Macrophage Imaging Within Human Cerebral Aneurysms Wall Using Ferumoxytol-Enhanced MRI: A Pilot Study


Objective—Macrophages play a critical role in cerebral aneurysm formation and rupture. The purpose of this study is to demonstrate the feasibility and optimal parameters of imaging macrophages within human cerebral aneurysm wall using ferumoxytol-enhanced MRI.

Methods and Results—Nineteen unruptured aneurysms in 11 patients were imaged using T2*-GE–MRI sequence. Two protocols were used. Protocol A was an infusion of 2.5 mg/kg of ferumoxytol and imaging at day 0 and 1. Protocol B was an infusion of 5 mg/kg of ferumoxytol and imaging at day 0 and 3. All images were reviewed independently by 2 neuroradiologists to assess for ferumoxytol-associated loss of MRI signal intensity within aneurysm wall. Aneurysm tissue was harvested for histological analysis. Fifty percent (5/10) of aneurysms in protocol A showed ferumoxytol-associated signal changes in aneurysm walls compared to 78% (7/9) of aneurysms in protocol B. Aneurysm tissue harvested from patients infused with ferumoxytol stained positive for both CD68+, demonstrating macrophage infiltration, and Prussian blue, demonstrating uptake of iron particles. Tissue harvested from controls stained positive for CD68 but not Prussian blue.

Conclusion—Imaging with T2*-GE–MRI at 72 hours postinfusion of 5 mg/kg of ferumoxytol establishes a valid and useful approximation of optimal dose and timing parameters for macrophages imaging within aneurysm wall. Further studies are needed to correlate these imaging findings with risk of intracranial aneurysm rupture. (Arterioscler Thromb Vasc Biol. 2012;32:1032-1038.)

Key Words: aneurysms • macrophages • magnetic resonance imaging • inflammation • ferumoxytol

Inflammation is increasingly being recognizing as contributing to the underlying pathophysiology of intracranial aneurysms.1 Both histopathologic evidence from human studies of aneurysm tissue2-4 and findings from animal models of cerebral aneurysms5,6 have lent support to the concept that inflammation is critical in the pathway of intracranial aneurysm formation and progression. There is evidence for macrophage infiltration in intracranial aneurysms,3,4 with associated increased activity of matrix metalloproteinases (MCP-2 and -9) leading to degradation of the extracellular matrix and weakening of the aneurysm wall.5,7 Although increased inflammation is hypothesized to contribute to progression toward rupture, there is currently no noninvasive means established to detect inflammation in intracranial aneurysms.

Ferumoxytol (AMAG Pharmaceuticals, Lexington, MA), an iron oxide nanoparticle coated by a carbohydrate shell, is a member of the class of nanoparticles known as ultrasmall superparamagnetic particles of iron oxide (USPIOs). The drug was developed as a treatment for iron deficiency anemia in patients with chronic renal failure and was approved by the FDA in 2009.8,9 However, it is gaining recognition for its utility in MRI and is increasingly being used in MRI studies both for its prolonged intravascular imaging characteristics as well as its utility as an inflammatory marker when imaged in a delayed fashion (as it is cleared by reticuloendothelial system macrophages).10-11 Ferumoxytol appears hypointense on T2*GE sequences and can appear hyperintense on T1 pulse-gated sequences. The drug can be visualized intravascularly for up to 72 hours but begins to clear within 24 hours and can be visualized intracellularly (secondary to macrophage-uptake) within 24 hours. Prior studies have indicated that peak visualization occurs at 24 to 28 hours.11

Given the macrophage-selective properties of ferumoxytol and the increasing validation of MR imaging with USPIO as a method to detect pathological inflammation, we sought to

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assess ferumoxytol-enhanced MRI as a technique to demonstrate inflammation in unruptured intracranial aneurysms. We hypothesized that ferumoxytol-associated loss of signal intensity would be visualized in the walls of intracranial aneurysms, consistent with inflammatory cell infiltrate. To assess this hypothesis and to determine the optimal dose and timing parameters to image macrophages within human cerebral aneurysm wall using ferumoxytol-enhanced–MRI, we undertook a pilot study of MR imaging of intracranial aneurysms, using the ultrasmall superparamagnetic particle of iron oxide, ferumoxytol.

