

Gadolinium Retention as a Safety Signal

Experience of a Manufacturer

Eric Lancelot, PharmD, PhD and Pierre Desché, MD

Objectives: The purpose of this manuscript is to review the successive regulatory actions and decisions following the initial publication by Kanda and colleagues in 2014 regarding gadolinium retention in the human brain after multiple gadolinium-based contrast agents (GBCAs) administrations.

Materials and Methods: Starting from 2014, the actions and decisions made by all regulatory authorities were collected and summarized region by region. Volumes of GBCA sales in 2018 per region and main countries are also presented as an indicator of patients' exposure to those products.

Results: All regulatory authorities agreed on the absence of evidence of any harmful effect of gadolinium retention in humans. However, based on the same amount of preclinical and clinical evidence available in adults and children, regulatory authorities used different approaches resulting in different actions and decisions regarding the labeling and market authorizations of GBCAs, as well as the specific actions requested to the manufacturers.

Conclusions: The manufacturers of GBCAs had to face different situations according to the countries, due to the different positions and expectations from regulatory agencies. They have adapted their responses to the different positions of the regulatory agencies and conducted specific preclinical and clinical investigations to provide the expected evidence. It is also their responsibility to continuously monitor the benefit-risk balance of the products and to propose risk minimization measures to the regulatory agencies.

Key Words: gadolinium retention, regulatory authorities, T1 hypersignal

(*Invest Radiol* 2019;55: 20–24)

HOW DID THE STORY START?

In March 2014, Kanda and colleagues first reported the presence of T1-weighted hyperintensities in the globus pallidus (GP) and dentate nucleus (DN) of adult human brain associated with cumulative doses of gadolinium-based contrast agents (GBCAs), namely, gadodiamide or gadopentetate dimeglumine, in patients with normal renal function.¹ Rapidly, this article was followed by several confirmatory publications.^{2,3} One year later, these T1 hypersignals were reported by several teams to be related to gadolinium (Gd) deposition in the GP and DN.^{4,5}

From preclinical experiments in translational animal models⁶ and a number of human studies, it became rapidly evident that there was again a difference between linear and macrocyclic GBCAs,^{7–10} thus reopening the scientific discussion about the stability of GBCAs and the potential release and deposition of Gd as discussed 10 years before for nephrogenic systemic fibrosis (NSF). The difference between linear and macrocyclic agents with regards to Gd deposition in the brain is highly supported by

the difference in their pharmacokinetic profiles, including their long-term biodistribution and excretion.¹¹ After the publication of numerous case reports, retrospective studies, and poorly controlled studies, several research groups issued some recommendations aiming at improving the methodological aspects and standardization of both preclinical studies¹² and clinical studies,¹³ and ultimately helping in the distinction between high-quality and poor-quality studies. The need for preclinical studies investigating Gd deposition in juvenile animal models and clinical studies in children has also been emphasized.^{14,15}

In the meantime, 2 independent research teams^{16,17} using translational animal models came to the same conclusions: the intact Gd chelate molecules of both linear and macrocyclic GBCAs that accumulate in the brain and are progressively eliminated over time should be differentiated from the permanent deposition of potentially dechelated Gd that is caused exclusively by linear GBCAs.¹⁸

In the following sections, we describe how the Gd retention issue was analyzed by the regulatory agencies and how complex was the situation faced by the marketing authorization holders (MAHs) over a relatively short period of time. For reference, Table 1 presents the total volumes of GBCAs sold in 2018 per region and main countries.

HOW MAY A FEW SCIENTIFIC PUBLICATIONS RAISE A SAFETY SIGNAL?

