

Prospective Multicenter Study of the Safety of Gadoteridol in 6163 Patients

Sung Bum Cho, MD, PhD,^{1*} A-Leum Lee, MD, PhD,² Hyuk Won Chang, MD,³
Kyeong Ah Kim, MD, PhD,⁴ Won Jong Yoo, MD, PhD,⁵ Jeong A. Yeom, MD,⁶
Myung Ho Rho, MD, PhD,⁷ Sung Jin Kim, MD,⁸ Yun-jung Lim, MD,⁹ and Miran Han, MD¹⁰

Background: The safety of gadolinium-based contrast agents is of fundamental importance.

Purpose: To determine the frequency and severity of immediate-type adverse reactions to approved doses of gadoteridol in patients referred for routine gadoteridol-enhanced MRI in actual clinical practice settings.

Study Type: Prospective, observational.

Population: In all, 6163 subjects were enrolled (mean age: 56.7 ± 15.4 years; range: 6–93 years).

Field Strength/Sequence: 1.5T and 3.0T.

Assessment: Assessment was of immediate adverse reactions by the investigating radiologist using the MedDRA System Organ Class and preferred term.

Statistical Tests: Summary statistics for continuous variables, descriptive statistics for demographic characteristics.

Results: Overall, 19 adverse events occurred in 13 (0.21%) patients, of which 15 in 10 (0.16%) patients were considered related to gadoteridol administration. These events were evenly distributed between male and female subjects and all occurred in adults. Twelve of the 15 related events in eight (0.13%) patients were considered mild in intensity (rapidly self-resolving), while the remaining three events in two patients (0.03%) were considered moderate in intensity. None were of severe intensity and no serious adverse events occurred.

Data Conclusion: The rate of immediate-type adverse events following exposure to approved doses of gadoteridol is extremely low, and mostly limited to transient and self-resolving symptoms.

Level of Evidence: 2

Technical Efficacy Stage: 5

J. MAGN. RESON. IMAGING 2020;51:861–868.

GADOLINIUM-BASED CONTRAST AGENTS (GBCAs) have long been considered relatively safe in terms of adverse events (AEs), especially when compared with iodinated contrast agents.¹ However, the emergence of nephrogenic systemic fibrosis (NSF) in 2006² and, more recently, concern over potential long-term health risks due to gadolinium (Gd) retention in brain and body tissues,^{3,4} has brought the issue of GBCA safety into sharp focus. The suspension in Europe of certain linear GBCAs⁵ and a general migration towards the use of macrocyclic GBCAs has further fueled the need for detailed information on individual GBCA safety.

Gadoteridol, the first macrocyclic GBCA approved in the USA, is classified by the European Medicines Agency (EMA)⁶ among the group of GBCAs that has the lowest risk of NSF and by the American College of Radiology (ACR)⁷ as a Group II agent (agents associated with few, if any, unconfounded cases of NSF). In animal studies, Gd retention has been found to be extremely low following the repeated administration of gadoteridol, and lowest in brain tissues when compared with Gd retention observed after repeated administration of other macrocyclic GBCAs.^{8–10} No instances of T₁ hyperintensity in the brain have yet been observed

View this article online at wileyonlinelibrary.com. DOI: 10.1002/jmri.26940

Received Jul 2, 2019, Accepted for publication Sep 9, 2019.

*Address reprint requests to: S.B.C., 73, Incheon-ro, Seongbuk-gu, Seoul, Korea. E-mail: anglercho@gmail.com

From the ¹Department of Radiology, Anam Hospital, College of Medicine, Korea University, Seoul, Korea; ²Department of Radiology, Soonchunhyang University Hospital, Gyeonggi-do, Korea; ³Department of Radiology, Dongsan Medical Center, Keimyung University, Daegu, Korea; ⁴Department of Radiology, Korea University Guro Hospital, Seoul, Korea; ⁵Department of Diagnostic Radiology, Bucheon St. Mary's Hospital, Catholic University of Korea, Gyeonggi-do, Korea; ⁶Department of Radiology, Pusan National University Yangsan Hospital, Gyeongsangnam-do, Korea; ⁷Department of Radiology, Kangbuk Samsung Hospital, Seoul, Korea; ⁸Department of Radiology, Chungbuk National University Hospital, Chungcheongbuk-do, Korea; ⁹Department of Radiology, Haeundae Paik Hospital, Busan, Korea; and ¹⁰Department of Radiology, Ajou University Medical Center, Suwon-si, Korea

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

following multiple exposure to approved doses of gadoteridol in adult or pediatric patients.