Methods

Study Population

Subjects with known unruptured, untreated intracranial aneurysm, presenting to the Neurosurgery service at the University of Iowa Hospitals and Clinics were prospectively enrolled in the study between January and September 2011. Patients with treated aneurysms (by coil embolization or surgical clipping) were excluded. Patients presenting with ruptured intracranial aneurysms were also excluded from the study to avoid interfering with timely treatment of ruptured aneurysms. Two patients with ruptured intracranial aneurysms were enrolled for tissue analysis alone and did not undergo the imaging protocol.

Adult patients (age ≥18 years) were considered eligible for the study—children were excluded. Pregnant women were excluded, as were persons with a history of allergy or hypersensitivity to iron or dextran or iron-poly saccharide preparations, patients requiring monitored anesthesia or IV sedation for MRI, patients with contraindication to MRI, patients with renal insufficiency, hepatic insufficiency or iron overload, and patients receiving combination antiretroviral therapy. The study protocol was approved by the University of Iowa Institutional Review Board and all enrolled patients gave written informed consent to participate. The study was funded by the University of Iowa Hospitals and Clinics Department of Neurosurgery.

Contrast Agent

Ferumoxytol was administered as a one-time dose to all patients enrolled in the study. Two study protocols were used. Patients enrolled in protocol A received a dose of 2.5 mg/kg at a dilution of 30 mg/mL. Patients in protocol B received a dose of 5 mg/kg at a dilution of 30 mg/mL. The safety data of the agent has been previously published,9,10 and the drug is commercially available as a treatment for iron-deficiency anemia. The off-label use of the drug in a research protocol was approved by the Institutional Review Boards at the University of Iowa and patients were monitored for adverse reactions to ferumoxytol infusion.

MRI Protocol

All MRI was completed on a Siemens 3T TIM Trio system. Patients completed a baseline MRI consisting of time-of-flight angiography and T2* GE sequences. The time-of-flight angiographic sequence was collected using a 3D multislab technique with the following parameters: TE = 3.6 ms, TR = 20 ms, field-of-view = 200 × 200 × 200 mm, matrix = 384 × 384 × 20, bandwidth = 165 Hz/pixel. Four slabs were collected with a 20% overlap. The T2* weighted sequence was collected using a 2D gradient-echo sequence with the following parameters: TE = 20 ms, TR = 500 ms, flip angle = 20 °, FOV = 220 × 220, matrix = 512 × 384, slice thickness/gap = 3.00/3.0 mm, bandwidth = 260 Hz/pixel. Protocol A involved imaging at 2 timepoints 24 hours apart. Protocol B involved two stages. Stage 1 involved imaging at 5 timepoints: preinfusion, immediately postinfusion, and 24, 72, and 120 hours postinfusion. This was modified to imaging at 3 timepoints for stage 2 of protocol B: preinfusion, immediately postinfusion, and 72 hours postinfusion.

MRI Analysis

Comparison of preinfusion, immediately postinfusion, and 24-, 72- and 120-hour postinfusion images was completed based on 2 different imaging protocols. A loss of signal intensity (from preinfusion to delayed postinfusion imaging) detected on T2* weighted sequences corresponding to extraluminal regions of the imaged lesions was considered a positive finding. Postinfusion images were coregistered to the baseline images using a rigid transformation and a mutual information similarity metric. Histogram matching was then performed between the 2 datasets before the baseline image was subtracted from the postinfusion image (ie, difference = postinfusion-baseline). The difference image allowed demonstration of a relative signal loss from baseline to postinfusion. Two neuroradiologists independently reviewed baseline, postinfusion, and difference images from all patients in a blinded fashion and rated change in loss of signal intensity (considered as consistent or inconsistent with uptake of ferumoxytol). The "percentage of agreement" and Kappa (κ) measurement of agreement were used to calculate interobserver agreement.

