Approved by FDA (2012) **Most popular one (Figure 3)**
		Trevo	Vessel perforation
		Revive	Haemorrhage
Aspiration Devises		Penumbra	Still under trial
		Quickcat	Not enough data
		PRONTO	Not enough data

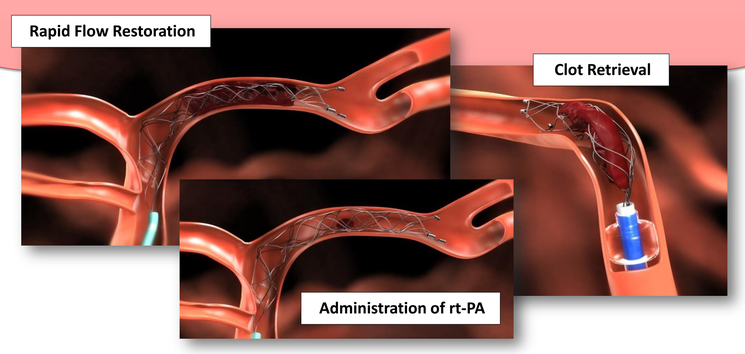

Figure 3. Performance of Solitaire FR Revascularization Device[3]

2. Cerebral protection and reparation by neuroprotective agents

Inhibition of the **ISCHEMIC CASCADE (Figure 5)** by blocking biochemical mediators of the ischemia-reperfusion alteration of the "penumbra area" which leads towards cellular death.

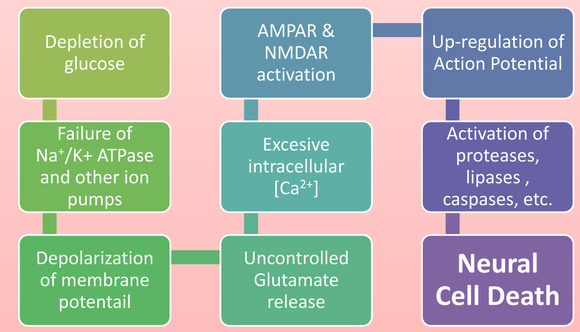

Figure 5. Events leading from ischemia to brain cells death.

Enhancement of the **endogenous brain repair system**

- **Delivery of trophic factors** (e.g. EPO, GCSF, IGF-1, bFGF)
- **Drugs with trophic effects** (citicoline, cerbrolysin)
- **Stem cells** (neuronal or mesenchimal)
- **Rehabilitation**

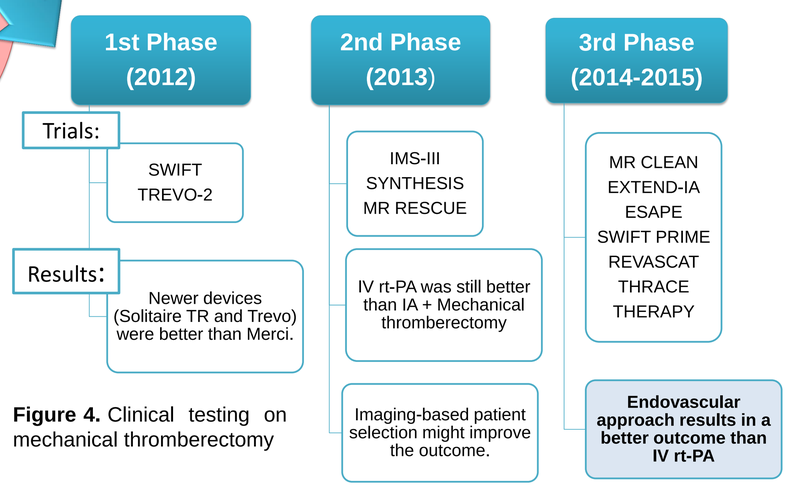

Figure 4. Clinical testing on mechanical thromberectomy

Research: New Approaches

Reperfusion Complication: Oxidative Stress

Early reperfusion can also result in a noxious increment of the oxidative stress. **Uric acid (UA),** an endogenous antioxidant, in combination with rt-PA attenuates middle cerebral artery (MCA) hypertrophy in rat models.[4]

URICO-ICTUS trial[5] tested the combination therapy in 500 patients suffering from AIS within 10 Spanish Stroke Centres finding no significative improvement (P = 0.09).