Comparatively little has been published on the frequency and type of immediate-type AEs following exposure to gadoteridol. To our knowledge, the last prospective observational study in a relatively large patient cohort (28,078 patients) was a single-center study published in 2011 that reported an overall AE rate of 0.7%.¹¹

Our aim was to further elucidate the safety of gadoteridol for routine clinical use across a broad spectrum of indications and patients at multiple centers.

Materials and Methods

This was a prospective, observational study involving nonselective, continuous enrollment of patients referred for contrast-enhanced (CE)-MRI with gadoteridol during routine daily clinical practice. It was an Institutional Review Board-approved, Health Insurance Portability and Accountability Act-compliant study that evaluated safety data for patients enrolled at 19 centers in South Korea between 31 December 2014 and 8 May 2018. All patients provided written informed consent for inclusion in the study. The study was sponsored by Bracco Diagnostics (Monroe, NJ).

Patients

Subjects were enrolled in a nonselective, continuous manner at each of 19 centers. The initial prospective enrolment target was 6000 patients evaluated as part of normal clinical routine without restrictions on age, clinical status, or MRI indication. There were no exclusion criteria. All patient demographic details (gender, age, weight) were recorded. If the subject's estimated glomerular filtration rate (eGFR) was measured, this was also recorded.

MRI

CE-MRI was performed with gadoteridol according to clinical routine at each center. All imaging studies were performed on commercially available 1.5T or 3.0T MRI equipment at each center. The indication(s) for the MRI examination and whether a perfusion scan was performed in addition to a standard imaging protocol was recorded for each subject, as were details as to whether the MRI examination was performed as the first exam for the subject or as an additional examination to gain more information on a previously identified disease.

The type of gadoteridol administration, ie, manual or power injector (including rate of injection of contrast and saline), total contrast volume and total saline volume (typically 20–30 mL) were recorded for each examination. The recommended administration dosage was 0.1 mmol/kg (0.2 mL/kg) as per the approved prescribing information (PI) for South Korea. For subjects suspected of having cerebral metastases or other poorly enhancing lesions of the central nervous system, a triple dose (0.3 mmol/kg [0.6 mL/kg]) was permitted as per the approved PI.

Safety Assessments

Subjects were monitored for any untoward medical occurrences from the time of gadoteridol administration for at least 30 minutes after completion of the MRI examination. All untoward medical occurrences were recorded in the Adverse Event section of a dedicated Case Report Form (CRF).

Events were classified as serious (death, life-threatening, requiring/prolonging hospitalization) or nonserious (mild: no disability/incapacity, self-resolving; moderate: no disability/incapacity requiring treatment; or severe: temporary and/or mild disability/incapacity requiring treatment). Event severity and its relationship to the contrast agent (not related, or possibly/probably related to exposure to gadoteridol) were determined by the investigating radiologist. All

TABLE 1. MRI Indication by Gender and Age

Indication	Gender		Age (years)		
	Male	Female	2–18	>18–64	≥ 65
Overall	2632	3531	52	4083	2028
Brain	1746	2190	31	2511	1394
Spine	157	138	4	179	112
Head and neck (not CNS)	462	335	12	559	226
Breast and chest	3	280	0	240	43
Upper abdomen	37	45	0	57	25
Lower abdomen	184	514	6	494	198
Musculoskeletal-joints	89	100	2	151	36
MR angiography	630	822	1	920	531
Other MRI indications	18	18	0	30	6

^a*A patient could have multiple indications.