Aneurysm-Dome Tissue Analysis

Ten patients were selected for aneurysm tissue analysis to detect presence of macrophages and ferumoxytol nanoparticles. This included five patients with unruptured aneurysms, who received ferumoxytol infusion 24 to 72 hours prior to planned elective surgery; 2 patients with unruptured aneurysms who did not receive ferumoxytol; and 3 patients with (small, large, and giant) ruptured aneurysms who did not receive ferumoxytol. The patients with ruptured aneurysms did not undergo the imaging protocol. The histological tissue analysis included H&E stain, CD68, and Prussian blue stain.

Results

Eleven patients harboring a total of 19 lesions completed the imaging study and were included in the image analysis protocol. An additional 8 patients were enrolled in the imaging study but were excluded from final analysis: 6 patients were unable to complete the study secondary to severe anxiety or contraindication to MRI; an additional 2 patients completed the imaging protocol but were not included in imaging analysis because of significant motion artifact and poor image quality. No enrolled patients had adverse events related to ferumoxytol infusion. The Table summarizes patient demographics, aneurysm characteristics, and imaging findings. Figure 1 is a flow chart summarizing the 2 protocols used in this pilot study.

Of the aneurysm patients who completed the study, 5 patients harbored large or giant (≥13 mm) unruptured intracranial aneurysms. The second of these patients (subject 2) suffered aneurysm rupture approximately 12 hours following her baseline MRI and ferumoxytol injection. She was able to complete the study and thus her postinfusion images represented ruptured status. An additional 6 patients with smaller (<13 mm) aneurysms completed the study. A total of 10 patients underwent aneurysm tissue analysis: 5 patients, who received ferumoxytol infusion, completed the imaging protocol, and subsequently had their aneurysm tissue analyzed following elective microsurgical clipping; and 5 patients (3 with ruptured aneurysms and 2 with unruptured aneurysms) who served as controls and had their aneurysm tissue collected for analysis following microsurgical clipping.
Intracranial Aneurysm Imaging Findings

Nineteen aneurysms in 11 patients were imaged and analyzed. Two were giant aneurysms (≥25 mm), 4 were large aneurysms (13≤≤<25 mm) and 13 were smaller (≤13 mm). In imaging protocol A (imaging at baseline and 24 hours postinfusion of 2.5 mg/kg ferumoxytol), 6 patients with 10 aneurysms were imaged. In this group, both giant aneurysms (subjects 1 and 2) were noted to have definite large magnitude ferumoxytol-associated loss of signal intensity within the aneurysm wall. One large aneurysm (subject 3) was noted to have a moderate amount of ferumoxytol-associated loss of signal intensity within the aneurysm wall. Two small aneurysms (subjects 5 and 6) had moderate signal change. One smaller aneurysm (subject 3) was judged by 1 neuroradiologist to have large amount of uptake due to ferumoxytol signal within aneurysm/arterial lumen and by reviewer 2 to be unable to accurately assess due to ferumoxytol signal within aneurysm/arterial lumen.

