Safety of Off-Label Use of Ferumoxtyol as a Contrast Agent for MRI: A Systematic Review and Meta-Analysis of Adverse Events

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Background: Ferumoxytol has been studied as an alternative to gadolinium-based MRI contrast agents, but regulatory body warnings currently limit its use.
Purpose: Estimate the adverse event rate in patients undergoing MRI with ferumoxytol as a contrast agent.
Study Type: Systematic review.
Population: Thirty-nine studies including 5411 ferumoxytol administrations in 4336 patients.
Assessment: Multiple databases were searched for studies using ferumoxytol as an off-label MRI contrast agent in any patient population as of April 2020. Studies were eligible for inclusion if they reported the number and severity of adverse events (classified by American College of Radiology [ACR] severity of acute reactions). Risk of bias was assessed using the ROBINS-I tool.
Statistical Tests: The proportion of administrations with adverse events was calculated using random effects meta-analysis of proportions.
Results: No deaths related to ferumoxytol administration were reported. Sixteen studies reported immediate adverse events in 3849 patients undergoing 4901 ferumoxytol administrations. Ninety-seven immediate adverse events were reported and the pooled adverse event proportion for immediate adverse events was 0.02 (95% confidence interval [CI] 0.02–0.02). Twenty-three studies reported time-unspecified adverse events in 487 patients undergoing 510 ferumoxytol administrations. Five time-unspecified adverse events were reported; the pooled adverse event proportion for time-unspecified adverse events was 0.01 (95% CI 0.00–0.04). 88% of adverse events were mild (90/102), 11% (11/102) were moderate, and 1% (1/102) was severe. Sixteen studies were at low risk of bias, 23 studies were at serious risk of bias. Subgroup analysis by patient population revealed no significant variability (adult vs. pediatric). No studies evaluated the use of ferumoxytol as an alternative to patients who had a prior hypersensitivity reaction to gadolinium-based contrast agents (GBCAs).
Data Conclusion: The overall adverse event rate for off-label ferumoxytol use as an MRI contrast agent is 2%, with rare severe reactions and no deaths. To date, there are no studies evaluating the safety of ferumoxytol as an alternative to GBCAs in patients with a prior hypersensitivity reaction.
Level of Evidence: 2
Technical Efficacy Stage: 5

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CONTRAST-ENHANCED (CE) magnetic resonance imaging (MRI) remains a critical diagnostic tool in clinical practice, with widespread application across virtually all body systems. Recent estimates indicate that ~30 million CE-MRI examinations are performed annually worldwide.[1] Gadolinium-based contrast agents (GBCAs) are the mainstay

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for virtually all CE-MRI examinations.[1] Overall, GBCAs have an excellent safety record and have been in use for decades. GBCAs have a very low incidence of immediate hypersensitivity reactions, which are typically mild in severity.[2,3]

Nevertheless, GBCAs are not without risk. Nephrogenic systemic fibrosis (NSF) is a chronic debilitating systemic sclerosing condition directly associated with GBCA use in patients with severely impaired renal function.[4] Although NSF has been essentially eradicated in modern practice through the use of newer protein-binding linear ionic and macrocyclic GBCAs,[5–8] physicians and patients remain concerned regarding the liberal use of GBCAs in patients with renal impairment and their associated risk of causing NSF. This is mainly due to the relative novelty of some of the newer GBCAs and relatively limited data indicating their safety, which has been obtained during an era where GBCAs were almost exclusively used only in patients with normal renal function.[4,9] Additional concerns regarding GBCAs have recently emerged following the report by Kanda et al describing gadolinium deposition in the brain, most specifically within the dentate nucleus and globus pallidus seen with repeated GBCA injections.[10] We now know, through further imaging and mass spectrometry studies in animals and humans both in vivo and ex vivo, that a small amount of gadolinium is retained in tissues (including the brain) following GBCA administration even in subjects with normal renal function and intact blood–brain barriers.[11,12] The clinical significance of these observations is not known and there is no evidence directly linking gadolinium retention to adverse clinical outcomes to date. Nevertheless, this remains a relatively immature topic and is of considerable concern and active investigation.[13–17]

Given the current uncertainty surrounding the adverse effects of gadolinium, alternative MRI contrast agents may be desirable and are actively being investigated.[18,19] Ferumoxytol (Feraheme, AMAG Pharmaceuticals, Waltham, MA) is an ultrasmall superparamagnetic iron oxide (SPIO) nanoparticle that has favorable magnetic and biological properties for use in MRI.[20,21] Ferumoxytol is gradually cleared from the blood pool by macrophages, with remaining iron oxide particles being taken up by the reticuloendothelial system (RES), particularly the liver, spleen, and bone marrow, making ferumoxytol safe for use in patients with endstage kidney disease or on dialysis.[18] Ferumoxytol it is not associated with NSF and is not known to be retained in other areas of the body other than the RES and has no known adverse effects related to RES retention.

Despite the favorable properties as an MRI contrast agent, ferumoxytol remains relatively limited for off-label use as an MRI contrast agent.[18,22–25] In November 2014, Health Canada issued a recall altering the administration of ferumoxytol, recommending dilution and infusion over a minimum of 15 minutes, as well as contraindicating its use in patients with any known history of drug allergy.[26] In March 2015, the United States Food and Drug Administration (FDA) issued a black-box warning about acute hypersensitivity reactions with administration of ferumoxytol due to 79 anaphylactic reactions with 18 fatalities, in ~1.2 million administrations.[27,28] A 2016 review of the therapeutic use of ferumoxytol examining safety data for close to 10,000 patients showed a favorable safety profile, with the three observed deaths considered unrelated to ferumoxytol.[28] Since this review, newer safety data for off-label MRI use of ferumoxytol has become available, necessitating an update.[29] The purpose of this systematic review is therefore to determine the rate of adverse events and evaluate the safety of ferumoxytol as an off-label MRI contrast agent.

Methods

This protocol was designed following best practices for systematic reviews of adverse events.[30] Reporting was guided by the PRISMA harms checklist for systematic reviews of adverse events.[31] Institutional Review Board approval is not required for this type of study at our institution.

Search and Inclusion

The search included MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL), with the assistance of an experienced hospital librarian. No language or date restrictions was applied. The database search was performed April 29, 2020. Original research that was not a case report or case series was eligible for inclusion; non-original research (reviews, commentary, letter to the editor) was excluded. Government adverse event reporting databases were excluded due to data heterogeneity, lack of data verification, and inability to determine the clinical context of ferumoxytol use (eg, as MRI contrast agent vs. other use). The full search strategy is presented in Appendix A1. Studies were eligible for inclusion if they reported patients (adult or pediatric) undergoing ferumoxytol administration for use as an MRI contrast agent with documentation of adverse events related to ferumoxytol administration with number, severity, and individual symptoms.

Initial screening of search results based on title and abstract was done by two reviewers F.A., L.T.). Any search result deemed potentially eligible by either reviewer was assessed at the full-text stage. Decisions about inclusion based on full text were made independently by two reviewers (F.A., L.T.). In the case of a disagreement, discussion with a third reviewer was used to reach a final decision (T.A.M.). The reference lists from included studies were checked for additional citations. If studies contained overlapping patient populations, the study with the largest sample size was used.