TABLE 2. Gadoteridol Dose by MRI Indication

Indication	Total patients (N)*	(%)	Gadoteridol dose (mmol/kg) \pm SD
Overall	6163		0.108 \pm 0.02
Brain	3936	(44.0)	0.109 \pm 0.02
Spine	295	(3.3)	0.109 \pm 0.02
Head (not CNS)	646	(7.2)	0.105 \pm 0.02
Neck (not CNS)	321	(3.6)	0.104 \pm 0.02
Chest (non MRA)	3	(0.0)	0.106 \pm 0.001
Breast	280	(3.1)	0.12 \pm 0.023
Upper abdomen			
Liver	3	(<0.1)	0.115 \pm 0.03
Kidneys	21	(0.2)	0.099 \pm 0.004
Pancreas	60	(0.7)	0.103 \pm 0.01
Other	5	(0.1)	0.101 \pm 0.006
Lower abdomen			
Cervix	291	(3.3)	0.103 \pm 0.01
Uterus	291	(3.3)	0.103 \pm 0.01
Ovaries	203	(2.3)	0.104 \pm 0.013
Fallopian tubes	148	(1.7)	0.104 \pm 0.012
Bowel	46	(0.5)	0.116 \pm 0.02
Bladder	19	(0.2)	0.106 \pm 0.016
Prostate	104	(1.2)	0.103 \pm 0.01
Other	121	(1.4)	0.102 \pm 0.013
Musculoskeletal-joints			
Shoulder	55	(0.6)	0.1 \pm 0.014
Elbow	8	(0.1)	0.108 \pm 0.026
Wrist, hand & fingers	17	(0.2)	0.105 \pm 0.017
Hip	67	(0.7)	0.101 \pm 0.008
Knee	10	(0.1)	0.107 \pm 0.006
Ankle & foot	14	(0.2)	0.112 \pm 0.018
Temporo-mandibular joint	1	(<0.1)	0.136
Soft tissues	9	(0.1)	0.106 \pm 0.018
Bones	10	(0.1)	0.101 \pm 0.017
Other	2	(0.0)	0.106 \pm 0.002
MR angiography			
Intracranial	1369	(15.3)	0.101 \pm 0.011
Supraaortic (carotid-vertebral)	518	(5.8)	0.101 \pm 0.009
Abdominal (aorto-iliac) / renal	1	(<0.1)	0.097

TABLE 2. Continued

Indication	Total patients (N)*	(%)	Gadoteridol dose (mmol/kg) \pm SD
Whole-body	37	(0.4)	0.1 \pm 0.002
Cardiac	6	(0.1)	0.158 \pm 0.059
Other MRI indications	36	(0.4)	0.101 \pm 0.009

*A patient could have multiple indications.

AEs were coded using the MedDRA System Organ Class and preferred term.¹²

Statistical Analysis

Sample size estimation was not applicable for this observational study. In general, summary statistics (mean, standard deviation, median, minimum, and maximum) were provided for continuous variables, and the number and percentage of patients in each category were provided for categorical data. Descriptive statistics were used to summarize demographic characteristics, MRI indication, contrast agent administration and AEs, and 95% confidence interval (CI) was provided to the estimations of the AE rate. Fisher's exact test was used to compare the difference between subgroups. All data summaries were generated using the statistical software SAS v. 9.3 (Cary, NC).

Results

Patients

A total of 6163 patients were enrolled, of which 2632 (42.7%) were male and 3531 (57.3%) female (Table 1). Patients were aged between 6 and 93 years with a mean (\pm standard deviation [SD]) of 56.7 ± 15.4 years. Enrolment by major age group was as follows: (2–18 years, $n = 52$ [0.84%]; >18–64 years, $n = 4083$ [66.3%]; ≥ 65 years, $n = 2028$ [32.9%]) (Table 1). The mean patient weight was 62.85 ± 11.16 kg. Overall, 5356 (86.9%) subjects were outpatients and 807 (13.1%) inpatients. Individual centers enrolled between 162 (2.6%) and 600 (9.7%) patients.