**Table. Patient Demographics, Aneurysm Characteristics, and Imaging Findings**

<table>
<thead>
<tr>
<th>Pt No.</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Location*</th>
<th>Size (mm)</th>
<th>Protocol</th>
<th>Findings</th>
<th>Neuroradiologist Comments</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>75</td>
<td>F</td>
<td>R vertebral</td>
<td>14×15</td>
<td>A</td>
<td>++</td>
<td>Large amount of uptake</td>
<td>Confusion, transient amnesia</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>F</td>
<td>L ICA</td>
<td>35×30</td>
<td>A</td>
<td>++</td>
<td>Large amount of uptake</td>
<td>Sentinel headache, visual loss, later aneurysm rupture</td>
</tr>
<tr>
<td>3</td>
<td>76</td>
<td>F</td>
<td>fusiform vertebrobasilar</td>
<td>26×15</td>
<td>A</td>
<td>++</td>
<td>Moderate amount of uptake</td>
<td>Headache, nausea</td>
</tr>
<tr>
<td>4</td>
<td>56</td>
<td>M</td>
<td>R MCA</td>
<td>7×8</td>
<td>A</td>
<td>–</td>
<td>No uptake</td>
<td>R facial pain</td>
</tr>
<tr>
<td>5</td>
<td>82</td>
<td>F</td>
<td>R Pcomm</td>
<td>6×4</td>
<td>A</td>
<td>++</td>
<td>Moderate amount of uptake</td>
<td>R arm and leg pain</td>
</tr>
<tr>
<td>6</td>
<td>52</td>
<td>F</td>
<td>L MCA</td>
<td>12×9</td>
<td>A</td>
<td>++</td>
<td>Moderate amount of uptake</td>
<td>Numbness and tingling of L arm and leg</td>
</tr>
<tr>
<td>7</td>
<td>67</td>
<td>F</td>
<td>R MCA</td>
<td>6×5</td>
<td>B</td>
<td>++</td>
<td>Moderate amount of uptake</td>
<td>Tremor</td>
</tr>
<tr>
<td>8</td>
<td>77</td>
<td>F</td>
<td>Basilar tip</td>
<td>14×13</td>
<td>B</td>
<td>++</td>
<td>Large amount of uptake</td>
<td>Headache and visual changes</td>
</tr>
<tr>
<td>9</td>
<td>78</td>
<td>F</td>
<td>Basilar tip</td>
<td>18×14</td>
<td>B</td>
<td>++</td>
<td>Large amount of uptake</td>
<td>Headache and vertigo</td>
</tr>
<tr>
<td>10</td>
<td>68</td>
<td>M</td>
<td>L MCA</td>
<td>9×10</td>
<td>B</td>
<td>–</td>
<td>No uptake</td>
<td>No uptake</td>
</tr>
<tr>
<td>11</td>
<td>44</td>
<td>M</td>
<td>R MCA</td>
<td>10×10</td>
<td>B</td>
<td>–</td>
<td>No uptake</td>
<td>No symptoms, incidental finding</td>
</tr>
</tbody>
</table>

*R indicates right; L, left; ICA, internal carotid artery; Acomm, anterior communicating artery; Pcomm, posterior communicating artery; MCA, middle cerebral artery.

**Figure 1.** A flow chart illustrating the 2 protocols used for intracranial aneurysms.

**Figure 2.** Protocol A: Anterior communicating artery aneurysm. Reviewer 1 rated small amount of ferumoxytol-associated signal change in aneurysm wall, whereas reviewer 2 did not appreciate any uptake within the aneurysm wall (subject 3).
gist to have a definite small amount of ferumoxytol-associated loss of signal intensity within the aneurysm wall, whereas the second reviewing neuroradiologist felt that the aneurysm wall could not be adequately assessed due to confounding visualization of the contrast agent (ferumoxytol) within the arterial (and aneurysm) lumen (Figure 2). In the remaining 4 aneurysms (1 large, 3 smaller in subjects 3 and 4, respectively) no ferumoxytol-associated loss of signal intensity was appreciated (Figure 3). In protocol B, first stage (imaging at baseline, immediately postinfusion, 24-, 72- and 120-hour postinfusion of 5 mg/kg of ferumoxytol) 2 patients with 4 aneurysms were imaged. All of these aneurysms (1 large and 3 small) had well-defined ferumoxytol-associated loss of signal intensity within the aneurysm wall, more pronounced at 72 hours postinfusion than at 24 hours postinfusion. At 120 hours postinfusion the signal change was notably diminished. This led to modifying protocol B to a second stage: imaging at baseline, immediately postinfusion and 72 hours postinfusion. In this stage, 3 patients with a total of 5 aneurysms (1 large and 4 small) were imaged. Three aneurysms (1 large and 2 small) showed clear evidence of ferumoxytol-associated loss of signal intensity within the aneurysm wall at 72 hours postinfusion. Two small aneurysms in this group did not show uptake of ferumoxytol at 72 hours postinfusion.

Overall, of the 19 aneurysms reviewed by our 2 neuroradiologists, there was a lack of agreement for only 1 aneurysm. Using simply “the percentage of agreement” to calculate the interobserver agreement, then one would calculate that to be 95%. If we use Kappa (κ) measurement of agreement, then the interobserver calculated agreement will be 89%.

