USPIO-Enhanced MRI Neuroimaging: A Review

Maria Gkagkanasiou, Agapi Ploussi, Maria Gazouli, Efstatios P. Efstatopoulos

From the Department of Computed Tomography, 251 HAF and VA Hospital (MG); Department of Radiology, Medical School, National and Kapodistrian University of Athens (AP, EPE); and Department of Basic Medical Science, Laboratory of Biology, School of Medicine, University of Athens, Athens, Greece (MG).

ABSTRACT

MRI is a powerful tool for the diagnosis and management for a variety of central nervous system (CNS) diseases. Ultrasmall superparamagnetic iron oxide (USPIO) nanoparticles are a novel category of MRI contrast agents that seem to play a crucial role in the imaging of CNS. Due to their physical properties, USPIOs act as blood pool agents. USPIOs improve visualization of tumor vasculature and relative cerebral blood volume measurements, tumor-associated inflammation, inflammatory-immune mediated disorders, stroke and vascular malformations. Ferumoxytol, a new type of USPIO agent, appears to have ideal characteristics for the imaging of CNS. The last few years, ferumoxytol has been successfully used to image CNS neoplasms, CNS inflammations and cerebral malformations offering useful information on cellular and molecular level. In addition, ferumoxytol studies focused on the pathophysiology of other CNS disorders like multiple sclerosis and epilepsy are already in progress. Aim of this review article is to provide the potential role of USPIO-enhanced MRI and the latest clinical applications of ferumoxytol agent in CNS imaging.

Keywords: Ultrasmall superparamagnetic iron oxide, ferumoxytol, central nervous system, MRI.

Acceptance: Received September 11, 2015. Accepted for publication October 23, 2015.

Correspondence: Address correspondence to Efstatios P. Efstatopoulos, PhD, 1 Rimini Str, 124 62 Haidari, Athens, Greece. E-mail: stathise@med.uoa.gr.

Disclosures: None.

DOI: 10.1111/jon.12318

Introduction

Central nervous system (CNS) disorders are a group of diseases including neoplasms, stroke, infections, structural and functional disorders, degeneration, multiple sclerosis (MS) as well traumatic brain injuries. Accurate imaging of CNS is of significant importance for both the diagnosis and management of neurological diseases.

Magnetic resonance imaging (MRI) is a great diagnostic tool that guides treatment decision for patients with CNS disorders. Exogenous contrast agents are used in more than 70% of CNS MRI studies, as they increase lesion conspicuity and improve visualization of blood vessels.

The current gadolinium-based contrast agents (GBCA) have limitations in medical imaging including: (i) the inconsistent and unreliable measurement of relative cerebral blood volume (rCBV) due to increased permeability across the endothelial barrier surrounding brain,1 (ii) the decreased half-life after intravenous administration,2 (iii) the risk of nephrogenic systemic fibrosis in patients with impaired kidney function,3 and (iv) the recently shown accumulation in basal ganglia, thalamus, pons and dentate nucleus.4

Recent advances in the use of iron oxide nanoparticles5–7 have contributed to improving the diagnostic efficacy of MR in the imaging of CNS. Ultrasmall superparamagnetic iron oxide (USPIO) agents provide significant advantages compared to conventional GBCA as they have a prolonged blood circulation time, they enable a direct information on the cellular infiltration associated with inflammations and they can be used safely even from patients with chronic kidney diseases.3,8

USPIO agents such as ferumoxytol are taken up by phagocytic cells (circulating monocytes/macrophages), pass through the blood brain barrier (BBB) and accumulate in the brain parenchyma, where an early phase of microglial activation, including gliosis and enzyme secretion is already in progress.9 Even though the FDA in a recent safety announcement made clear that ferumoxytol should only be administered diluted as an intravenous (IV) infusion over a minimum of 15 minutes,10 our research revealed several studies where USPIO agents were given as a bolus for the purposes of first pass perfusion imaging.11,12 At late time points, USPIOs accretion is obvious in areas with or without BBB dysfunction that may be basically related to inflammation from any reason. The accumulation of USPIO-labeled cells within and around CNS disorders, such as tumors, can be depicted on MRI images and it is evaluated by the differences in signal intensity between pre- and post-USPIO images.

