Imaging Applications of Ferumoxytol for MRI: Focusing on the Vasculature and Inflammation

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Disclosure

OHSU, Portland Veterans Affairs Medical Center (PVAMC) and the Department of Veterans Affairs have a significant financial interest in Fennec, a company that may have a commercial interest in the results of this research and technology. Dr. Neuwelt, inventor of technology licensed to Fennec, has divested himself of all potential earnings. These potential conflicts of interest were reviewed and managed by the OHSU Integrity Program Oversight Council and the OHSU and PVAMC Conflict of Interest in Research Committees.

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• Gadolinium may deposit in the dentate nucleus and globus pallidus
• New alternative contrast agents should be tested
What is Ferumoxytol?

- FDA approved for iron replacement
- Used off label for MRI
- Safe in patients with impaired renal function

Overview

- What is ferumoxytol?
- Imaging of inflammation
  - CNS
  - Outside the CNS
- Imaging of the vasculature
  - CNS
  - T2*
  - Steady state cerebral blood volume maps
- Outside the CNS
- Is it safe?
- Summary

Ferumoxytol biological time course

- Ferumoxytol in the blood pool
- Ferumoxytol inside phagocytic cells
- Iron from ferumoxytol incorporated in body's iron stores
Ferumoxytol (red) is in the same location as macrophages and astrocytes.

Ferumoxytol is a GBCA with a molecular size of 1-30 nm, a plasma half-life of 0.2 hours to 15 hours, and locations in brain parenchyma and blood pool. It is eliminated via the kidney and reticuloendothelial system.

Gadolinium vs Ferumoxytol:
- **GBCA**
  - Molecular size: 1 nm
  - Plasma half-life: 0.2 hour
  - Location: brain parenchyma
  - Elimination: kidney
- **Ferumoxytol**
  - Molecular size: 30 nm
  - Plasma half-life: 15 hours
  - Location: extra- and intracellular, blood pool to brain parenchyma, reticuloendothelial system

Gadolinium has a dynamic phase within 1 hour and a delayed phase beyond 24 hours, while Ferumoxytol has extracellular and intravascular phases.
Possibilities with Ferumoxylol

Vascular imaging

Perfusion map
T2* Steady state map
Inflammation
T2 T1

Pre-contrast

Dynamic

Blood pool

Delayed phase

Injection 24h time

Imaging vasculature
CNS
T2*

Imaging vasculature- blood pool phase

Normal vasculature

Gd-T1  T2*  Fe T1  T2*
Fe 1 mg/kg  Fe 3 mg/kg  Fe 7 mg/kg

Imaging vasculature- blood pool phasec

Abnormal vessels in tumors

Pre-T1  Gd-T1  Fe  T2*
Fe 1 mg/kg  Gd  T1  Fe  7 mg/kg
**Imaging vasculature - blood pool phase**

- T1 Gd
- T2* no contrast
- T2* w + 3mg/kg ferumoxytol

**Imaging vasculature - blood pool phase**

- Pre-T2*
- Fe-T2* 1 mg/kg
- Fe-T2* 3 mg/kg
- Fe-T2* 7 mg/kg

**Imaging vasculature - blood pool phase**

- Residual tumor around surgical cavity
- Optimization
  - Dose
  - Sequence

- Pre 1 mg/kg
- 3 mg/kg
- 7 mg/kg
- SWI
- mFFE
Prior to ferumoxytol

After ferumoxytol

Arteriovenous malformation in 7 year-old patient

Ning P et al. Magnetic Resonance Imaging
Imaging vasculature
CNS
Steady state blood volume imaging

Dynamic vs. Steady State CBV

Dynamic
• TEMPORAL > spatial resolution

Steady state
• very high spatial resolution

Steady state CBV is easily acquired with ferumoxytol

Calculation of steady state blood volume maps

IV. injection of ferumoxytol
ΔR2* map calculation after co-registration
3D T2* image unenhanced
3D T2* image post ferumoxytol
Steady State CBV map

Evolution of blood volume mapping 2013

Ferumoxytol
Control
CBV map (2005)
CBV map (2009)
Steady State CBV map (2013)
Advantages:
• high resolution
• 3D
• lack of echo spacing distortion
• possibly quantitative – remains intravascular
Dynamic vs. Steady State CBV

DSC: Matrix 64 x 64 gadoteridol
SWI: Matrix 300 x 450 ferumoxytol

>100 x more voxels

Accurate overlay with T1w scans
superior targeting of malignant area

Glioblastoma follow up
Pre surgery

Glioblastoma follow up
Post surgery, before CRT
Glioblastoma follow up
1 month post CRT

Malignant primary brain tumor (anaplastic astrocytoma, grade 3)

No hotspot

Dose

Sequence

Optimization

Imaging vasculature
non- CNS

High-resolution steady state CBV map - Clinical advantages
Searching for tumor hotspot

mFFE

SWI

3 mg/kg

1 mg/kg

7 mg/kg
**First pass vs. steady state MR Angiography and Venography**

**First pass MR angiography**
- Limited by breath held duration
- Motion artifact
- Bolus needed

**Steady state MR angiography**
- Long imaging window
- Higher resolution
- Fewer motion artifacts
- Improved signal-to-noise ratio
- Highly reproducible
- No bolus needed