**Intracranial Aneurysm Tissue Analysis Findings**

Ten patients underwent aneurysm tissue analysis. Five were patients with unruptured aneurysms who received ferumoxytol infusion and completed the imaging protocol. CD68+ and Prussian blue stains were both positive in all 5 of these aneurysms. Although double staining was not technically feasible, colocalization was used to verify presence of iron particles within macrophages cytoplasm localized only to the adventitial layer of the aneurysm wall. No nanoparticles were seen in the extracellular matrix and/or outside the cells in the tissues analyzed. Also no particles were seen at the interface of the intra-aneurysmal blood and the inner surface of the aneurysm dome.

In the remaining 5 (control) patients who did not receive ferumoxytol nor undergo the imaging protocol (2 with unruptured aneurysms and 3 with ruptured aneurysms), CD68 was positive (indicating presence of macrophages) and Prussian blue stain was negative (indicating absence of iron particle, ferumoxytol) in all 5 aneurysms.

**Discussion**

USPIO-enhanced MRI allows for the detection of phagocytic activity of inflammatory cells such as macrophages. Several animal and human studies have shown USPIO to accumulate in atherosclerotic plaques in the abdominal aorta and internal carotid artery. This method provides investigators the ability to noninvasively assess the inflammatory status of atherosclerotic lesions and objectively measure the effects of anti-inflammatory pharmacological interventions on these lesions.12–18

Although inflammation is increasingly being understood to be a key component to the pathophysiology of intracranial aneurysms, there is no current noninvasive method to demonstrate this feature. To our knowledge, this is the first report to demonstrate macrophage imaging within cerebral aneurysm wall using ferumoxytol-enhanced MRI.

**Intracranial Aneurysm Findings: Comparison Between the 2 Different Protocols**

In protocol A where patients received 2.5 mg/kg of ferumoxytol and were imaged at baseline and 24 hours postinfusion, ferumoxytol-associated loss of signal intensity was detected in 50% (5 out of 10) of patients harboring aneurysms (3 large/giant and 2 small). In the protocol B with a higher dose of ferumoxytol...
(5 mg/kg) and delayed imaging (stage 1: baseline, 24, 72, and 120 hours postinfusion; stage 2: baseline, and 72 hours postinfusion), we were able to detect ferumoxytol-associated loss of signal intensity at 72 hours postinfusion in 7 out of 9 (78%) aneurysms (2 large and 5 small). This may be related to use of an increased dose of ferumoxytol. However, the finding may also be in part due to the fact that ferumoxytol is a blood-pooling agent and with delayed imaging time, more macrophages are able to phagocytose these nanoparticles, facilitating detection by MRI. In this subset of 9 aneurysms (protocol B), imaging at 72 hours postinfusion revealed the maximal signal changes corresponding to uptake of the iron oxide nanoparticles by macrophages (Figure 4).

**Figure 5.** Representative histological sections from 4 aneurysm walls. 

- **A**, Unruptured right MCA aneurysm post ferumoxytol infusion. 
  - A1, H&E stain (×100); 
  - A2, Prussian blue stain showing iron oxide nanoparticles seen mostly in the adventitia; 
  - A3, higher magnification of Prussian blue stain demonstrating iron oxide nanoparticles; 
  - A4, CD68 showing positive staining for macrophages. 

- **B**, Unruptured right MCA aneurysm post ferumoxytol infusion. 
  - B1, CD68 showing positive staining for macrophages; 
  - B2, Prussian blue stain demonstrating iron oxide nanoparticles. 

- **C**, Unruptured right pericallosal artery aneurysm post ferumoxytol infusion. 
  - C1, CD68 showing positive staining for macrophages; 
  - C2, Prussian blue stain demonstrating iron oxide nanoparticles. 

- **D**, Ruptured left MCA giant aneurysm without ferumoxytol. 
  - D1, H&E stain (×100); 
  - D2, CD68 showing macrophage-rich layers of aneurysm wall, specifically the adventitia; 
  - D3, Prussian blue staining for iron particles is negative; 
  - D4, CD68 and Prussian blue double stain demonstrates evidence of macrophage infiltration without evidence of iron particles. 