The aim of this review study is to provide the potential role of USPIO-enhanced MRI and the latest clinical applications of ferumoxytol agent in CNS imaging. In addition, CNS studies using similar to ferumoxytol USPIO agents are briefly discussed.

The Use of Ferumoxytol as Contrast Agent in MRI

Characteristics

Ferumoxytol is an USPIO nanoparticle approved by Food and Drug Administration (FDA) in 2009 for the treatment of iron deficiency anemia. The brand name of the drug is RIENSO in Europe and FERAHEME in United States. Recently, ferumoxytol is used off-label as contrast agent for MR imaging in a wide range of clinical applications including oncology, cardiovascular and CNS imaging. In March 2015, FDA strengthened the existing instructions for ferumoxytol administration...
warning that the use of ferumoxytol may cause severe hypersensitivity reactions like anaphylactic shock.\textsuperscript{10,13} Initial symptoms may include hypotension, syncope, unresponsiveness and cardiac arrest. According to the new safety guidelines, FDA recommends:\textsuperscript{10}

- against use of Feraheme in patients with history of allergic reactions to any intravenous (IV) iron replacement product;
- only diluted IV infusion of Feraheme over at least 15 minutes. Feraheme should not be administered as an undiluted IV injection;
- closely monitor patients for severe allergic reactions, including monitoring blood pressure and pulse during Feraheme administration and for at least 30 minutes after each injection;
- carefully consideration of the potential risks and benefits of Feraheme administration in elderly patients with multiple or serious medical conditions, as these patients may experience more severe reactions;
- carefully consideration of the potential risks and benefits of Feraheme administration in patients with a history of multiple drug allergies. Patients with multiple drug allergies may also be at higher risk.

The carbohydrate-coated ferumoxytol has a hydrodynamic diameter of 30 nm and a long blood half-life of approximately 14 hours. It is considered a negative contrast agent due to its strong T2 and T2* effects. In addition, ferumoxytol has intrinsic T1 shortening properties that can produce high signal result, using appropriate pulse sequences.\textsuperscript{14} Ferumoxytol, under monitoring, can be administered intravenously for first time pass dynamic perfusion in CNS imaging.\textsuperscript{11,12} At later time points (approximately 24 hours after infusion) ferumoxytol is located in areas of BBB dysfunction which are highly associated with inflammation or, like other USPIOs in areas with no or minimal BBB alterations, such as demyelinating lesions that do not show gadolinium enhancement.\textsuperscript{15-17} To our knowledge, ferumoxytol is the only available USPIO agent in the European market at the moment.

\
Mechanism of action

As it is known, GBCA are rapidly extravasate into the intercellular space in areas of BBB dysfunction\textsuperscript{1} and are eliminated from intravascular space via the renal system. In contrast, USPIOs cross the BBB through phagocytosis and trapped from inflammatory cells. A small percentage of nanoparticles pass the BBB and part of the extravagated nanoparticles is absorbed by phagocytic cells.\textsuperscript{18,19}

Concerning their magnetic properties, USPIOs cause a strong decrease of the T2 and T2* relaxation times which appear as dark areas on T2/T2*-weighted images. Therefore, USPIOs are mainly behaved as T2 or negative contrast agents. Nevertheless, since USPIOs have significant longitudinal relaxivities, can be also used as T1 contrast agents resulting in a hyperintensity on T1 images (bright areas).\textsuperscript{14} USPIOs show superior T1-enhancement at lower magnetic field strengths using standard T1-weighted sequences. A comparison between MRI scans of 1.5T and 3T using ferumoxytol in patients with CNS malignancies revealed that T1 Turbo Spin Echo (TSE) sequences at 1.5T strength resulted in greater changes in signal intensity compared with T1 TSE sequences at 3T.\textsuperscript{20,21}