Data Extraction

After a pilot of the data extraction form on one study by two authors (F.A., L.T.), the following data from included studies was extracted independently and in duplicate: first author, journal and year of publication, number of patients, timing of adverse events (immediate, within 1 hour; unspecified, time of adverse events not reported), study population (adult, pediatric, mixed), patient age (mean or median), quantity of ferumoxtyol injected, rate of ferumoxytol injection, as well as the number, severity, and specific symptoms of reported adverse events related to ferumoxtyol injection (adverse event classification of severity prespecified from the American College of Radiology [ACR] Manual on Contrast Media v. 2020, Appendix A2). Data extraction was performed using Microsoft Excel (Redmond, WA).

Risk of Bias (Quality) Assessment

Risk of bias of studies reporting adverse events related to ferumoxytol administration were assessed using the ROBINS-I tool as per contemporary best practice.[30,32,33]

Data Analysis

The proportion of ferumoxtyol administrations with adverse events were summarized in a forest plot for each primary study. A summary estimate of proportion of administrations with adverse events were calculated using random effects meta-analysis of proportions using the "*metaprop*" function in R for both immediate and time-unspecified adverse events. The severe adverse event proportion was estimated in aggregate between immediate and time-unspecified adverse events due the to scarcity of severe adverse events reported, which was decided post-hoc. I^2 values were presented for each meta-analysis performed. Subgroup analysis was planned to assess variability in patient population, ferumoxytol dose, ferumoxytol injection rate, and risk of bias (low risk of bias vs. studies at risk of bias). Data analysis was done using R, v. 3.6.3 (R Foundation for Statistical Computing; Vienna, Austria).

Results

Our search identified 476 unique results. Three hundred twenty-four results were excluded after title and abstract screening, with 152 results undergoing full-text screening. After full-text screening 39 studies were included in the systematic review. A study flow diagram with reasons for exclusion during full-text screening is presented in Fig. 1. Per-result reasons for exclusion during full-text screening are presented in Appendix A3. Included studies reported 4336 patients undergoing 5411 ferumoxytol administrations for off-label use as an MRI contrast agent. Sixteen studies reported immediate adverse events in 3849 patients undergoing 4901 ferumoxytol administrations. Twenty-three studies reported time-unspecified adverse events in 487 patients undergoing 510 ferumoxytol administrations. A summary of patient demographics and adverse events within included studies related to ferumoxytol administration are reported in Table 1 (immediate adverse events) and Table 2 (time-unspecified adverse events). The pooled adverse event proportion for immediate adverse events was 0.02 (95% confidence interval [CI] 0.02–0.02), with 97 total adverse events reported (87 mild adverse events, 10 moderate adverse events, zero severe adverse events or deaths). The pooled adverse event proportion for time-unspecified adverse events was 0.01 (95% CI 0.00–0.04), with five total adverse events reported (three mild adverse events, one moderate adverse event, one severe adverse event, zero deaths). Adverse event proportion for each primary study, with pooled adverse event proportion, are presented for immediate and time-unspecified adverse events in Figs. 2 and 3, respectively. Overall (aggregate of immediate and time-unspecified) severe adverse event proportion was 0.0001 (95% CI 0.00–0.01).

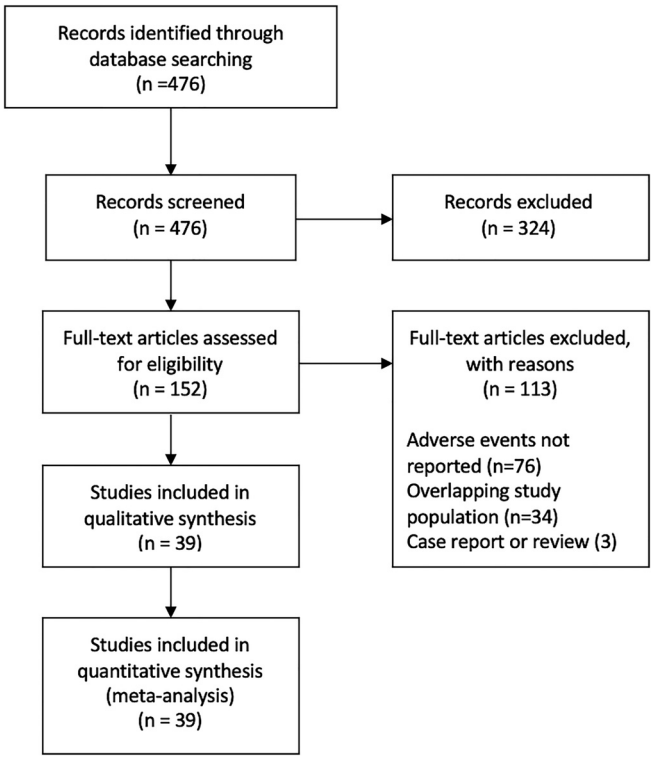

FIGURE 1: PRISMA flow diagram depicting included and excluded studies in the present systematic review and meta-analysis.

No deaths related to diagnostic use of ferumoxytol were reported. The majority of adverse events were mild (88% [90 of 102 adverse events]), 11% (11/102) were moderate, and 1% (1/102) were severe. Mild adverse events most frequently included headache, nausea, vomiting, and pruritis.[30,36] Moderate adverse events were mostly allergic-type reactions including urticaria, erythema, pruritis, and laryngospasm.[29,34] The one incidence of laryngospasm occurred in a pediatric patient undergoing cardiac MRI at the

TABLE 1. Characteristics of Studies Reporting Immediate Adverse Events to Ferumoxytol When Used as an Off-Label MRI Contrast Agent

First author, year of publication, study period, reference	Patient population	Age (mean or median*)	Ferumoxytol dose	Patients	Injections	Adverse events	Mild	Moderate	Severe	Overall risk of bias
Bravo, 2013[34] (NR)	Adult	NR	NR	136	136	6	5	1	0	Low risk
Dattoli, 2018 (2013–2015)	NR	NR	6 mg/kg	178	178	1	1	0	0	Low risk
Dosa, 2011 (2008–2010)	Adult	47	510 mg	36	36	0	0	0	0	Low risk
Fananapazir, 2017 (2014–2015)	Adult	51	3 mg/kg	33	33	0	0	0	0	Low risk
Harisinghani, 2007 (NR)	Adult	53.8	4 mg/kg	10	10	0	0	0	0	Low risk
Iv, 2019 (2015–2017)	Adult	57.8	5 mg/kg	10	10	0	0	0	0	Low risk
Lai, 2017 (June-Feb 2016)	Pediatric	3 days*	3 mg/kg	21	21	0	0	0	0	Low risk
Muehe, 2016 (2009–2015)	Mixed	NR	5 mg/kg or 4 doses of 1.5-3 mL/s	68	85	4	4	0	0	Low risk
Nakamoto, 2013 (NR)	Adult	60.3	4 mg/kg	4	4	0	0	0	0	Low risk
Nguyen, 2019 (2003–2018)	Mixed	58*	2–11 mg/kg	3215	4240	83	75	8	0	Low risk
Schubert, 2017 (NR)	Adult	44.3	2–4 mg/kg	12	12	0	0	0	0	Low risk
Stirrat, 2019 (2015–2016)	Adult	NR	4 mg/kg	21	21	0	0	0	0	Low risk
Stoumpos, 2019 (2015–2016)	Adult	59.8	4 mg/kg	25	25	0	0	0	0	Low risk
Turkbey, 2015 (2011–2012)	Adult	60	4–7.5 mg/kg	16	16	1	0	1	0	Low risk
Turkbey, 2020 (2014–2017)	Adult	63	7.5 mg/kg	44	44	2	2	0	0	Low risk
Usman, 2020 (NR)	Adult	73*	5 mg/kg	20	30	0	0	0	0	Low risk

NR = not reported.
The * indicates patient age values that are a median rather than a mean.