The definition of a safety signal is given in the module IX of the guidelines on good pharmacovigilance practices as published in October 2017 by the European Medicines Agency (EMA): “A safety signal is an information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.” In the present case, the cumulative doses of GBCAs represent “the intervention” and the T1 hypersignals in GP and DN of patients with normal renal function stand for “the event.” Within the EMA, the assessment of the benefit-risk balance of medicinal products is managed by the Pharmacovigilance Risk Assessment Committee (PRAC). One of the responsibilities of the PRAC is to assess the safety signals that have been detected, validated, and confirmed by the Agency. As stated in the pharmacovigilance practices, “In its consideration of a signal, the PRAC should agree on a prioritisation based on the individual patient and public health impact of the potential change to the benefit-risk balance. Depending on the prioritisation, an analysis of the need for further assessment or for any immediate recommendation for action should be made, taking into account the time frame proposed by the Agency that detected the signal.”

HOW WAS THIS SAFETY SIGNAL MANAGED IN EUROPE?

The PRAC reviewed all available literature and data related to the accumulation of Gd in the brain and recommended in January 2016 some actions to be implemented: first, removal of the statement that the GBCAs do not pass the intact blood-brain barrier from the summary of product characteristics (SmPC); and second, request to update the safety specifications in the risk management plan of each product

Received for publication June 18, 2019; and accepted for publication, after revision, July 8, 2019.

From Guerbet, Roissy CDG Cedex, France.

Conflicts of interest and source of funding: E. Lancelot and P. Desché are employees of Guerbet.

Correspondence to: Eric Lancelot, PharmD, PhD, Guerbet, BP57400, 95943 Roissy CDG Cedex, France. E-mail: eric.lancelot@guerbet.com.

Copyright © 2019 The Author(s). Published by Wolters Kluwer Health, Inc. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

ISSN: 0020-9996/20/5501–0020

DOI: 10.1097/RLI.0000000000000605

TABLE 1. 2018 GBCA Volumes (in Liters) From ECMIG, GCMIG, and CMIG

Europe	205,084
European Union	171,186
Turkey	16,950
Russia	8406
Switzerland	7609
Others	933
North America	148,223
USA	141,180
Canada	7043
Asia Pacific	93,883
China	48,905
Japan	15,116
South Korea	10,982
India	4708
Australia	3935
Others	10,227
Latin America	55,926
Brazil	41,910
Others	14,016
Middle East and Africa	9984

ECMIG indicates European Contrast Media Industry Group; GCMIG, Global Contrast Media Industry Group; CMIG, Contrast Media Industry Group.

to reflect these findings. The PRAC also considered that the knowledge about the brain accumulation of Gd and its clinical consequences needed to be further investigated, which would require a review at European Union (EU) level. Therefore, the European Commission (EC) initiated on March 2016 a referral under Article 31 of Directive 2001/83/EC to allow further investigation of the accumulation of Gd in the brain with 2 objectives: (1) to consequently recommend any appropriate studies to be conducted, and (2) to consult with relevant experts to provide meaningful clinical advice to healthcare professionals. Finally, considering the accumulation of Gd in different body tissues other than brain, this review would also enable an assessment of the whole safety profile of the GBCAs in view of their use in magnetic resonance imaging (MRI) and magnetic resonance angiography. A rapporteur and a co-rapporteur were identified, and in over a 1-year period, all MAHs had to respond to 4 successive lists of preclinical and clinical outstanding issues, and attended 1 expert group meeting (mainly radiologists with an expertise in the field) and 2 oral explanations at PRAC meetings. The first list of questions is presented in Table 2. In March 2017, the PRAC recommended to the Committee for Human Health and Medicinal Products (CHMP) to suspend the linear GBCAs (except gadoxetate) and to maintain the macrocyclic ones with a labeling update. This recommendation was appealed by 2 MAHs and the whole process was restarted. Over a 4-month period, all MAHs had to respond to a new list of outstanding issues, attended a second expert group meeting (mainly radiologists with an expertise in the field), and then 2 oral explanations, one at the PRAC and one at the CHMP. Representatives from other health authorities, including the Food and Drug Administration (FDA), were invited to listen as observers to the discussions during some sessions. This time, the PRAC recommendation was to suspend the linear GBCAs (unfavorable benefit-risk balance), except gadobenate and gadoxetate for liver imaging only, and to maintain the macrocyclic agents (favorable benefit-risk balance) with a labeling update. In section 4.1—Therapeutic indications of the labeling, it was specified that the “product” should be used only when diagnostic information is essential and not available with unenhanced MRI. In section 4.2—Posology and method of administration, it was