In general, ferumoxytol studies for the imaging of CNS are based on two methods: (a) cerebral blood volume (CBV) measurements at early time points after ferumoxytol administration, and (b) iron levels measurement to detect abnormal iron uptake from vessel wall or brain parenchyma at 24-48 hours after ferumoxytol administration.\textsuperscript{7}

Due to its physiochemical characteristics (large particle size and long half-time), ferumoxytol remains in the blood circulation for a prolonged time.\textsuperscript{13} The blood pool characteristics of ferumoxytol provide an excellent window for cellular uptake before its excretion. It is clear that ferumoxytol combines all those characteristics that makes it an ideal agent for cerebral imaging and especially for the measurement of CBV. Measurements of CBV can start immediately after injection, when the dispersion of ferumoxytol reaches a stable state in the brain and a CBV brain map can be generated at very high resolution in just a few minutes.\textsuperscript{11,12}

Since ferumoxytol is mainly composed of iron, its uptake is closely related to the activity of macrophages and microglia with phagocytic properties,\textsuperscript{19,22} and therefore to the presence of inflammation in the brain. Thus, ferumoxytol is used to image the iron uptake in many neuroinflammatory diseases. This type of imaging needs to be conducted 24-48 hours after ferumoxytol injection to allow uptake by phagocytic cells.

Clinical Applications in CNS

Research strategy

For this review article, literature search was identified through PubMed database for publication from January 2000 to June 2015, limited on human studies. To improve the retrieval, cited references associated to the articles were also used. For our search we use the following keywords: “iron oxide nanoparticles as contrast agents and magnetic resonance imaging,” “(U)SPIO and MRI in CNS,” “ferumoxytol and CNS imaging.”

Results

The keyword search for using ferumoxytol-enhanced MRI in CNS imaging identified nine original articles (Table 1). The search indicated that ferumoxytol contrast agent has been used to image CNS neoplasms, CNS inflammations and cerebral aneurysms.

Tumor imaging

Tumor vascularity and the distribution of a significant number of activated cells seems to play the most important role in the contrast-enhancement imaging properties of CNS tumors.\textsuperscript{21} A large number of macrophages and activated microglia have

<table>
<thead>
<tr>
<th>Study</th>
<th>Brain Disorder</th>
<th>No of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuwelt et al\textsuperscript{20}</td>
<td>CNS neoplasms\textsuperscript{*}</td>
<td>12</td>
</tr>
<tr>
<td>Dosa et al\textsuperscript{24}</td>
<td>CNS neoplasms\textsuperscript{*}</td>
<td>26</td>
</tr>
<tr>
<td>Gahramanov et al\textsuperscript{11}</td>
<td>Glioblastoma multiforme</td>
<td>14</td>
</tr>
<tr>
<td>Farell et al\textsuperscript{25}</td>
<td>CNS lymphoma</td>
<td>12/20</td>
</tr>
<tr>
<td>Farell et al\textsuperscript{25}</td>
<td>CNS inflammatory diseases\textsuperscript{**}</td>
<td>8/20</td>
</tr>
<tr>
<td>Dosa et al\textsuperscript{29}</td>
<td>Vascular malformations</td>
<td>19</td>
</tr>
<tr>
<td>Hasan et al\textsuperscript{30}</td>
<td>Cerebral aneurysms</td>
<td>22</td>
</tr>
<tr>
<td>Hasan et al\textsuperscript{32}</td>
<td>Cerebral aneurysms</td>
<td>11</td>
</tr>
<tr>
<td>Hasan et al\textsuperscript{31}</td>
<td>Brain AVMs</td>
<td>4</td>
</tr>
</tbody>
</table>

\textsuperscript{*}Primary and secondary brain neoplasms.