Kidney function (eGFR [mL/min]) was determined in 1202 (19.5%) patients. The mean (\pm SD) eGFR was 84.82 ± 22.37 . A total of 113/1202 (9.4%) patients had eGFR measurements of <60 mL/min. Among these 113 patients, seven had eGFR measurements between 15 and 29 mL/min while two had eGFR measurements of <15 mL/min.

MRI

Imaging was performed on a range of MR scanners (Siemens, Erlangen, Germany [1866; 30.3%]; GE, Milwaukee, WI [2087; 33.9%]; Philips, Best, Netherlands [2210; 35.9%]) mainly at 3T (3707 [60.1%]) and 1.5T (2452 [39.8%]). Just four (0.1%) patients were imaged at 1T. Perfusion imaging was performed in 106 (1.7%) patients.

Indications for the MRI examinations across all patients are presented in Table 1. Imaging was performed as a first

exam to detect or exclude disease in a patient with symptoms/signs in 3166 (51.4%) patients or as an additional investigation to confirm disease or gain more information on a previously identified disease in 2997 (48.6%) patients. Specific reasons for the additional investigations were to gain a better understanding of an unclear/inconclusive diagnosis (482/2997 [16.1%]), better define the extent of disease

TABLE 3. Summary of Adverse Events

		Adverse events <i>n</i> (%)	Adverse events related to gadoteridol <i>n</i> (%)
		95% CI (%)	95% CI (%)
Number of patients dosed ^a		6163	6163
Number of adverse events		19	15
Number (%) of patients with adverse event(s)		13 (0.21) (0.12, 0.36)	10 (0.16) (0.09, 0.30)
Number of patients with adverse events by intensity ^b	Mild	9 (0.15) (0.08, 0.28)	8 (0.13) (0.07, 0.26)
	Moderate	4 (0.06) (0.04, 0.21)	2 (0.03) (0.01, 0.12)
	Severe	0	0
Number of patients with special situation(s) involving gadoteridol ^c		1 (0.02) (0.00, 0.09)	0
Number of patients with serious adverse event(s)		0	0
Number of deaths		0	0

^aDenominator for percentages.

^bIf a patient experienced >1 adverse event, the patient was counted once at the maximum intensity.

^cContrast extravasation resulting in pain and swelling at the injection site.

TABLE 4. Summary of All Postdose Adverse Events and Potentially Related Adverse Events by Gender and Age Group

Subgroup/category		Subjects	No. (%) of patients with at least 1 adverse event	
		(N = 6163)	All adverse events (n = 13)	Gadoteridol-related adverse events (n = 10)
Gender n (%)	Male	2632 (42.7)	7	6
	Female	3531 (57.3)	6	4
	P-value*		0.418	0.342
Age group	2 to 11 years	11 (0.2)	0	0
	12 to 18 years	41 (0.7)	0	0
	>18 to 40 years	901 (14.6)	2	2
	41 to 64 years	3182 (51.6)	5	4
	65 to 74 years	1276 (20.7)	4	4
	75 to 84 years	704 (11.4)	2	0
	≥85 years	48 (0.8)	0	0
	P-value*		0.7243	0.4570

*P-values determined using Fisher's exact test.

TABLE 5. Comparison of Adverse Drug Reactions to Macrocyclic GBCAs in Multicenter, Prospective Observational Studies

GBCA	Reference	No. of patients	Overall ADR rate	Serious ADRs
Gadoteridol	This study	6,163	0.16%	0.0%
Gadoteric acid	13	84,621	0.34%	<0.01%
	14	35,499	0.09%	<0.01%
	15	3,444	0.93%	0.0%
Gadobutrol	16	3,710	0.59%	0.03%
	17	23,708	0.7%	0.02%
	18	3,337	0.99%	0.03%

(909/2997 [30.3%]), follow-up surgical (1107/2997 [36.9%]) or nonsurgical (813/2997 [27.1%]) treatment, or "other" (98 [3.3%]).