TABLE 2. Characteristics of Studies Reporting Adverse Reaction Events to Ferumoxytol When Used as an Off-Label MRI Contrast Agent, Time-Unspecified

First author, year of publication, study period, reference	Patient population	Age (mean or median*)	Ferumoxytol dose	Patients	Injections	Adverse events	Mild	Moderate	Severe	Overall risk of bias
Aghighi, 2018, (NR)	Mixed	NR	5 mg/kg	26	26	0	0	0	0	Serious risk
Bashir, 2013 (2011–2012)	Adult	54.4	253 mg	16	16	0	0	0	0	Serious risk
Bashir, 2013 (NR)	Adult	62.8	3 mg/kg	17	17	0	0	0	0	Serious risk
Bhatia, 2019 (2016–2018)	Pediatric	10.7	3 mg/kg	14	14	0	0	0	0	Serious risk
Corwin, 2016 (NR)	Adult	56.9	3 mg/kg	15	15	0	0	0	0	Serious risk
D'Arceuil, 2013 (NR)	NR	NR	510 mg	8	8	0	0	0	0	Serious risk
Fananapazir, 2014 (2011–2012)	Adult	63.3	3 mg/kg	61	61	0	0	0	0	Serious risk
Farrell, 2012 (NR)	NR	NR	NR	20	20	0	0	0	0	Serious risk
Florian, 2014 (2010–2011)	Adult	54	510 mg	17	17	0	0	0	0	Serious risk
Fredrickson, 2017 (NR)	NR	NR	3 mg/kg	13	13	0	0	0	0	Serious risk
Hasan, 2012 (2011–2012)	Adult	59.3	2.5–5 mg/kg	22	22	0	0	0	0	Serious risk
Iv, 2018 (2014–2017)	Mixed	13.5	3 mg/kg	21	21	0	0	0	0	Serious risk
Knobloc, 2019 (NR)	Adult	34	4 mg/kg	20	20	0	0	0	0	Serious risk
Li, 2005 (NR)	Adult	60	2–4 mg/kg	12	12	1	1	0	0	Serious risk
McDermott, 2013 (NR)	Adult	64	6 mg/kg	13	13	0	0	0	0	Serious risk
Muehe, 2018 (2015–2016)	Mixed	18.9	5 mg/kg	20	20	1	1	0	0	Serious risk
Neuwelt, 2007 (2004–2005)	Adult	51.2	4 mg/kg	12	12	0	0	0	0	Serious risk
Rivera-Rivera, 2019 (NR)	Adult	32	5 mg/kg	22	22	1	1	0	0	Serious risk
Schindler, 2017 (NR)	NR	NR	510 mg	9	9	0	0	0	0	Serious risk
Stirrat, 2017 (NR)	Adult	58.4	4 mg/kg	31	54	0	0	0	0	Serious risk
Storey, 2012 (NR)	Adult	NR	5 mg/kg	6	6	0	0	0	0	Serious risk
Vesey, 2018 (NR)	NR	NR	4 mg/kg	31	31	0	0	0	0	Serious risk
Wise-Faberowski, 2018[35] (2014–2015)	Pediatric	4	3–5 mg/kg	61	61	2	0	1	1	Serious risk

NR = not reported.

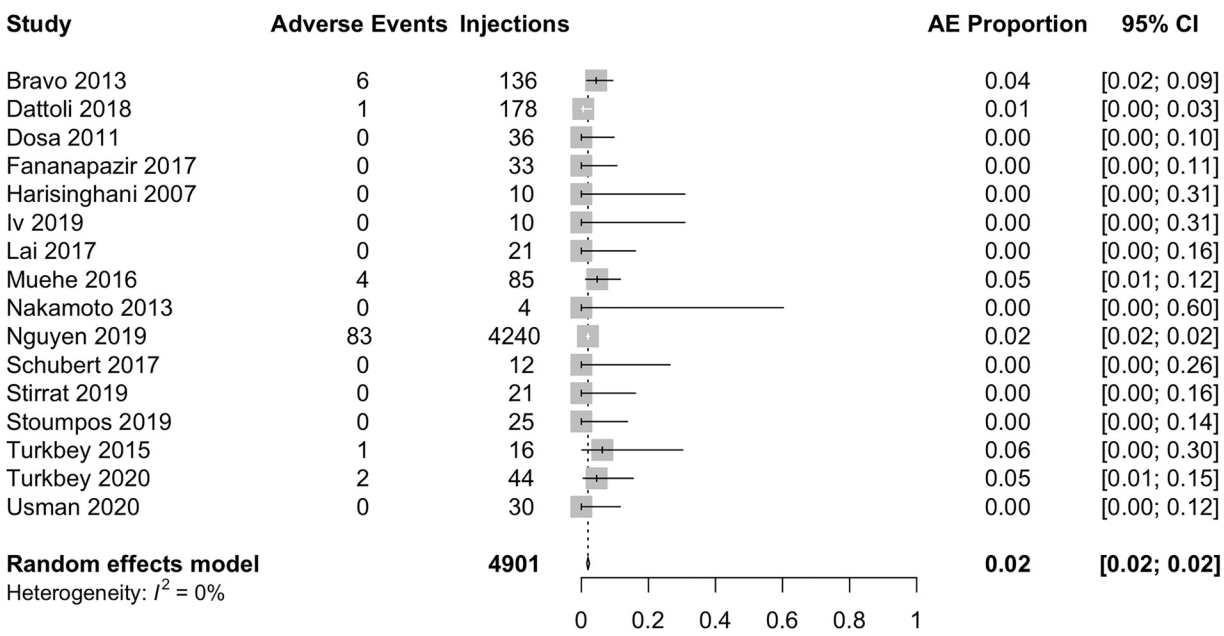

FIGURE 2: Adverse event rate in studies reporting immediate adverse events to ferumoxytol when used as an off-label MRI contrast agent.