\textsuperscript{**}MS, ADEM, PTLD, tumefactive demyelination, lymphoid infiltrate, chronic encephalitis.
been reported to be present within and around malignant brain tumors.\textsuperscript{22} Glioma characterization by MRI perfusion is one of the very promising applications of dynamic MRI.\textsuperscript{12} Early extravascular leakage of gadolinium contrast agents, results in erroneous estimation of relative cerebral blood volume (rCBV) and mid transfer time (MTT).\textsuperscript{1,23} and constitute a fundamental problem of current MR perfusion technique. Nevertheless, there are several correction methods to improve the accuracy of perfusion MR imaging such as preload dosing, double echo correction and baseline subtraction.\textsuperscript{1}

Neuwelt et al.,\textsuperscript{20} in a pilot study demonstrated that ferumoxytol, as an intravascular contrast agent in the “early phase,” can give accurate information about tumor perfusion. An intravascular contrast agent would be helpful in the determination of early tumor response after anti-angiogenetic therapy. The investigators also performed time of flight (TOF) angiography 15 minutes after ferumoxytol administration. The TOF angiography allowed visualization of smaller blood vessels and tumor vascularity while the phenomenon of “contamination,” caused by leakage into extravascular space was minimal compared to that, observed in TOF images after gadolinium administration. Although the results from delayed ferumoxytol enhancement T1-weighted images are preliminary, they can be used in future studies for the correlation between the effects of therapies and the ferumoxytol enhancement. Ferumoxytol may be an indicator of peritumoral accumulation of macrophages. The scientists observed that the area of ferumoxytol enhancement expanded gradually with time, but never beyond the area of increased T2-weighted signal.

Dosa et al.,\textsuperscript{24} in an intrapatient comparison of gadoteridol (gadolinium contrast agent) and ferumoxytol, showed that the 24-hour ferumoxytol enhancement covered a larger area compared to the 25-minute enhancement study. In some patients, the area extended beyond the border of the lesions delineated by gadoteridol on T1-weighted images that might reflect intracellular trapping of iron oxides by macrophages (Fig 1). The investigators also found a correlation between the intensity and morphology of the USPIO enhancement, and the tumor malignancy. This observation is based on the concept that high grade gliomas showed enhancement both within and around the tumor and particularly prominent around necrosis, whereas low grade gliomas and benign tumors, like meningiomas, showed minimal peritumoral signal intensity changes, or no enhancement. In the same study researchers verified that USPIOs are suitable for first pass and steady state measurements allowing precise quantification of perfusion studies, due to their low leakage rate (Fig 2).

The differentiation between true tumor progression and pseudoprogression is important for both diagnosis and treatment. Gahramanov et al\textsuperscript{11} compared rCBV measurement after GBCA and ferumoxytol injection using clinical course and anatomical MRI data. The study demonstrated that high-gadolinium rCBV most likely represents tumor recurrence, while pseudoprogression and actively growing tumors show low-gadolinium rCBVs. So, they suggested the use of a blood pool agent that does not leak significantly through BBB during dynamic susceptibility weighted contrast-enhanced MRI (DSC-MRI) data acquisition. In this perspective, ferumoxytol showed high rCBV values in true progression and low rCBV values in regression and proved to be superior to gadolinium. In combination with the GBCA enhancement, researchers proposed two groups of patients: the one group included patients with
increased GBCA enhancement and low ferumoxytol rCBV (pseudoprogression), while the second included patients with either high ferumoxytol rCBV only at the periphery of large areas of GBCA enhancement or decreased ferumoxytol rCBV after radiotherapy compared to pre radiotherapy values, but still elevated [Fig 3].

According to Farell et al, areas of USPIO-enhancement for T2-weighted scans, could be potential sites for biopsy additionally to conventional post contrast T1-weighted scans with GBCAs. The results of the study were also consistent with the fact that demyelinating or inflammatory lesions show low rCBV, whereas CNS lymphoma demonstrates elevated rCBV values. The latest does not permit reliable differentiation from high-grade glioma.

**Inflammatory-immune mediated disorders**

MS and acute disseminated encephalomyelitis (ADEM) are immune mediated disorders of CNS. Macrophages have been suggested to play a major role in axonal injury. There are several clinical trials in progress on whether ferumoxytol could become a sensitive and specific marker of active inflammation in MS.