Patients received gadoteridol at a mean dose of 0.108 ± 0.02 mmol/kg bodyweight with minimal variations across indications (Table 2). Only three patients received a gadoteridol dose of 0.3 mmol/kg or above.

Adverse Events

Overall, 19 AEs occurred in 13 (0.21%) patients who received gadoteridol. Of these 19 events, 15 in 10 (0.16%)

patients were considered possibly or probably related to gadoteridol administration (Table 3). These events were evenly distributed between male and female subjects and all occurred in adults (Table 4). Twelve of the 15 related events in eight (0.13%) patients were considered mild in intensity. The remaining three events in two (0.03%) patients were considered moderate in intensity and were hypersensitivity reactions in male patients of 60 and 68 years of age. Both patients were referred for supra-aortic MR angiography and were undergoing an MRI examination for the first time. Both hypersensitivity reactions began 20–30 minutes after

gadoteridol administration, were treated with antihistamines and steroids, and resolved within 45–60 minutes. Mild nausea and vomiting considered possibly related to gadoteridol administration were reported by 3/6163 (0.05%) patients. All patients with AEs quickly recovered without sequelae. There were no serious AEs, ie, no AEs that were considered life-threatening, required hospitalization, resulted in persistent or significant disability/incapacity, required intervention to prevent permanent impairment or damage, or resulted in death.

eGFR measurements were available for only three patients who experienced AEs (one not related to gadoteridol administration; two with events considered possibly related). In all three cases, the recorded eGFR was >60 mL/min. Of the 10 patients with possibly related AEs, one received a gadoteridol dose of 0.09 mmol/kg, seven received a dose of 0.1 mmol/kg, and two received a dose of 0.13 mmol/kg.

Discussion

In assessing GBCA safety it is important to distinguish prospectively-designed studies in which exposure is assessed at baseline and subjects are followed over time for adverse reactions, from retrospective assessments in which rates of reactions, and conclusions regarding safety, are based on a historical observation period. Whereas retrospective assessments offer the possibility to include large numbers of patients, they are inherently subject to various forms of bias (eg, information and selection bias), thus tempering the conclusions and interpretations that can be drawn. Conversely, prospective assessments permit accurate recording of all relevant information, allowing more solid conclusions and more reliable comparison with similarly designed prospective studies. By the same token, it is important to distinguish prospective, multicenter studies that allow objective assessment of data with minimal subjectivity, from single-center studies whose findings and conclusions might be inherently subjective and prone to misinterpretation and bias. The results of our prospective, multicenter, observational study reveal an overall rate of AEs related to gadoteridol administration of 0.16% (10/6163). This rate falls very much in the lower half of the range indicated by the ACR, who state that the rate of immediate-type adverse reactions for GBCAs administered at clinical doses (0.1–0.2 mmol/kg for most GBCAs) ranges from 0.07–2.4%.⁷ Moreover, it bears excellent comparison with adverse reaction rates reported for other macrocyclic GBCAs in similarly designed prospective, multicenter observational studies^{13–18} (Table 5). Among the adverse reactions reported, nausea and vomiting were the most frequent, reported by three (0.05%) patients overall and accounting for 40% (6/15) of all the reactions considered possibly related to gadoteridol administration. This rate compares favorably with rates reported for both gadoteric acid (nausea: 0.02–0.41%; vomiting: 0.01–0.1%^{13–15}) and gadobutrol (nausea: 0.23–0.3%; vomiting: 0.06–0.1%^{16–18}).

Notable is that there was no effect of age on the incidence of AEs. Events considered to be gadoteridol-related were reported in only four of 2028 (0.2%) subjects aged ≥65 years compared with six of 4135 (0.15%) subjects aged <65 years. No events considered gadoteridol-related were reported for any of the 52 subjects aged <18 years. These findings again compare favorably with reports for other macrocyclic GBCAs.^{19,20} Finally, there was no specific imaging application and no other specific patient demographic that was more associated with AEs than any other.