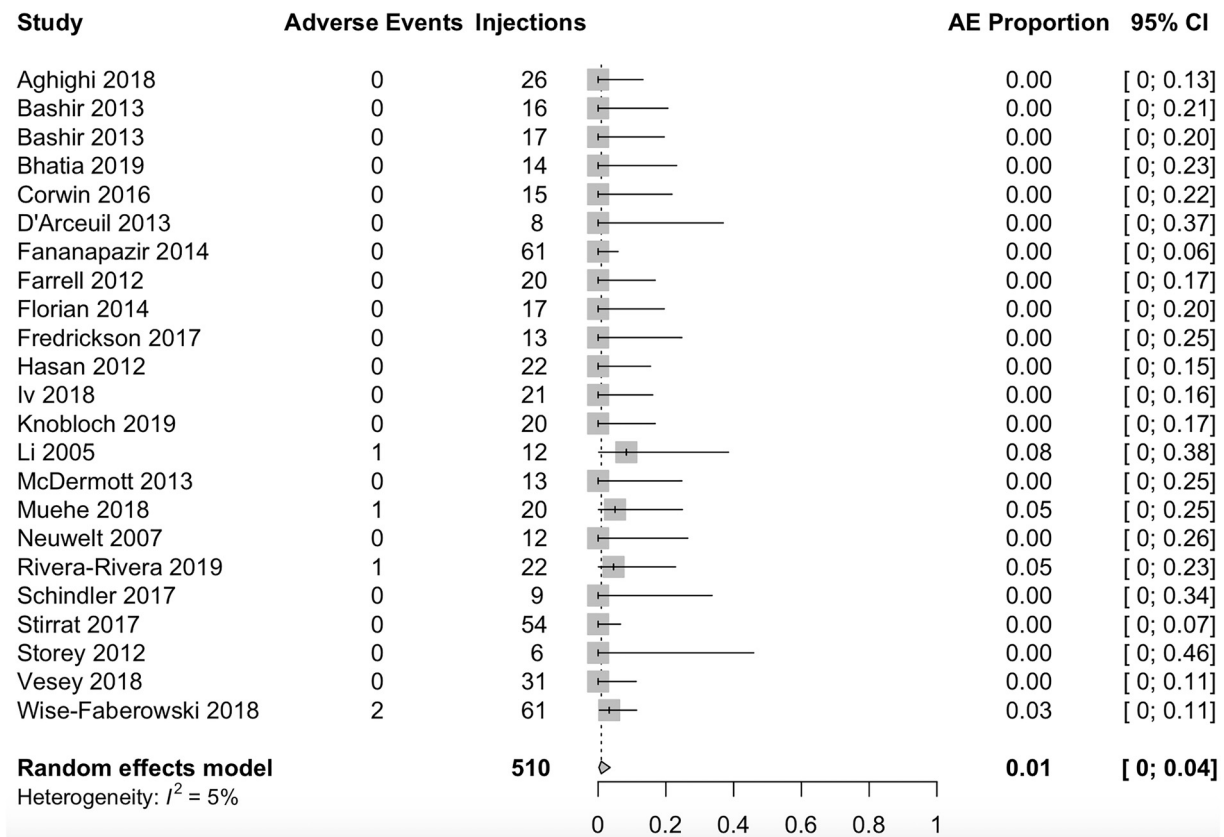

FIGURE 3: Adverse event rate in studies reporting time-unspecified adverse events to ferumoxytol when used as an off-label MRI contrast agent.

time of emergence from anesthesia at the completion of the imaging procedure and did not directly coincide with ferumoxytol administration.[35] One patient had a vasovagal reaction that was treated with a saline bolus and IV atropine to uneventful resolution of symptoms.[34] In one review of multicenter ferumoxytol use by Nguyen et al, there were two moderate adverse events, which received medical therapy.[30] One patient developed stomach pain, headache, emesis, and

TABLE 3. Per-Domain and Overall ROBINS-I Risk of Bias Assessment for Included Studies

Study	Confounding	Selection bias	Bias in measurement classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Immediate adverse events								
Bravo, 2013 (NR)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Dattoli, 2018 (2013–2015)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Dosa, 2011 (2008–2010)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Fananapazir, 2017 (2014–2015)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Harisinghani, 2007 (NR)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Iv, 2019 (2015–2017)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Lai, 2017 (June-Feb 2016)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Muehe, 2016 (2009–2015)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Nakamoto, 2013 (NR)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Nguyen, 2019 (2003–2018)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Schubert, 2017 (NR)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Stirrat, 2019 (2015–2016)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Stoumpos, 2019 (2015–2016)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Turkbey, 2015 (2011–2012)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Turkbey, 2020 (2014–2017)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Usman, 2020 (NR)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Time-unspecified adverse events								
Aghighi, 2018, (NR)	Low risk	Low risk	Low risk	Low risk	Moderate risk	Serious risk	Low risk	Serious risk
Bashir, 2013 (2011–2012)	Low risk	Low risk	Low risk	Low risk	Low risk	Serious risk	Low risk	Serious risk
Bashir, 2013 (NR)	Low risk	Low risk	Low risk	Low risk	Low risk	Serious risk	Low risk	Serious risk

TABLE 3. Continued

Study	Confounding	Selection bias	Bias in measurement classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Bhatia, 2019 (2016–2018)	Low risk	Low risk	Low risk	Low risk	Low risk	Serious risk	Low risk	Serious risk
Corwin, 2016 (NR)	Low risk	Low risk	Low risk	Low risk	Low risk	Serious risk	Low risk	Serious risk
D'Arceuil, 2013 (NR)	Low risk	Low risk	Low risk	Low risk	Low risk	Serious risk	Low risk	Serious risk
Fananapazir, 2014 (2011–2012)	Low risk	Low risk	Low risk	Low risk	Low risk	Serious risk	Low risk	Serious risk
Farrell, 2012 (NR)	Low risk	Low risk	Low risk	Low risk	Low risk	Serious risk	Low risk	Serious risk
Florian, 2014 (2010–2011)	Low risk	Low risk	Low risk	Low risk	Low risk	Serious risk	Low risk	Serious risk
Fredrickson, 2017 (NR)	Low risk	Low risk	Low risk	Low risk	Low risk	Serious risk	Low risk	Serious risk
Hasan, 2012 (2011–2012)	Low risk	Low risk	Low risk	Low risk	Low risk	Serious risk	Low risk	Serious risk
Iv, 2018 (2014–2017)	Low risk	Low risk	Low risk	Low risk	Low risk	Serious risk	Low risk	Serious risk
Knobloc, 2019 (NR)	Low risk	Low risk	Low risk	Low risk	Low risk	Serious risk	Low risk	Serious risk
Li, 2005 (NR)	Low risk	Low risk	Low risk	Low risk	Low risk	Serious risk	Low risk	Serious risk
McDermott, 2013 (NR)	Low risk	Low risk	Low risk	Low risk	Low risk	Serious risk	Low risk	Serious risk
Muehe, 2018 (2015–2016)	Low risk	Low risk	Low risk	Low risk	Low risk	Serious risk	Low risk	Serious risk
Neuwelt, 2007 (2004–2005)	Low risk	Low risk	Low risk	Low risk	Low risk	Serious risk	Low risk	Serious risk
Rivera-Rivera, 2019 (NR)	Low risk	Low risk	Low risk	Low risk	Low risk	Serious risk	Low risk	Serious risk
Schindler, 2017 (NR)	Low risk	Low risk	Low risk	Low risk	Low risk	Serious risk	Low risk	Serious risk
Stirrat, 2017 (NR)	Low risk	Low risk	Low risk	Low risk	Low risk	Serious risk	Low risk	Serious risk
Storey, 2012 (NR)	Low risk	Low risk	Low risk	Low risk	Low risk	Serious risk	Low risk	Serious risk
Vesey, 2018 (NR)	Low risk	Low risk	Low risk	Low risk	Low risk	Serious risk	Low risk	Serious risk
Wise-Faberowski, 2018[35] (2014–2015)	Low risk	Low risk	Low risk	Low risk	Low risk	Serious risk	Low risk	Serious risk

transient hypotension and was given IV fluids. The other patient developed pruritis during infusion and subsequent hives, vomiting, and chest pain, due to which imaging was terminated and diphenhydramine, solumedrol, and Zantac were given.[30] The only severe adverse event was a suspected anaphylactic reaction in which a patient developed hypotension and was treated with vasopressors and intubation.[35]