specified that the lowest dose that provides sufficient enhancement for diagnostic purposes should be used. The dose should be calculated based on the patient's body weight and should not exceed the recommended dose per kilogram of body weight detailed in this section. This recommendation was validated by the CHMP. During the validation process by the EC, 3 countries expressed their concerns (Poland, Czech Republic, and Italy) and requested a Standing Committee to be held in Brussels in November. On November 23, 2017, the decision was formally taken and announced by the EC and it became applicable in all EU countries. The whole process is summarized in Figure 1, and the decision made by the EC is presented in Table 3. The member states of the EU were given the possibility to delay the implementation of subsequent actions for up to 12 months in case a medical need would not be met after marketing authorization suspension for the concerned GBCAs. The delivery of the information to healthcare professionals was made using a Dear Healthcare Professional Communication (DHPC) with variable delays from country to country ranging from approximately 2 weeks in Ireland to 8 months in Greece. In most EU countries, the dissemination of the DHPC was initiated within 4 to 7 weeks after the MAHs received the approvals on the content of the letters in local languages from their health authorities. These letters were sent by the MAHs to the healthcare professionals and concomitantly published on some regulatory authority Web sites. The United Kingdom took the option of announcing the EC decision on their authority Web site only without sending a DHPC letter. The information for healthcare professionals is summarized in Table 4.

HOW WAS THIS SAFETY SIGNAL MANAGED IN THE REST OF THE WORLD?

North America

In the United States, with the same amount of information, the FDA managed the situation in a different way. In July 2015, the FDA published a safety announcement saying that “After being administered, GBCAs are mostly eliminated from the body through the kidneys. However, trace amounts of gadolinium may stay in the body long-term. Recent studies conducted in people and animals have confirmed that gadolinium can remain in the brain, even in individuals with normal kidney function. Available information does not identify any adverse health effects.”¹⁹

In May 2017, the FDA published an update to the previous safety announcement saying the following: “Review to date has not identified adverse health effects from gadolinium retained in the brain after the use of gadolinium-based contrast agents (GBCAs) for magnetic

TABLE 2. First List of Questions From Pharmacovigilance Risk Assessment Committee

- Information in the SmPC about the risks of Gd accumulation in the brain or other tissues?
- Safety data to evaluate the risk of Gd accumulation in the brain with your GBCA?
- Evidence on Gd deposition in the brain with your GBCA?
- Mechanism of transfer of Gd into the brain and chemical form?
- Possible clinical implications of Gd accumulation in the brain?
- Groups of patients for whom the use of your GBCA has particular clinical advantages?
- Full benefit/risk assessment of your GBCA in the currently approved indications?
- Proposals and justifications for any risk minimization measures?
- Previous, planned, and ongoing studies into this area for your GBCA?

SmPC indicates summary of product characteristics; Gd, gadolinium; GBCA, gadolinium-based contrast agent.