As might be expected, the overall incidence of AEs considered gadoteridol-related in this study (0.16%) was lower than the rate of adverse reactions (0.67%) reported in a previous, large (28,078 patients), prospective, single-center observational study conducted in the United States between July 2007 and December 2009.¹¹ Possible explanations for the different rates reported include cultural differences in the interpretation and reporting of AEs and the fact that event interpretation and reporting in a single-center study over a comparatively short time course (30 months in the study by Morgan et al¹¹) is likely performed by the same, comparatively few, investigators, potentially leading to interpreter bias. In this regard it has been shown previously that the reporting of AEs can vary widely across individual healthcare workers and imaging centers even within the same local healthcare system.²¹

To consider also is that the study by Morgan et al¹¹ was performed at the height of the NSF crisis when the safety of all GBCAs was extremely heavily scrutinized, not only by physicians themselves but also by medicolegal professionals. Under such circumstances it is possible that the higher rate of reported reactions reflected a more general overreporting of AEs during that period. Finally, it should also be borne in mind that the study by Morgan et al¹¹ was initiated just 6 months after the initial selective introduction of gadoteridol into the department due to concerns over NSF. As the authors themselves noted,¹¹ the initial rate of AEs over the first 3 months was higher before decreasing steadily over the remainder of the study. The authors ascribed this observation to possibly reflecting the Weber effect, which describes transient elevations in the rates of AEs after the introduction of a new drug or changes in the use of an existing drug.^{22,23} However, it is widely recognized that the elevation in AE reporting due to the Weber effect tends to peak in the second year after introduction.^{24–26} Given that the duration of the study was only 30 months after the adoption of gadoteridol, it is possible the true impact of the Weber effect might not have been fully appreciated at the time and that the reaction rate reported represents longer-term overreporting.

Concerns over NSF and, more recently, Gd retention^{27,28} have led to a widespread migration from linear GBCAs to macrocyclic GBCAs for routine clinical use. Although studies to date suggest that GBCA exposure has no

long-term detrimental effects on human health either in terms of direct impact on tissue integrity,^{29–31} or global clinical disability,^{32,33} the possibility of long-term effects is nevertheless a major area of current concern.⁵ Although assessment of potential long-term safety issues was beyond the scope of this observational study, it is worth noting that all studies thus far performed in animals to evaluate Gd retention in brain and body tissues following GBCA exposure have shown that gadoteridol is retained to a lesser extent and cleared more rapidly than other GBCAs, including other macrocyclic GBCAs.^{8–10} Specifically, it appears that the unique molecular features of the gadoteridol molecule (low molecular weight and viscosity, neutrality, and high lipophilicity) are sufficient to markedly affect GBCA elimination behavior,^{9,34} leading to lower levels of retained Gd in the first weeks/months after exposure.^{8–10} Given that one rat year equates to roughly 30 human years,³⁵ the reduced amount of Gd determined in rat brain and body tissues at weeks/months after gadoteridol administration would equate to several years in humans, if the findings in animals are considered indicative of the human situation. This may be very relevant if future studies do indeed demonstrate an unequivocal impact of GBCA exposure on human health.

In conclusion, our prospective, multicenter, observational study of 6163 subjects ranging in age from 6 to 93 years and covering a wide spectrum of imaging applications confirmed the excellent safety profile of gadoteridol for routine CE-MRI examinations. The incidence of gadoteridol-related adverse reactions (0.16%) compares favorably with rates reported for other macrocyclic GBCAs evaluated in similarly designed prospective studies. In the absence of any clinically-relevant differences in r1-relaxivity, which might otherwise impact image quality and/or diagnostic performance relative to other macrocyclic GBCAs,^{36,37} and given the demonstrably lower Gd retention and faster Gd clearance seen in animals after repeated gadoteridol exposure,^{8–10} gadoteridol can be considered one of the safer GBCAs for routine CE-MRI.