The risk of bias was classified according to the ROBINS-I tool and is presented per-domain per study in Table 3. Overall risk of bias for included studies are included in Tables 1 and 2. The most common source of bias was the "bias in measurement of outcome" domain. If studies reported follow-up regimen and the minimum time of monitoring of 30 minutes after ferumoxtyol administration, risk of bias was judged to be low. A 30-minute monitoring threshold was extrapolated based upon contemporary guidance for monitoring patients at increased risk of reaction after GBCA administration, given the regulatory warnings surrounding ferumoxytol.[26,27,36] If studies did not report an adequate follow-up regimen or retrospectively searched for adverse events from unmonitored ferumoxytol administrations, the risk of bias was judged to be serious. Sixteen studies reporting immediate adverse events were judged to be at low risk of bias and 23 studies reporting time-unspecified adverse events were judged to be at serious risk of bias.

Subgroup analysis by patient population (adult vs. pediatric vs. mixed) for both immediate (P = 0.89) and time-unspecified (P = 0.71) adverse events revealed no significant variability. Subgroup analysis for ferumoxytol dose (mg/kg), ferumoxytol injection rate (mg/s), and risk of bias (low risk of bias vs. studies at risk of bias) were not performed, as ferumoxytol dose and injection rate were reported heterogeneously and incompletely (weight-based vs. total dose; ml per second vs. total injection time) across studies. The risk of bias was entirely homogenous within studies reporting immediate (low risk) and time-unspecified (serious risk) adverse events; therefore, subgroup analysis was not performed.

Discussion

In this systematic review and meta-analysis, we report the overall rate of adverse events using ferumoxytol as an off-label MRI contrast agent. We found that ferumoxytol has a rate of adverse events as estimated by meta-analysis to be 2%. Moreover, there was a low reported incidence of severe adverse events, with minor and moderate adverse events encompassing 99% of reactions. The adverse events that were observed in our study were most often mild and only rarely precluded completion of the MRI examination. There are no studies that evaluated the safety of ferumoxytol as an off-label MRI contrast agent in patients who have had prior hypersensitivity reaction to GBCAs.

Our aggregate findings support recent studies, suggesting that ferumoxytol can be used as a contrast agent in MRIs due to its low risk of severe adverse events.[29,30] Ferumoxytol can be substituted as a blood pool contrast agent for CE-MRA of both the arterial and venous systems in patients in whom GBCA administration is unsuitable.[18,29] It may be a preferable agent to GCBAs in patients that have endstage kidney disease or who are on dialysis, since ferumoxytol is cleared by the reticuloendothelial system and is not associated with NSF (acknowledging that ACR Group 2 GBCAs pose a negligible risk of NSF).[18,22] The list of clinical indications for which ferumoxytol has been successfully performed is growing.[23,24,37,38]

In a previous meta-analysis by Behzadi et al, the aggregate immediate hypersensitivity reaction rate among GBCAs was shown to vary by class.[2] After excluding first-generation linear nonionic agents (ie, gadopentetate dimeglumine, gadoversetamide, and gadodiamide), which are seldom used in modern clinical practices due to heightened risk of NSF,[39] the reported rate of immediate hypersensitivity reactions to macrocyclic GBCAs and protein-binding linear-ionic GBCAs was 0.16% and 0.17%, respectively.[2] Our results indicate that off-label use of ferumoxytol as an MRI contrast agent has a higher adverse event rate than when compared to date for modern ACR Group 2 and 3 GBCAs; however, the overall adverse event rate remains low, at 2%, with only one reported severe reaction and no deaths. In the same meta-analysis by Behzadi et al, most immediate hypersensitivity reactions to GBCAs were mild; however, severe adverse events occurred in 0.005% of injections, with two deaths (one each for gadobenate dimeglumine and gadobutrol).[2] The rate of severe adverse events related to ferumoxytol is estimated to be 0.01%, higher than the reported severe adverse event rate in the meta-analysis by Behzadi et al[2]; however, comparison between GBCAs and ferumoxytol is limited, given the wide disparity in number of total administrations between the two class of contrast agents.

Managing patients with a prior immediate hypersensitivity to GBCA is a challenge in clinical practice. Although recommended by the ACR, a meta-analysis by Walker et al recently showed that corticosteroid premedication prior to repeat exposure to the same GBCA is likely not an effective method to prevent a subsequent breakthrough reaction to GBCA, which occurs in ~40% of patients.[40] The same meta-analysis demonstrated that empirically switching GBCAs or using allergy skin testing prior to repeat exposure are unproven, and in the few reported cases where this strategy has been attempted in patients with prior severe reaction to GBCA, documented severe reactions have reoccurred at the time of repeat exposure to a different GBCA.[40] It has been speculated that ferumoxytol may have a role in patients with a prior GBCA reaction[41]; however, there are no published data to support this hypothesis. Moreover, Health Canada

issued a warning contraindicating the use of ferumoxytol in patients with any prior history of drug allergy and the FDA has a black-box warning regarding the risk of allergic reactions to ferumoxytol.[26,27] The results of our study may lessen concerns regarding adverse events to the off-label use of ferumoxytol when used as an MRI contrast agent and could lead to future study of the agent for patients who have a prior reaction to GBCA.

Limitations

Our review has several limitations that merit consideration. Twenty-three included studies did not report the timing of monitoring for adverse events, causing these studies to be at serious risk of bias. The reporting of ferumoxytol dose and injection rate was incompletely and heterogeneously reported across the included studies, precluding meaningful subgroup analysis of these important clinical variables. We did not observe any studies that reported the use of ferumoxytol in patients with a prior immediate hypersensitivity reaction to GBCA, which is an important potential application that requires further study.

Conclusion

In conclusion, off-label use of ferumoxytol as an MRI contrast agent has an overall adverse event rate estimated to occur in ~2% of administrations with rare severe reactions and zero deaths. Compared to GBCAs, ferumoxytol offers the potential benefits of having no risk of causing NSF, even in patients with severe renal impairment, and has not been associated with retention in the body outside of the reticuloendothelial system, which is not known to have any adverse outcome in patients. Although ferumoxtyol could be an alternative MRI contrast agent in patients with prior GBCAs immediate hypersensitivity reactions, our study demonstrates that ferumoxytol not been studied for this application to date. Black-box warnings from advisory bodies regarding the use of ferumoxytol in patients with prior allergy should be reconsidered in light of our results, as these warnings limit the clinical use of ferumoxtyol as an alternative contrast agent, particularly in patients with prior allergy to GBCA.