As mentioned earlier, Farell et al demonstrated that ferumoxytol images show signal changes on T1 and T2 weighted sequences in demyelinating diseases and, in some patients, different enhancement patterns compared to GBCA-enhanced scans. These differences in mechanism of enhancement might discriminate patients with different degrees of inflammation that may have prognostic or therapeutic significance. Based on their preliminary results, researchers showed that rCBV values for primary CNS lymphoma (PCNSL) and lymphoproliferative disorders are much higher than rCBV values for tumefactive demyelinating lesions.

**Vascular malformations-cerebral aneurysms**

Vascular malformations of the brain and spinal cord are usually classified into four categories: capillary telangiectasias, cavernomas, developmental venous anomalies (DVAs) and arteriovenous malformations (AVMs). The presence of inflammatory cells, including lymphocytes and macrophages, is associated with AVMs formation, lesion progression and rupture. As the risk of intracranial aneurysms (IAs) and AVMs rupture is believed to be relevant to the accumulation of macrophages and other inflammatory cells and enzymes, a non-invasive method for the detection and quantification of inflammations is necessary.

In 2011, Dosa et al showed that ferumoxytol improves the detection of CNS VMs on susceptibility-weighted imaging (SWI) scans. It has become clear that the ferumoxytol induced susceptibility effects, shorten the transverse T2 and T2* relaxation times and cause low (dark) signal on the T2*-sensitive sequences, such as SWI. In the case of AVMs, SWI can only be used to delineate small lesions without hemorrhage. This is mainly due to their rapid blood flow. In this study, the researchers found superiority of ferumoxytol over gadoreridol in depiction of five VMs that were completely unnoticeable on the pre- and post- gadoreridol images. Additional tributary veins were revealed in all patients with DVAs. Although they had hypothesized that the 24-hour ferumoxytol scan would provide information about inflammatory cell component of VM in patients with DVAs and in case of spinal cord AVM, ferumoxytol was still in the intraluminal space at 24 hours. Moreover, no change in cavernomas, between the 25-minute images and the 24-hours images was observed. It was unclear for the researchers whether those findings indicate that there was ferumoxytol uptake at low concentrations, or that there were few macrophages to take up the USPIOs. The signal changes observed 24 hours after ferumoxytol injection and the absence of enhancement 25 minutes after injection in capillary telangiectasias was attributed to delayed wash in and washout kinetics of large molecular-weight ferumoxytol.

As it is known, inflammation is involved in the formation and rupture of IAs and AVMs. The natural history of these lesions remains uncertain making the decision to intervene or not a difficult and subjective task. Therefore, the need of using non-invasive tools to differentiate cerebrovascular lesions that are at high risk of rupture and require intervention, from “stable” lesions is growing.

In 2012, Hasan et al studied 22 patients with unruptured aneurysms 24 hours after infusion of ferumoxytol and carried out some important conclusions over instability and probability of rupture. According to the study, aneurysms show early signal changes (within 24 hours), late signal changes (at 72 hours) or no signal changes on T2* depending on the uptake of ferumoxytol by macrophages in their walls. The study suggests that aneurysms with early MRI signal changes on the
T2* gradient-echo (GRE), are at higher risk of rupture as compared with aneurysms with late or no signal changes. These changes are produced by increased uptake of nanoparticles by macrophages localized within aneurysm walls (active inflammatory process). The fact that inflammatory cells and molecules, such as COX-1 and COX-2, were found to be expressed higher in aneurysms with early signal changes and their expression was similar to ruptured aneurysms strengthen further this hypothesis. Aneurysms with early signal change, are unstable, with high risk of rupture, as all early-high-signal aneurysms in the study, that were managed conservatively, progressed to rupture in less than 6 months. The researchers also provided the evidence that inflammation may be one of the causal factors of cerebral aneurysms rupture in humans rather than a consequence of rupture.