References

- Hunt CH, Hartman RP, Hesley GK. Frequency and severity of adverse effects of iodinated and gadolinium contrast materials: Retrospective review of 456,930 doses. *AJR Am J Roentgenol* 2009;193:1124–1127
- Grobner T. Gadolinium: A specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? *Nephrol Dial Transplant* 2006;21:3604–3605 [Erratum, *Nephrol Dial Transplant* 2006;21:1745].
- Gulani V, Calamante F, Shellock FG, Kanal E, Reeder SB; International Society for Magnetic Resonance in Medicine. Gadolinium deposition in the brain: Summary of evidence and recommendations. *Lancet Neurol* 2017;16:564–570.
- McDonald RJ, Levine D, Weinreb J, et al. Gadolinium retention: A research roadmap from the 2018 NIH/ACR/RSNA Workshop on Gadolinium Chelates. *Radiology* 2018;289:517–534.
- Available at: https://www.ema.europa.eu/documents/referral/gadolinium-article-31-referral-emas-final-opinion-confirms-restrictions-use-linear-gadolinium-agents_en.pdf. Accessed 20 December 2018.
- European Society of Urogenital Radiology (ESUR) guidelines on contrast agents. Version 10.0. March 2018. Available at: <http://www.esur-cm.org>. Accessed 20 December 2018.
- American College of Radiology (ACR) Manual on contrast media. Version 10.3. June 2018. Available at: <https://www.acr.org>. Accessed 20 December 2018.
- McDonald RJ, McDonald JS, Dai D, et al. Comparison of gadolinium concentrations within multiple rat organs after intravenous administration of linear versus macrocyclic gadolinium chelates. *Radiology* 2017;285:536–545.
- Bussi S, Coppo A, Botteron C, et al. Differences in gadolinium retention after repeated injections of macrocyclic MR contrast agents to rats. *J Magn Reson Imaging* 2018;47:746–752.
- Jost G, Frenzel T, Boyken J, et al. Long-term excretion of gadolinium-based contrast agents: Linear versus macrocyclic agents in an experimental rat model. *Radiology* 2019;180135.
- Morgan DE, Spann JS, Lockhart ME, Winningham B, Bolus DN. Assessment of adverse reaction rates during gadoteridol-enhanced MR imaging in 28,078 patients. *Radiology* 2011;259:109–116.
- Available at: <https://www.meddra.org>. Accessed 20 March 2019.
- Maurer M, Heine O, Wolf M, Durmus T, Wagner M, Hamm B. Tolerability and diagnostic value of gadoteric acid in the general population and in patients with risk factors: Results in more than 84,000 patients. *Eur J Radiol* 2012;81:885–890.
- Soyer P, Dohan A, Patkar D, Gottschalk A. Observational study on the safety profile of gadoterate meglumine in 35,499 patients: The SECURE study. *J Magn Reson Imaging* 2017;45:988–997
- Ishiguchi T, Takahashi S. Safety of gadoterate meglumine (Gd-DOTA) as a contrast agent for magnetic resonance imaging: Results of a post-marketing surveillance study in Japan. *Drugs R D* 2010;10:133–145.
- Glutik K, Hahn G, Kuvvetli P, Endrikat J. Safety of gadobutrol: Results of a non-interventional study of 3710 patients, including 404 children. *Acta Radiol* 2019;60:873–879.
- Prince MR, Lee HG, Lee CH, et al. Safety of gadobutrol in over 23,000 patients: The GARDIAN study, a global multicentre, prospective, non-interventional study. *Eur Radiol* 2017;27:286–295.
- Tsushima Y, Awai K, Shinoda G, et al. Post-marketing surveillance of gadobutrol for contrast-enhanced magnetic resonance imaging in Japan. *Jpn J Radiol* 2018;36:676–685.
- Glutik K, Bhargava R, Hahn G, et al. Safety of gadobutrol in more than 1,000 pediatric patients: Subanalysis of the GARDIAN study, a global multicenter prospective non-interventional study. *Pediatr Radiol* 2016;46:1317–1323.
- Scala M, Koob M, de Buttet S, Bourrinet P, Felices M, Jurkiewicz E. A pharmacokinetics, efficacy, and safety study of gadoterate meglumine in pediatric subjects aged younger than 2 years. *Invest Radiol* 2018;53:70–79.
- Bleicher AG, Kanal E. Assessment of adverse reaction rates to a newly approved MRI contrast agent: Review of 23,553 administrations of gadobenate dimeglumine. *AJR Am J Roentgenol* 2008;191:W307–311.
- Weber JCP. Epidemiology of adverse reactions to nonsteroidal antiinflammatory drugs. In: Rainsford KD, Velo GP, eds. *Advances in inflammation research*, Vol 6. New York: Raven; 1984:1–7.
- Hartnell NR, Wilson JP. Replication of the Weber effect using post-marketing adverse event reports voluntarily submitted to the United States Food and Drug Administration. *Pharmacotherapy* 2004;24:743–749.
- Davenport MS, Dillman JR, Cohan RH, et al. Effect of abrupt substitution of gadobenate dimeglumine for gadopentetate dimeglumine on rate of allergic-like reactions. *Radiology* 2013;266:773–782.
- Fakhran S, Alhilali L, Kale H, Kanal E. Assessment of rates of acute adverse reactions to gadobenate dimeglumine: Review of more than