Protocol Registration

PROSPERO CRD42020190886.

Role of Funders

None of the funding bodies listed had any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the article; and decision to submit the article for publication.

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APPENDIX A1: SEARCH STRATEGY

Database: Embase Classic+Embase <1947 to 2020 April 29>, Ovid MEDLINE(R) ALL <1946 to April 29, 2020>, EBM Reviews - Cochrane Central Register of Controlled Trials <March 2020>

Search Strategy:

1. (Feraheme or ferumoxytol or rienso).mp. (1907)
2. exp Magnetic Resonance Imaging/ (1401035)
3. (mri or magnetic resonance imag*).tw,kw. (999526)
4. 2 or 3 (1621603)
5. 1 and 4 (1030)
6. exp animals/ not humans/ (17829035)
7. 5 not 6 (510)
8. **7 use medall (240) Medline**
9. **7 use cctr (30) Cochrane**
10. *ferumoxytol/ (2366)
11. (Feraheme or ferumoxytol or rienso).tw. (1407)
12. 10 or 11 (3192)
13. exp nuclear magnetic resonance imaging/ (945684)
14. (mri or magnetic resonance imag*).tw. (956301)
15. 13 or 14 (1391002)
16. 12 and 15 (995)
17. (exp animals/ or animal experiment/) not exp humans/ (10412862)
18. 16 not 17 (795)
19. **18 use emczd (435) Embase**
20. 8 or 9 or 19 (705)
21. remove duplicates from 20 (491)
22. **21 use medall (240) Medline**
23. **21 use emczd (239) Embase**
24. **21 use cctr (12) Cochrane**

APPENDIX A2: AMERICAN COLLEGE OF RADIOLOGY (ACR) CONTRAST MANUAL V. 2020 ADVERSE EVENT CLASSIFICATION42

Severity	Allergic-like	Physiologic
Mild	• Limited urticaria / pruritis • Cutaneous edema • Limited "itchy"/ "scratchy" throat • Nasal congestion • Sneezing / conjunctivitis / rhinorrhea	• Limited nausea / vomiting • Transient flushing / warmth / chills • Headache / dizziness / anxiety / altered taste • Mild hypertension • Vasovagal reaction that resolves spontaneously
Moderate	• Diffuse urticaria / pruritis • Diffuse erythema, stable vital signs • Facial edema without dyspnea • Throat tightness or hoarseness without dyspnea • Wheezing / bronchospasm, mild or no hypoxia	• Protracted nausea / vomiting • Hypertensive urgency • Isolated chest pain • Vasovagal reaction that requires and is responsive to treatment
Severe	• Diffuse edema, or facial edema with dyspnea • Diffuse erythema with hypotension • Laryngeal edema with stridor and/or hypoxia • Wheezing / bronchospasm, significant hypoxia • Anaphylactic shock (hypotension + tachycardia)	• Vasovagal reaction resistant to treatment • Arrhythmia • Convulsions, seizures • Hypertensive emergency

APPENDIX A3: STUDIES EXCLUDED AFTER FULL TEXT REVIEW WITH REASONS

Author	Year	Study title	Reason for exclusion
Aghighi	2016	Speeding up PET/MR for cancer staging of children and young adults	Adverse events not reported
Aghighi	2018	Magnetic resonance imaging of tumor-associated macrophages: Clinical translation	Adverse events not reported
Alam	2013	Nanoparticle enhanced CMR□a novel method of investigating myocardial inflammation & dysfunction	Adverse events not reported
Alam	2013	Nanoparticle enhanced MRI: A novel method of investigating myocardial inflammation	Adverse events not reported
Alford	2016	MRI of tumor associated macrophages in pediatric patients with malignant lymphomas and sarcomas	Adverse events not reported
Ambert-Pompey	2012	Correlation between neurocognitive function and total T2-weighted MRI signal abnormality in patients with brain tumors	Adverse events not reported
Aoki	2017	Macrophage imaging of cerebral aneurysms with ferumoxytol: An exploratory study in an animal model and in patients	Adverse events not reported
Barajas	2019	Combined iron oxide nanoparticle ferumoxytol and gadolinium contrast enhanced MRI define glioblastoma pseudoprogression	Adverse events not reported
Bowser	2016	Incidental ferumoxytol artifacts in clinical brain MRI	Adverse events not reported
Brown	2015	Ferumoxytol enhanced MRI for lymph node staging in prostate cancer	Adverse events not reported
Brown	2015	Ferumoxytol enhanced MRI for lymph node staging in genitourinary cancers	Adverse events not reported
Campeau	2016	Magnetic resonance imaging findings of the brain related to intravenous administration of ferumoxytol	Adverse events not reported
Cheng	2016	Comprehensive motion-compensated highly accelerated 4D flow MRI with ferumoxytol enhancement for pediatric congenital heart disease	Adverse events not reported
Chin	2018	Intraluminal assessment of coronary arteries with ferumoxytol-enhanced magnetic resonance angiography	Case report or review
Christen	2013	High-resolution cerebral blood volume imaging in humans using the blood pool contrast agent ferumoxytol	Adverse events not reported
Daghem	2019	USPIO-enhanced magnetic resonance coronary angiography compared to computed tomography coronary angiography	Adverse events not reported
Dattoli	2018	Efficacy of ferumoxytol as a lymphatic contrast agent in prostate cancer	Adverse events not reported
Doolittle	2009	Iron-oxide nanoparticles as magnetic resonance contrast agents: Expanding their potential beyond iron replacement therapy	Adverse events not reported
Dosa	2011	MRI using ferumoxytol improves the visualization of central nervous system vascular malformations	Overlapping populations

APPENDIX A3. Continued

Author	Year	Study title	Reason for exclusion
Elhalawani	2020	Data from a terminated study on iron oxide nanoparticle magnetic resonance imaging for head and neck tumors	Adverse events not reported
Ersoy	2004	Blood pool MR angiography of aortic stent-graft endoleak	Overlapping populations
Farrell	2013	Using iron oxide nanoparticles to diagnose CNS inflammatory diseases and PCNSL	Adverse events not reported
Finn	2016	Ferumoxytol MR angiography for pre-TAVR assessment	Overlapping populations
Firkins	2017	Comorbidities in survival of adults with a glioblastoma	Adverse events not reported
Florian	2013	Beneficial effect of intravenous iron administration on left ventricular remodelling in patients with acute st-elevation myocardial infarction-a cardiovascular magnetic resonance (CMR) study	Adverse events not reported
Gahramanov	2012	Radiographic diagnosis of pseudoprogression and correlation with survival of patients with glioblastoma after chemoradiotherapy using dynamic susceptibility-weighted contrast-enhanced perfusion MRI with ferumoxytol vs. Gadoteridol	Adverse events not reported
Gahramanov	2013	Pseudoprogression of glioblastoma after chemo- and radiation therapy: Diagnosis by using dynamic susceptibility-weighted contrast-enhanced perfusion MRI with ferumoxytol vs. gadoteridol and correlation with survival	Adverse events not reported
Gahramanov	2011	Potential for differentiation of pseudoprogression from true tumor progression with dynamic susceptibility-weighted contrast-enhanced magnetic resonance imaging using ferumoxytol vs. gadoteridol: A pilot study	Adverse events not reported
Gasper	2011	Development of a rapid, high resolution magnetic resonance imaging protocol for the assessment of arteriovenous fistula remodeling	Adverse events not reported
Gunn	2013	Imaging behavior of the normal adrenal on ferumoxytol-enhanced MRI: Preliminary findings	Adverse events not reported
Hamilton	2011	Comparative analysis of ferumoxytol and gadoteridol enhancement using T1- and T2-weighted MRI in neuroimaging	Adverse events not reported
Hamilton	2016	Ferumoxytol-enhanced MRI differentiation of meningioma from dural metastases: A pilot study with immunohistochemical observations	Overlapping populations
Hanneman	2016	Assessment of the precision and reproducibility of ventricular volume, function, and mass measurements with ferumoxytol-enhanced 4D flow MRI	Adverse events not reported
Hasan	2013	Early change in ferumoxytol-enhanced magnetic resonance imaging signal suggests unstable human cerebral aneurysm-a pilot study	Adverse events not reported
Hasan	2013	Imaging aspirin effect on macrophages in the wall of human cerebral aneurysms using ferumoxytol-enhanced MRI: Preliminary results	Adverse events not reported
Hasan	2012	Macrophage imaging within human cerebral aneurysms wall using ferumoxytol-enhanced MRI: A pilot study	Overlapping populations

