USPIO-enhanced MRI for monitoring neuroinflammation: How many irons in the fire?

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Declaration of Conflict of Interest or Relationship

Speaker Name: Marlène Wiart

I have the following conflict of interest to disclose with regard to the subject matter of this presentation:

✓ **Company name**: Guerbet

**Type of relationship**: Research grants and stipends (Ferumoxtran-10)

✓ **Company name**: AMAG

**Type of relationship**: Research contract (Ferumoxytol)
Brain inflammation is a hallmark of many neurological diseases

Chronic diseases
- Multiple sclerosis
- Alzheimer’s disease
- Intracranial aneurysms

Acute diseases
- Traumatic brain injury
- Stroke
- Migraine
Microglia/Macrophages (M/M) represent a therapeutic target in neuroinflammatory diseases

Adapted from Huang YC et al. Acta Pharmacologica Sinica 2013
May M/M serve as MRI biomarkers of brain inflammation?

Principle of USPIO-enhanced MRI

- Pathophysiology
- Diagnosis / Prognosis
- Patient stratification
- Treatment monitoring

Intravenous injection of magnetic nanoparticles

24h-48h

In vivo phagocytosis of magnetic nanoparticles by macrophages

Cell labeling

☑️ Pathophysiology
☑️ Diagnosis / Prognosis
☑️ Patient stratification
☑️ Treatment monitoring
Ultrasmall superparamagnetic particles of iron oxide (USPIO)

• **Ferumoxtran-10:**
  ‘Historical’ USPIOs, now stopped
• **Ferumoxytol:**
  Currently the only FDA-approved USPIO BUT ‘off-label’ use for radiology

**Effect on T1, T2 & T2* relaxivities**

**Pharmacokinetic**

- Ferumoxytol, high molecular weight, plasma half-life: 14–21 h

**Clinical applications**

- Macrophage phagocytosis
  - Toth and others, Kidney Int, 2017
USPIO-enhanced MRI

Proof-of-Concept in a mouse model of ischemic stroke

USPIOs are taken up by macrophages in vivo after ischemic stroke

USPIOs internalization may be monitored by MRI

Stroke (pMCAO) → i.v. USPIO injection → MRI → Sacrifice

T1-weighted images, gradient-echo imaging


Hypothesis for USPIO-enhanced MRI working mechanisms in the pMCAO model of ischemic stroke

1. M/M activation
2. i.v. injection of USPIOs
3. USPIOs leakage in the brain through damaged barriers (BBB and/or BCSFB)
4. In situ phagocytosis by M/M
5. 24h-48h post-injection most USPIOs have been phagocytozed

Seeing is believing...

Evidence of nanoparticle (NP) phagocytosis from intravital 2-γ μscopy in ischemic stroke

Pre-contrast

Post-contrast

Signal void due to magnetic NPs

% of cells with internalized nanoparticle extralesional area

% of cells with internalized nanoparticle lesional area

pMCAO

CX3CR1-GFP

NanoGd / CX3CR1-GFP colocalization

48h

Hubert V, Wiart M et al, in prep
Can USPIO-enhanced MRI be used for treatment monitoring?

Pre-clinical neuroimaging study: Proof-of-Concept

Can USPIO-enhanced MRI be used for treatment monitoring? Pre-clinical neuroimaging study: Example of application

Administration of M2-polarized macrophages i.v.

Clinical applications of USPIO-enhanced MRI in neurology

Seminal works

Ischemic stroke

Nighoghossian N, Wiart M et al, Stroke 2007

Multiple Sclerosis

Tourdias T et al, Radiology 2012
Can USPIO-enhanced MRI be used for treatment monitoring?
Clinical neuroimaging study (1/2)

Patients with intracranial aneurysms

Adapted from Hasan D et al, J Am Heart Assoc 2013
Can USPIO-enhanced MRI be used for treatment monitoring? 
Clinical neuroimaging study (2/2)

Patients with migraine attack

Mouse model of migraine attack

Khan S et al, Cephalgia 2019
Can USPIO-enhanced MRI be used to detect neuroinflammation w/o USPIOs accumulating in the brain parenchyma?

- Choroid plexus are “gates to the brain” Schwartz et al, Nat Rev Immununol 2013
- ChPs are involved in the early physiopathology of neuroinflammatory disorders
  - multiple sclerosis, Alzheimer’s disease, stroke, SIRS ...
USPIO-enhanced MRI of the choroid plexus is an early marker of neuroinflammation

Mouse model of neuroinflammation (LPS i.p.)

Hubert V, Wiart M et al, Scientific Reports 2019
Take home messages

• Microglia/Macrophages may serve as imaging biomarkers of neuroinflammation thanks to USPIO-enhanced MRI

• Some USPIOs may be used in patients (although ‘off-label’): USPIO-enhanced MRI has already been used for investigating a range of neurological diseases in the clinical field

• USPIO-enhanced MRI has the potential to monitor the effects of drug treatment in neurological diseases
  → But difficulty to quantify the MR signal
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