- 130,000 administrations in 7.5 years. *AJR Am J Roentgenol* 2015;204:703–706.
26. Forbes-Amrhein MM, Dillman JR, Trout AT, et al. Frequency and severity of acute allergic-like reactions to intravenously administered gadolinium-based contrast media in children. *Invest Radiol* 2018;53:313–318.
27. Kanda T, Fukusato T, Matsuda M, et al. Gadolinium-based contrast agent accumulates in the brain even in subjects without severe renal dysfunction: Evaluation of autopsy brain specimens with inductively coupled plasma mass spectroscopy. *Radiology* 2015;276:228–232.
28. Murata N, Gonzalez-Cuyar LF, Murata K, et al. Macrocyclic and other non-group 1 gadolinium contrast agents deposit low levels of gadolinium in brain and bone tissue: Preliminary results from 9 patients with normal renal function. *Invest Radiol* 2016;51:447–453.
29. Eisele P, Konstandin S, Szabo K, et al. Sodium MRI of T1 high signal intensity in the dentate nucleus due to gadolinium deposition in multiple sclerosis. *J Neuroimaging* 2017;27:372–375.
30. Eisele P, Szabo K, Ebert A, et al. Diffusion-weighted imaging of the dentate nucleus after repeated application of gadolinium-based contrast agents in multiple sclerosis. *Magn Reson Imaging* 2019;58:1–5.
31. Mallio CA, Piervincenzi C, Gianolio E, et al. Absence of dentate nucleus resting-state functional connectivity changes in nonneurological patients with gadolinium-related hyperintensity on T1-weighted images. *J Magn Reson Imaging* 2019;50:445–455.
32. Welk B, McArthur E, Morrow SA, et al. Association between gadolinium contrast exposure and the risk of parkinsonism. *JAMA* 2016;316:96–98.
33. Cocozza S, Pontillo G, Lanzillo R, et al. MRI features suggestive of gadolinium retention do not correlate with Expanded Disability Status Scale worsening in multiple sclerosis. *Neuroradiology* 2019;61:155–162.
34. Aime S. Differences in molecular structure markedly affect GBCA elimination behavior. *Radiology* 2019;291:267–268.
35. Sengupta P. The laboratory rat: Relating its age with human's. *Int J Prev Med* 2013;4:624–630.
36. Shen Y, Goerner FL, Snyder C, et al. T1 relaxivities of gadolinium-based magnetic resonance contrast agents in human whole blood at 1.5, 3, and 7 T. *Invest Radiol* 2015;50:330–338.
37. Maravilla KR, Smith MP, Vymazal J, et al. Are there differences between macrocyclic gadolinium contrast agents for brain tumor imaging? Results of a multicenter intraindividual crossover comparison of gadobutrol with gadoteridol (the TRUTH study). *AJNR Am J Neuroradiol* 2015;36:14–23.