**MRA/MRV with Ferumoxylol**

**Aortic dissection**
- First pass
- Steady state
- False lumen

**Venous thrombosis**
- CT venography
  - Poorer vascular definition
- Steady state MRA/MRV

**Inferior vena cava occlusion**
- Detailed vascular anatomy
  - with steady state MRA/MRV

JP Finn et al. 2016
TAVR workup with ferumoxytol MRA/MRV

Endoleak workup

CTA
Steady state MRA with Ferumoxytol

Negative for endoleak
Endoleak present

MUSIC
Multiphase, Steady-State Imaging with Contrast Enhancement
4D imaging of the beating heart

First pass
CA-MRA vs.
4D MUSIC
With ferumoxytol

MUSIC
Vascular ring workup

Volume-rendered reconstruction from a single frame of a 4D MUSIC
Clinical utility of ferumoxytol MRA and MRV

**Vascular**
- Vascular integrity
- Vascular mapping for venous access
- Stenosis assessment
- Organ transplant workup
- Assess the status of renal transplant

**Cardiac**
- Congenital heart disease

**Imaging vasculature- Liver hemangioma**

**Imaging inflammation CNS**
62 year old female with suspected glioblastoma

Most malignant, most common primary brain tumor in adults, median survival ~15 months

Pathology confirmed glioblastoma

Standard treatment of glioblastoma

GBM patient

- Surgery
- Radiation + Temodar (CRT)
- Monthly Temodar

- MRI 6 weeks
- > 6 months

RANO criteria:
Progression if enhancing area increases >25%

**Treatment response assessment**
- True tumor progression - neovascularization
- Discontinue current treatment
- New chemotherapy
- Repeated surgery
- Symptomatic therapy (steroids, Avastin)
- Pseudoprogression (10-30%) - inflammation
- Continue current therapy (Temodar)
- Treat symptoms (steroids, Avastin)

- Correct differential diagnosis is very important!
- Perfusion MRI with Ferumoxytol enables correct diagnosis

**Diagnosis of pseudoprogression in GBM patients can predict better outcome**

**Imaging inflammation**
PCNSL

**Imaging inflammation – multiple sclerosis**
Mismatch between gadolinium- and USPIO-enhanced images
New biopsy from Fe uptake: Demyelinating disease

- Rheumatological diseases
- Acute and chronic inflammatory kidney disease
- Diabetic foot, osteomyelitis
- Crohn’s disease activity

Inflammation is visible with ferumoxytol

A Neuwelt et al. JMRI, 2016
Pancreatic inflammation

Gaglie et al. 2015

Increased pancreatic nanoparticle accumulation in patients with Type-1 diabetes

Lymph node imaging with ferumoxytol

Hamilton et al.

Imaging inflammation - hepatitis

Healthy control  NASH

Ferumoxytol

Imaging inflammation - cardiovascular

Delayed phase- T1 and T2 enhancement

T1 enhancement
- Plaque analysis
- Vessel wall visualization
- Infectious disease follow up

T2 enhancement
- Myocardial infarction
Imaging inflammation with ferumoxytol
other possibilities

• Mononuclear phagocytic system dysfunction measurements in liver
• Graft dysfunction and rejection after transplantation

Prolonged signal in spleen and liver after ferumoxytol

Is it safe?
**How to administer ferumoxytol?**

**IV bolus or slow injection?**
- Prior label allowed bolus injection of 510mg within 17 seconds (very rapid injection)

**Post marketing safety data**
- 1.3 million administrations total
- 99 severe hypersensitivity reactions (0.008%)
- 18 of which were fatal (0.0014%)  

**Boxed warning and label changes in March 2015**

The FDA recommends slow infusion of 510mg ferumoxytol (diluted in 50-200 mL) over 15 minutes when used for iron replacement.

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**Safety data of Ferumoxytol at OHSU in CNS imaging**

- 671 ferumoxytol infusions in 331 patients
  - 4mg/kg or 510mg total dose
  - All bolus injections, 1:1 diluted, 3mL/s
  - No severe hypersensitivity reactions within 1 day
  - Non-severe reactions associated with ferumoxytol:
    - Hypertension 2.38%
    - Nausea 1.24%
    - Headache 1.04%
    - Diarrhea 0.85%
    - Back Pain 0.73%
    - Vomiting 0.60%

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**Ferumoxytol and Cancer Publications 1981 – 2016**

From a PubMed search "ferumoxytol" and "cancer"
### Summary

**Potential clinical value of ferumoxytol in brain MRI**
- Alternative to gadolinium
  - For patients with kidney disease
  - If gadolinium deposition is a concern
- Supplements gadolinium
  - To answer specific questions
    - Neuroinflammation
- Unique intravascular applications
  - Abnormal vascularity
  - High resolution blood volume maps

### Take home message

Gadolinium enhanced brain MRI is standard of care, and additional ferumoxytol may help to answer specific questions, by improved assessment of vasculature and inflammation.
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Thank you for your attention!