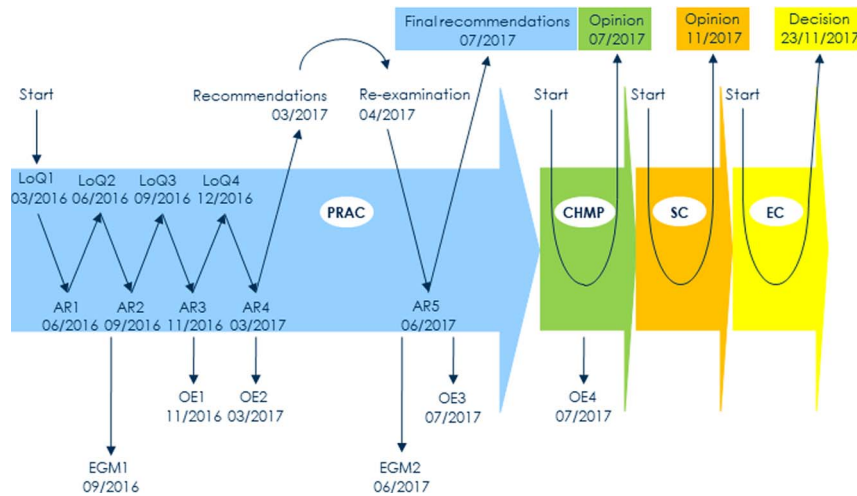


FIGURE 1. Timelines of the EU referral procedures on GBCAs. LoQ indicates list of questions; AR, assessment report; EGM, expert group meeting; OE, oral explanation; PRAC, Pharmacovigilance Risk Assessment Committee; CHMP, Committee for Human Health and Medicinal Products; SC, Standing Committee; EC, European Commission.

resonance imaging (MRI). All GBCAs may be associated with some gadolinium retention in the brain and other body tissues. However, because we identified no evidence to date that gadolinium retention in the brain from any of the GBCAs, including GBCAs associated with higher retention of gadolinium, is harmful, restricting GBCA use is not warranted at this time. We will continue to assess the safety of GBCAs and plan to have a public meeting to discuss this issue in the future[...]. We evaluated scientific publications and adverse event reports submitted to FDA. Some human and animal studies looked at GBCA use over periods longer than a year. These publications and reports show that gadolinium is retained in organs such as the brain, bones, and skin. The publications show that linear GBCAs retain more gadolinium in the brain than macrocyclic GBCAs. However, our review did not identify adverse health effects related to this brain retention[...]. We are reviewing the labels of other GBCAs to determine if changes are needed.²⁰

In September 2017, the Medical Imaging Division of the FDA organized a meeting with a panel of experts (advisory committee) where all manufacturers were invited to present their position on the Gd retention issue. Soon after, in December 2017, all MAHs received a letter from the FDA with 4 main requests: (1) uniform changes in product safety labeling across the GBCA class, either linear or macrocyclic; (2) a medication guide listing the new safety information for the patients; (3) an enhanced pharmacovigilance monitoring using a

specific form; and (4) a postmarketing requirement (PMR) including preclinical studies in mice and nonhuman primates and a clinical study. The main objective of the preclinical study in mice is to evaluate the behavioral, neurological, and histopathological changes during postnatal development and in adult mice. The objective of the preclinical study in juvenile nonhuman primates is to evaluate the behavioral, neurological, and histopathological changes over time. The objective of the prospective longitudinal clinical study is to assess the potential long-term consequences of at least 5 injections of GBCAs on motor and cognitive functions in adult subjects neurologically normal compared with matched controls. The manufacturers are currently working together to conduct this PMR according to the same preclinical and clinical protocols.

On February 15, 2018, an international meeting convened by the National Institute of Biomedical Imaging and Bioengineering and cosponsored by the American College of Radiology, the Radiological Society of North America, and the National Institutes of Health was held to discuss the current knowledge and knowledge gaps, and to identify and prioritize future research initiatives regarding the mechanisms, biological importance, and clinical implications of Gd retention. Attendees including an international group of researchers, GBCA manufacturers, and representatives of the FDA were invited based on their expertise in a diverse set of scientific and clinical disciplines relevant to the study of the chemistry, analytical methods, clinical manifestations,