APPENDIX A3. Continued

Author	Year	Study title	Reason for exclusion
Heckman	2019	An ounce of caution: Superparamagnetic iron oxide nanoparticle based magnetic resonance imaging contrast-associated anaphylaxis	Adverse events not reported
Hedgire	2014	Evaluation of renal quantitative T2 changes on MRI following administration of ferumoxytol as a T2 contrast agent	Adverse events not reported
Hedgire	2014	Enhanced primary tumor delineation in pancreatic adenocarcinoma using ultrasmall super paramagnetic iron oxide nanoparticle-ferumoxytol: An initial experience with histopathologic correlation	Overlapping populations
Hedgire	2018	Ultrasmall superparamagnetic iron oxide nanoparticle uptake as noninvasive marker of aortic wall inflammation on MRI: Proof of concept study	Overlapping populations
Hope	2015	Vascular imaging with ferumoxytol as a contrast agent	Overlapping populations
Horvath	2018	Quantitative comparison of delayed ferumoxytol T1 enhancement with immediate gadoteridol enhancement in high grade gliomas	Adverse events not reported
Huang	2019	Ferumoxytol-enhanced MRI for surveillance of pediatric cerebral arteriovenous malformations	Adverse events not reported
Huang	2019	Surveillance of residual pediatric brain arteriovenous malformations using ferumoxytol-based ASL and SPGR magnetic resonance series	Adverse events not reported
Joshi	2012	Comparison of in vivo magnetic resonance and positron emission tomography imaging in patients with abdominal aortic aneurysms	Adverse events not reported
Kallianos	2017	Ferumoxytol MRA for transcatheter aortic valve replacement planning with renal insufficiency	Adverse events not reported
Klenk	2014	Ionising radiation-free whole-body MRI vs. (18)F-fluorodeoxyglucose PET/CT scans for children and young adults with cancer: A prospective, nonrandomised, single-centre study	Overlapping populations
Lai	2016	Feasibility of nonanesthesia neonatal and young infant cardiac magnetic resonance imaging	Adverse events not reported
Li	2007	Lower extremity deep venous thrombosis: Evaluation with ferumoxytol-enhanced MRI and dual-contrast mechanism-preliminary experience	Adverse events not reported
Luhar	2016	Contrast-enhanced magnetic resonance venography in pediatric patients with chronic kidney disease: Initial experience with ferumoxytol	Overlapping populations
MacGillivray	2012	In vivo assessment of cellular inflammation following acute myocardial infarction	Adverse events not reported
Maralani	2018	Hypoxia detection in infiltrative astrocytoma: Ferumoxytol-based quantitative BOLD MRI with intraoperative and histologic validation	Adverse events not reported
Mertan	2016	Ferumoxytol enhanced MRI for the detection of lymph node involvement in prostate cancer	Adverse events not reported
Mertan	2017	Ferumoxytol enhanced MRI for the detection of lymph node metastases in prostate cancer	Adverse events not reported
Morales	2018	Evaluation of Meso-Rex bypass with ferumoxytol contrast enhanced MRI	Adverse events not reported

APPENDIX A3. Continued

Author	Year	Study title	Reason for exclusion
Muehe	2019	Ferumoxytol does not impact standardized uptake values on PET/MR scans	Adverse events not reported
Nakamoto	2013	Ferumoxytol-enhanced neuroimaging in HIV-associated neurocognitive disorder	Overlapping populations
Nayak	2015	High-resolution, whole-body vascular imaging with ferumoxytol as an alternative to gadolinium agents in a pediatric chronic kidney disease cohort	Overlapping populations
Nasseri	2012	Does pseudoprogression occur beyond 3 months following standard chemoradiation therapy in glioblastoma patients?	Adverse events not reported
Ndalo	2018	Ferumoxytol whole body vascular imaging including the central nervous system in pediatric patients: A single center's initial experience	Overlapping populations
Netto	2016	Misleading early blood volume changes obtained using ferumoxytol-based magnetic resonance imaging perfusion in high grade glial neoplasms treated with bevacizumab	Adverse events not reported
Neuwelt	2014	Diagnosis of pseudoprogression using ferumoxytol perfusion MRI in patients with glioblastoma to predict better outcome	Adverse events not reported
Neuwelt	2009	Ultrasmall superparamagnetic iron oxides (USPIOs): A future alternative magnetic resonance (MR) contrast agent for patients at risk for nephrogenic systemic fibrosis (NSF)?	Case report or review
Neuwelt	2014	The importance of delayed pseudoprogression and the problem with RANO in GBM	Adverse events not reported
Nguyen	2016	4D Multiphase steady state imaging with contrast (MUSIC) enhancement using ferumoxytol: A new paradigm in pediatric congenital heart disease	Adverse events not reported
Nguyen	2017	4D MUSIC CMR: Value-based imaging of neonates and infants with congenital heart disease	Overlapping populations
Nguyen	2018	Ferumoxytol-enhanced MR angiography for vascular access mapping before transcatheter aortic valve replacement in patients with renal impairment: A step toward patient-specific care	Overlapping populations
Nguyen	2017	Ferumoxytol enhanced black-blood cardiovascular magnetic resonance imaging	Overlapping populations
Nguyen	2017	MRI with ferumoxytol: A single center experience of safety across the age spectrum	Overlapping populations
Nguyen	2016	Ferumoxytol across the age spectrum: A single center experience of safety	Overlapping populations
Ning	2016	Hemodynamic safety and efficacy of ferumoxytol as an intravenous contrast agent in pediatric patients and young adults	Overlapping populations
Prince	2003	A pilot investigation of new superparamagnetic iron oxide (ferumoxytol) as a contrast agent for cardiovascular MRI	Overlapping populations
Ramanathan	2014	Lesion characterization with ferumoxytol MRI in patients with advanced solid tumors and correlation with treatment response to MM-398, nanoliposomal irinotecan (nal-IRI)	Adverse events not reported