The same group, revealed a study on the extent of macrophage infiltration in brain AVMs. Although the study faced several limitations, including the limited number of patients, the use of two different protocols and two different magnet strengths, the investigators showed that it can be possible to demonstrate USPIO-vascular wall localization in AVM nidus and discern it from persistent intravascular ferumoxytol nanoparticles if imaging is performed 5 days after injection (Fig 4). It is yet to be clarified if ferumoxytol uptake could be used as a prognostic factor for the risk of spontaneous rupture of the AVMs.

Hasan and colleagues sought to evaluate the effects of acetyl salicylic acid (ASA) on inflammatory cells and molecules in the walls of human cerebral aneurysms using ferumoxytol-enhanced MRI and histological techniques. The major conclusion of the study is that ASA treatment may reduce the inflammatory response in the walls of unruptured human cerebral aneurysms. No MRI signal changes were observed in the control group of no aspirin, while the MRI signal decreased in the ASA group. This means that ASA treatment decreased the uptake of ferumoxytol by macrophages. They also observed a histologically reduction in macrophages and expression on inflammation molecules, such as COX-2, in aneurysms from patients treated with ASA and then underwent microsurgical clipping for treatment of their aneurysms and immunostaining with monoclonal antibodies.

A recent study determined the optimal time window for USPIO-enhanced MRI in the case of cerebral aneurysm wall. The researchers’ observed hyperenhancement in T2* images 72 hours after infusion of 5mg/kg ferumoxytol within the aneurysm wall.

**Other Studies Using USPIO Agents**

Regarding stroke imaging with USPIOs, during our literature research, it was noticed that there is no study with the use of ferumoxytol contrast agent. The potential for USPIO-enhanced MRI to image macrophages in human ischemic stroke lesions has tested with the use of ferumoxtran-10 [COMBINEX]. Ferumoxtran-10 is also an USPIO contrast agent which has similar physical properties with ferumoxytol. Inflammation seems to have a primary role in the pathophysiology of stroke with the activation of microglia cells. It is yet to be verified whether USPIO enhancement at early stages of stroke reflects microglia activation, hematogenous macrophage recruitment, or both, as this would require prior passage of free USPIO through blood brain barrier.

In the first study, Saleh et al showed that the USPIO-related T1 enhancement at late stage is mainly caused by hematogenous macrophages which take up USPIOs in the periphery and...
later on, invade the ischemic brain tissue. The gradual signal loss, on T2/T2* weighted images, was due to macrophage clearance of the contrast agent from the circulation.

In 2007, Saleh et al\(^{35}\) revealed a far more heterogeneous pattern at earlier stages of ischemic lesion development. USPIO enhancement was presented in only 30% of the patients, which is consistent with the previous mentioned study of a more delayed time course of hematogenous macrophage recruitments into ischemic brain lesions. They also observed spatial heterogeneity of USPIO enhancement consisting with more rapidly progression of ischemic tissue damage and macrophage infiltration in the subcortical core of the infraction than in cortical areas, where there is predominant activation of resident microglia. Studies with the use of ferumoxylol are yet to be carried out on patients with stroke.

The same limitation was faced regarding multiple sclerosis (MS) imaging, as the search revealed only few investigators specifically focused on demyelinating lesions of MS. In one of the studies, Dousset et al\(^{36}\) provided the utility of the USPIO ferumoxtran-10 compared with GBCA, in the same patients with MS. Signal changes with ferumoxtran-10 appear to occur primarily in areas, where macrophage infiltration might take place. In a total of 57 enhanced lesions, 31 were detected with both GBCA and USPIO contrast agents. From the remaining 26 lesions, two specific enhancement patterns were identified: one with gadolinium only (n: 24) and the other with USPIO only (n: 2). The two lesions that showed USPIO-enhancement only, have the feature of phagocytic activity in brain parenchyma, without detectable BBB permeability, and would not have been diagnosed if only gadolinium contrast agent would have been administered. Therefore, aside from areas of blood-brain barrier disruption, areas of USPIO signal changes on T1 and T2 images reveal inflammatory processes.