**Validation of Ferumoxytol Uptake by Histology in Intra-Cerebral Aneurysms**

The immunohistological findings in the 5 patients who received ferumoxytol were consistent with the results of T2* MRI: colocalization of positive stain for Prussian blue (positive for iron particles) and CD68 (positive for macrophages)
(Figure 5). These nanoparticles were localized in the cytoplasm of macrophages found only in the adventitial layer of the aneurysm wall negating the hypothesis that these nanoparticles could be found in the extracellular matrix of the aneurysm wall. Also the findings of negative staining of Prussian blue and positive staining of CD68+ in the control group (did not receive ferumoxytol) emphasize the fact that these nanoparticles are not inherently found in the aneurysm wall due for an example to hemosiderin secondary to microbleeding.

Also of interest, both of the aneurysms that did not demonstrate ferumoxytol-associated loss of signal intensity with protocol B imaging at 72 hours were noted to have significant calcification detected on CT and confirmed at surgery in the surgically treated patient.

Comparison of Characteristics of Patients and Aneurysms With Versus Without Ferumoxytol Uptake
Although it was noted that the 72 hour postinfusion imaging timepoint best demonstrated ferumoxytol-associated loss of signal intensity, similar changes were clearly noted in some patients as early as 24 hours postinfusion. Four patients with observed signal change at 24 hours postinfusion were noted to be symptomatic from their aneurysm. This finding may be consistent with a hypothesis that inflammatory processes such as macrophage infiltration may be more prevalent in biologically active or higher risk aneurysms. Of the 5 patients noted to have significant ferumoxytol-associated imaging changes at 24 hours postinfusion, 1 patient presented with symptoms of sentinel headache and mass effect resulting in visual loss and had subsequent aneurysm rupture (following enrollment and completion of baseline MRI). Another patient presented with headache and nausea and was noted to have marked enlargement on serial imaging of the (presumed) symptomatic vertebralbasilar aneurysm (it was felt that her several other aneurysms were likely asymptomatic). Following completion of the study and an unsuccessful attempt at endovascular treatment, the patient suffered a fatal aneurysmal hemorrhage. A third patient with a large aneurysm and positive finding of ferumoxytol-associated loss of signal intensity also suffered a fatal aneurysmal hemorrhage following completion of the study. Although it is unclear from this small sample whether ferumoxytol-associated loss of signal intensity is associated with increased risk of aneurysm rupture, this is a question of interest for future studies.

Among the aneurysms in which a ferumoxytol-associated loss of signal intensity was not appreciated at an early stage (24-hour postinfusion imaging), several possible explanations are considered, including (1) susceptibility artifact related to surrounding bony anatomy obscuring the visualization of the aneurysm wall making assessment of ferumoxytol-associated signal change suboptimal; (2) suboptimal dose of ferumoxytol (2.5 versus 5 mg/kg); (3) suboptimal timing of imaging (24 hours postinfusion versus 72 hours postinfusion); and (4) less inflammatory activity suggestive of a possibly stable aneurysm. Calcification in the aneurysm wall is also postulated to affect imaging findings.

Future studies could test a hypothesis of whether ferumoxytol-associated loss of signal intensity on MRI has any relation to risk of aneurysm rupture. However, this study lacks the appropriate methodology and power to make such an assessment.

Limitations
Limitation of this study is the relatively small number of patients enrolled. Despite this limitation sufficient data were obtained to reveal consistent patterns of labeling and demonstrate the potential clinical utility of this method. Another limitation to this technique (USPIO MRI) is the need to perform imaging 72 hours after injection of the contrast agent. Also at this point, quantification of USPIO uptake in aneurysm wall is difficult.

Future Investigations
Further studies are needed to correlate these imaging findings with risk of intracranial aneurysm rupture. This technique could be a useful tool to study the link between inflammation and vascular lesions, such as aneurysm growth and/or rupture.

Conclusion
This pilot, proof-of-principle study establishes that infusion dosing of 5 mg/kg of ferumoxytol and imaging at 72 hours postinjection using T2* GE MRI demonstrates an optimal dose and timing parameters for macrophages imaging within aneurysm wall.

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Disclosures
None.

References


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