APPENDIX A3. Continued

Author	Year	Study title	Reason for exclusion
Ramanathan	2014	Pilot study in patients with advanced solid tumors to evaluate feasibility of ferumoxytol (FMX) as tumor imaging agent prior to MM-398, a nanoliposomal irinotecan (nal-IRI)	Adverse events not reported
Rivera-Rivera	2018	Comparison of ferumoxytol-based cerebral blood volume estimates using quantitative R1 and R2 relaxometry	Adverse events not reported
Rivera-Rivera	2019	Measurements of cerebral blood volume using quantitative susceptibility mapping, R2 relaxometry, and ferumoxytol-enhanced MRI	Overlapping populations
Ruangwattanapaisarn	2015	Ferumoxytol as an off-label contrast agent in body 3 T MR angiography: A pilot study in children	Overlapping populations
Schindler	2017	Ultrasmall superparamagnetic iron oxide nanoparticle enhanced MRI at 7-Tesla in multiple sclerosis	Adverse events not reported
Schindler	2018	Ultrasmall superparamagnetic iron oxide nanoparticle-enhanced MRI at 7-Tesla in MS	Adverse events not reported
Schwein	2017	Feasibility of three-dimensional magnetic resonance angiography-fluoroscopy image fusion technique in guiding complex endovascular aortic procedures in patients with renal insufficiency	Adverse events not reported
Semple	2013	Quantitative myocardial inflammation assessed using a novel USPIO magnetic resonance imaging acquisition and analysis protocol	Adverse events not reported
Sethi	2017	The use of magnetic resonance imaging with ferumoxytol for annulus sizing in patients with chronic kidney disease undergoing transcatheter aortic valve replacement	Adverse events not reported
Shahrouki	2018	Ferumoxytol-enhanced magnetic resonance angiography for preprocedural vascular planning in patients with chronic kidney disease	Overlapping populations
Shahrouki	2019	High resolution, 3-dimensional ferumoxytol-enhanced cardiovascular magnetic resonance venography in central venous occlusion	Overlapping populations
Smits	2016	Noninvasive differentiation between hepatic steatosis and steatohepatitis with MRI enhanced with USPIOs in patients with nonalcoholic fatty liver disease: A proof-of-concept study	Adverse events not reported
Smits	2017	Evaluation of ultrasmall superparamagnetic iron-oxide (USPIO) enhanced MRI with ferumoxytol to quantify arterial wall inflammation	Adverse events not reported
Stirrat	2015	Ultrasmall superparamagnetic particles of iron oxide-enhanced magnetic resonance imaging in the assessment of cellular inflammation after myocardial infarction	Adverse events not reported
Stirrat	2014	Ultrasmall supraparamagnetic particles of iron oxide-enhanced magnetic resonance imaging in the assessment of cellular inflammation after myocardial infarction	Adverse events not reported
Stirrat	2016	Ferumoxytol-enhanced magnetic resonance imaging methodology and normal values at 1.5 and 3 T	Adverse events not reported
Stoumpos	2019	Ferumoxytol MR angiography vs. CT angiography for the assessment of potential kidney transplant recipients	Adverse events not reported

APPENDIX A3. Continued

Author	Year	Study title	Reason for exclusion
Stoumpos	2019	Ferumoxytol mr angiography vs. Doppler us for vascular mapping before haemodialysis arteriovenous access creation	Adverse events not reported
Stoumpos	2017	Ferumoxytol-enhanced magnetic resonance angiography for the assessment of patients with complex anatomy due for vascular access creation	Overlapping populations
Stoumpos	2018	Ferumoxytol-enhanced magnetic resonance angiography for the assessment of potential kidney transplant recipients	Overlapping populations
Stoumpos	2019	Ferumoxytol magnetic resonance angiography: A dose-finding study in patients with chronic kidney disease	Overlapping populations
Szidonya	2016	Late ferumoxytol enhancement aids the differentiation between meningiomas and metastases	Adverse events not reported
Thompson	2012	Dual contrast perfusion MRI in a single imaging session for assessment of pediatric brain tumors	Overlapping populations
Turkbey	2014	Ferumoxytol (feraheme) for lymph node imaging in prostate cancer	Overlapping populations
Tyagi	2018	Novel contrast mixture achieves contrast resolution of human bladder wall suitable for T1 mapping: Applications in interstitial cystitis and beyond	Case report or review
Usman	2018	Utility of ferumoxytol-enhanced 3 dimensional MRI in the assessment of carotid atheroma inflammation	Adverse events not reported
Varallyay	2013	High-resolution steady-state cerebral blood volume maps in patients with central nervous system neoplasms using ferumoxytol, a superparamagnetic iron oxide nanoparticle	Adverse events not reported
Varallyay	2017	Visualisation of normal and abnormal brain vasculature with different ferumoxytol doses	Adverse events not reported
Varallyay	2017	What does the boxed warning tell us? Safe practice of using ferumoxytol as an MRI contrast agent	Overlapping populations
Vasanawala	2015	Freebreathing cardiovascular MRI with ferumoxytol	Adverse events not reported
Velasquez	2016	Comparison of ferumoxytol (FERRAHEME) and gadolinium as intravenous contrast agents in pediatric patients undergoing cardiac magnetic resonance imaging (MRI) under general anesthesia	Adverse events not reported
Walker	2015	Ferumoxytol-enhanced magnetic resonance angiography is a feasible method for the clinical evaluation of lower extremity arterial disease	Overlapping populations
Weber	2019	Performance of aortic annular assessment by 3d transesophageal echocardiography or magnetic resonance angiography with ferumoxytol in patients with CKD undergoing TAVR	Adverse events not reported
Wells	2020	Pharmacokinetics of ferumoxytol in the abdomen and pelvis: A dosing study with 1.5- and 3.0-T MRI relaxometry	Overlapping populations
Yilmaz	2013	Imaging of myocardial infarction using ultrasmall superparamagnetic iron oxide nanoparticles: A human study using a multi-parametric cardiovascular magnetic resonance imaging approach	Adverse events not reported

APPENDIX A3. Continued

Author	Year	Study title	Reason for exclusion
Yilmaz	2011	Assessment of infarcted myocardium using ultrasmall superparamagnetic iron-oxide (USPIO) nanoparticles: Preliminary results of a multiparametric CMR approach	Adverse events not reported
Yoshida	2020	Intermodality feature fusion combining unenhanced computed tomography and ferumoxytol-enhanced magnetic resonance angiography for patient-specific vascular mapping in renal impairment	Overlapping populations
Zhou	2017	Accelerated ferumoxytol-enhanced 4D multiphase, steady-state imaging with contrast enhancement (MUSIC) cardiovascular MRI: Validation in pediatric congenital heart disease	Overlapping populations
Zucker	2018	Free-breathing pediatric chest MRI: Performance of self-navigated golden-angle ordered conical ultrashort echo time acquisition	Adverse events not reported
Zucker	2018	Free-breathing ferumoxytol-enhanced MRI for preoperative renal transplant vascular mapping in infants and children	Adverse events not reported