In another research, Tourdias et al\(^{15}\) compared MR images of MS lesions of 24 patients after gadolinium contrast agents and ferumoxtran-10, among different clinical phenotypes of MS and over time. The researchers concluded that the combination of gadolinium and USPIO in patients with MS can help identify additional active lesions even in progressive forms of MS. More specifically, the combination of the two contrast agents enabled the detection of 51% more lesions compared with gadolinium alone as well as the detection of additional lesions in both relapsing and progressive forms of the disease. Lesions that enhance with both agents may display a more aggressive course than those that enhance with only one contrast agent. However, a similar study performed by Manninger et al\(^{16}\) in 7 patients with MS revealed that ferumoxtran-10 imaging showed less or no enhancement in the majority of the lesions compared to the Gadolinium (Gd) enhanced imaging.

Vellinga et al\(^{37}\) using SHU555C USPIO agent, presented three patterns of USPIO enhancement: focal, ring like and previously T1-hypointensity that return to isointensity. Each of these patterns provided additional information regarding the different impacts of BBB leakage, cell-mediated mechanisms and repair mechanisms on the underlying pathology. Nevertheless, the authors insist on further investigations that could possibly validate their assumptions.

Except the studies specially focused on focal disease patterns of USPIO enhancement, Vellinga et al\(^{37}\) in a following study, using the same USPIO agent tried to connect the subtle differences observed on T1 images after USPIO injection in normal appearing white matter of patients with MS, with the hypothesis that this could reflect diffuse inflammation in white matter, long before axonal loss and demyelination occurs.

**Limitations**

The small cohort of patients enrolled in most studies, is one of the limitations that should be taken into consideration. Another limitation of USPIO agents for CNS imaging applications is their intrinsic inability to be reliably differentiated from remaining brain iron signal (ie hemorrhage related to stroke, trauma or AVM).\(^{7}\) In addition, there is scarce research work regarding the long-term clearance of these agents from the CNS. The optimal dose, the injection and scanning timing are some of the parameters that have to be determined for each category of CNS disorders.

The off-label use of ferumoxylol as a contrast agent, apart from ethical issues (written informed consent may be required), raises serious safety concerns, as the risk for unexpected adverse outcomes is high. Just recently, FDA placed a boxed warning to highlight the risk that ferumoxylol administration can cause...
life-threatening allergic reactions. The new safety guidelines are
strongly recommended health care professionals to administer
ferumoxytol only diluted by IV infusion under close monitoring
of blood pressure and pulse. Some radiology departments
have established detailed guidelines for optimal administration
of ferumoxytol that comply with the latest safety announcement
of the FDA.

Apart from the adverse events, such as hypersensitivity re-
actions, additional issues, like iron accumulation to organs, and
iron-induced oxidative stress, have to get clarified. Ferumox-
ytol is an iron oxide nanoparticle, coated with a polyglucose
sorbitol carboxymethyl ether especially designed to isolate free
iron from plasma environment until phagocytized by Reticu-
loendothelial (RES) cells. Thus, by shielding the iron core, the
potential of allergic reactions and oxidative stress, which seems
to be the link between inflammation and cellular damage, is
minimalized. A recent study by Johnson et al. investigated
the degree of renal toxicity of three intravenous iron products,
with ferumoxytol among them. The researchers measured the
level of chemokines such as MCP-1, and markers of cytotoxicity
and acute renal injury and collected data that indicate low ox-
idative stress potential. Nevertheless, other studies show close
relevance between intravenous iron and increased urinary pro-
tein excretion. In 2012, Storey et al. studied the variety of iron
clearance rate among healthy individuals after ferumoxytol ad-
ministration, which range from 3 to 11 months for complete
elimination, and they, among others investigators, pointed
out the problem of erroneous estimation of iron storage organs,
such as liver by altering signal on MR images. From this point of
view, the frequency of iron-particles administration for di-
agnostic purposes must be limited. In addition to that, further
investigation is warranted regarding the impact of the small size
of those particles on the duration of their intravascular life,
before they get recognized by RES cells.