Sub-group re-analysis[6] → positive findings:

1. Pre-treatment hyperglycaemia
2. Early vessel recanalization (in moderate strokes)
3. Women

As a result of this positive outcome, a new trial is being planned: **UPRIGHT**[6].

Restorative therapies:

Enhancement of growth factors (e.g. GAP-43, MARCKS, CAP23, and BDNF).
Blockade of negative factors (e.g. Nogo-A, chondroitin sulphate, and ephrin A5).

In order to **generate new neurons (**lateral ventricle and dentate gyrus) which would migrate to the ischemic area.[7]

Antidepressants have shown a positive indirect effect e.g. Fluoxetine (Prozac) at the FLAME study.

Upregulation of Fibrinogenolysis

Fibrinogenolysis **(Figure 6)** can increase its catalytic efficiency with the activation of the **AnnexinA2-plasminogen-tPA complex**. Administration of recombinant A2 allows to lower the rt-PA dose, preventinig HT.[8]

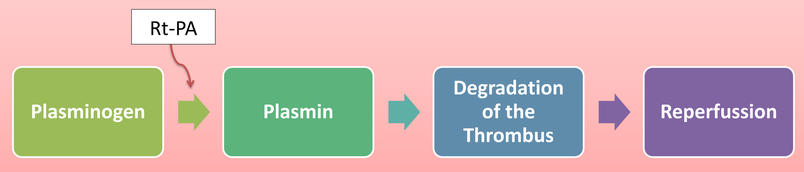

Figure 6. Fibrinogenolysis and the action of rt-PA

Imaging-based Patient Selection

Characterizing the **Ischemic Penumbra (Figure 7)**, the region where the reperfusion efforts focus, with new **penumbral imaging devices**.[9]

Positively tested in three trials:
DEFUSE, EPITHET and DEFUSE-2.

DEFUSE-3 is being conducted at the moment by Stanford University (USA).

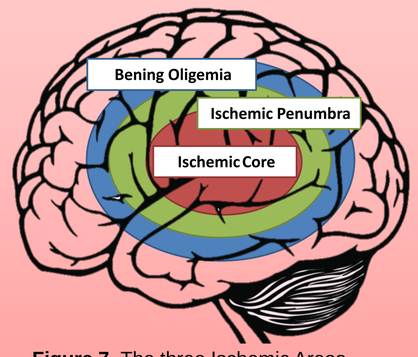

Figure 7. The three Ischemic Areas

Prevention of Haemorrhagic Transformation (HT)

This spectrum of hemorrhages within the area the area of the stroke might be produced by the reperfusion process performed by rt-PA .

Approach: **NEUROPROTECTIVE AGENTS**[10]

- **Inhibitors of MMP-2 and MMP-9:** these matrix metallopeptidases are up-regulated.
- **Deferoxamine (DFX):** promising chelating agent produced by *S. pilosus*.
- **Estrogen:** reduces brain swelling and edema.
- **Cilostazol (Pletal):** quinolone-derivate with protective effect over endothelium.
- **Glybyride (Glibenclamide):** DMII medication which inhibits sulfonylurea receptors e.g. SUR1 which is up-rergulated after ischemia.

Conclusions:

- The pharmacological approach of IS has reached a point where rt-PA, cannot be object of further improvement.
- The future of this treatment is the combination of rt-PA with either, other compounds or mechanical devices.
- Mechanical thromberectomy is already included hospitalization and treatment protocols, displaying great results.
- Neuroprotective therapies, e.g. Uric Acid, are still under trial but showing promising outcome.

References:

1.Krishnamurthi R V et al. Lancet Glob Heal. 2013 Nov; 1(5):e259–81.
2.Balasubramaian A et al. J Stroke. 2015;17(2):127–37.
3. International Neuro Products | Flow Restoration | SolitaireTM FR Revascularization Device | Covidien
4.Amaro S et al. Expert Rev Cardiovasc Ther. 2016;14(4):407–9.
5.Chamorro A et al. Lancet Neurol 2014;13:453–460.
6.Llull L et al. Curr Neurol Neurosci Rep. 2016;16(1):1–11.
7.Adams H & Nudo R. Ann Neurol. 2008;141(4):520–9.
8.Kim J & Hajjar KA. Front Biosci. 2002 Feb 1;7:d341–8.
9.Manning N et al. Stroke. 2014;45(2):640–4.
10.Jiang Y et al. Front Cell Neurosci. 2015;9(10):397.

Treball de Fi de Grau
Facultat de Biociències 2015-2016