Conclusion: Future Perspectives
Iron oxide nanoparticles tend to be a novel category of MRI
contrast agents that can provide useful information in the imag-
ing of CNS regarding tumor type, extend, residual tumor, ther-
apeutic responses to anti-angiogenetic chemotherapies, differ-
entiation between true progression and pseudoprogression, risk
of rupture in IAs or in AVMs and relapse in MS. The different
patterns of enhancement may provide differential diagnostic
information relative to both blood brain barrier integrity and to
phagocytic activity in various types of CNS lesions.

In addition, in 2012 ferumoxytol was used by Qui et al. in
the evaluation of functional brain activation in healthy vol-
unteers. The researchers, besides the limitation of small sample
size, observed quite good, but not perfect, overlap in regions ac-
tivated with contrast-enhanced functional blood volume imag-
ing (CBV), compared to Blood Oxygen Level Dependent (BOLD),
less susceptibility artifacts and a gain in CNR.

Regarding future studies, researchers focus on quantification
of MRI signal loss on the aneurysm’s wall, which allow more
objective assessment of the imaging findings. Due to the ma-
ajor role of inflammation in the pathophysiology of vasospasm,
the use of ferumoxytol in imaging subarachnoid hemorrhage
(SAH) and CNS angitis may have great potential. Up to June
2016, researchers in Stanford University, California, is expected
to have completed a project on effectiveness of ferumoxytol
contrast agent at revealing inflammatory activity, in patients with
relapsing remitting MS using ultrahigh field strength (7T)
magnets. In the field of epilepsy, even though it is not usu-
ally seen as a neuroinflammatory disease, there is strong evi-
dence that neuroinflammation is involved in the pathogenesis
of epilepsy. The advantages of ferumoxytol are most signifi-
cant in the imaging of CBV, which is an established marker of
epileptogenic focus. In a study in progress, which expected to
be completed in August 2016, researchers are trying to better
localize the epileptogenic focus using CBV mapping with the
use of ferumoxytol.

In conclusion, literature review shows that USPIO agents
improve visualization of tumor vasculature and rCBV measure-
ments, tumor-associated inflammation, inflammatory-immune
mediated disorders, stroke and vascular malformations. One
of their great advantages is that they can be used even in pa-
ients with renal dysfunction. Although USPIOs seem to open
new vista in the CNS imaging using MR, more studies in a
larger cohort of patients, taking into consideration the new FDA
warnings for the safe use of ferumoxytol, are necessary for their
establishment in clinical routine.

References
crane blood volume maps corrected or contrast agent extravasation
significantly correlate with glioma tumor grade, whereas uncorrected
2. Aime S, Caravan P. Biodistribution of gadolinium-based contrast
agents, including gadolinium deposition. J Magn Reson Imaging
magnetic iron oxides (USPIOs): a future alternative magnetic re-
sonance (MR) contrast agent for patients at risk for nephrogenic
4. McDonald R, McDonald J, Kallmes D, et al. Intracranial gadolin-
ium deposition after contrast-enhanced MR imaging. Radiology
2015;275:772-82.
for the study of central nervous system. Prog Neurobiol
2014;123:18-36.
diagnosis and therapy in the central nervous system: report of
the Eleventh Annual Blood-Brain Barrier Disruption Consortium
oxide nanoparticles: diagnostic magnetic resonance imaging and
potential therapeutic applications in neurooncology and central
nervous system inflammatory pathologies, a review. J Cereb Blood
weighted magnetic resonance imaging contrast agents. Int J Mol
resonance imaging of brain-immune interactions. Front Cell Neu-
rosi 2014;8:389.
entiation of pseudoprogression from true tumor progression with
dynamic susceptibility-weighted contrast-enhanced magnetic reso-
nance imaging using ferumoxytol versus gadoteridol: A pilot study.
cerebral blood volume maps in patients with central nervous sys-
tem neoplasms using ferumoxytol, a superparamagnetic iron oxide


47. https://clinicaltrials.gov/ct2/show/NCT01973517