TABLE 3. Decisions of the European Commission

Product	Type (Formulation)	Recommendation
Artirem/Dotarem (gadoteric acid)	Macrocyclic (IV)	Maintain
Artirem/Dotarem (gadoteric acid)	Macrocyclic (intra-articular)	Maintain
Gadovist (gadobutrol)	Macrocyclic (IV)	Maintain
Magnevist (gadopentetic acid)	Linear (IV)	Suspend
Magnevist (gadopentetic acid)	Linear (intra-articular)	Maintain
Multihance (gadobenic acid)	Linear (IV)	Restrict use to liver scans
Omniscan (gadodiamide)	Linear (IV)	Suspend
Optimark (gadoversetamide)	Linear (IV)	Suspend
Primovist (gadoxetic acid)	Linear (IV)	Maintain
Prohance (gadoteridol)	Macrocyclic (IV)	Maintain

IV indicates intravenous.

TABLE 4. Information for Healthcare Professionals Following the Decisions From the European Commission

- Gd deposition in the brain has been confirmed by mass spectrometry and increases in signal intensity in brain tissue [...].
- No adverse neurological effects, such as cognitive or movement disorders, have been attributed to Gd deposition in the brain with any GBCAs [...].
- Healthcare professionals should use GBCAs only when essential diagnostic information cannot be obtained with unenhanced scans.
- Healthcare professionals should always use the lowest dose that provides sufficient enhancement for diagnosis [...].
- Healthcare professionals in the EU will be sent a letter with information about EMA's review of GBCAs.

Gd indicates gadolinium; GBCA, gadolinium-based contrast agent; EMA, European Medicine Agency; EU, European Union.

or health-related effects of retained Gd. This led to a research roadmap that was recently published.²¹

In Canada, in March 2017, Health Canada imposed a class effect leading to safety labeling updates of the Canadian product monographs. These updates contained information on the greater risk of Gd accumulation in the brain with repeated administrations of linear GBCAs. In March 2018, additional product monograph updates included key messages for healthcare professionals: *“Use of macrocyclic agents may be preferable in certain patients such as those for whom repeated GBCA doses may need to be considered due to individual clinical circumstances and in other potentially vulnerable patients such as children and pregnant women.”*

Asia-Pacific Area

In March 2017, the Therapeutic Goods Administration requested information from the MAHs about the estimated patient exposure to GBCAs in Australia. In September 2017, the product information was updated with the mention that Gd accumulates in the brain but at a higher level after multiple administrations of linear than macrocyclic GBCAs. Despite the lack of knowledge on the clinical significance of this phenomenon, use of the lowest effective dose and careful benefit-risk assessment before multiple administrations was recommended.

In July 2017, the Ministry of Food and Drug Safety in South Korea requested the MAHs to submit all the information about Gd retention they had provided to the EMA. In December 2017, they distributed safety letters to their domestic healthcare professionals and consumer organizations to inform them about this issue and the different assessments made by the EMA and the FDA. They concluded the process by requesting an update of the product information mentioning the possible accumulation of Gd in the brain.

Similarly, the Pharmaceuticals and Medical Devices Agency in Japan performed a thorough analysis of the available evidence of Gd accumulation and safety-related concerns. In November 2017, they requested that the package inserts of the GBCAs be revised with the addition of 2 recommendations: (1) careful consideration as to restricting GBCA use to clinical circumstances in which the information provided by the contrast is necessary; and (2) the use of macrocyclic GBCA is a primary choice, and a linear GBCA is used when the use of a macrocyclic GBCA is not adequate because of a history of adverse effects.²²

In December 2017, the Chinese Food and Drug Administration published the Chinese Adverse Drug Reaction Information Bulletin (no. 76) informing the recipients about the risk of Gd accumulation in the brain and providing advices to the medical staffs, the patients, and the MAHs. Accordingly, in April 2018, the Chinese product information was updated with the mention that GBCAs can cause trace amounts of Gd to accumulate in the brain and other body tissue, and that such accumulation is greater after repeated administration of linear GBCAs.

In June 2018, the Drug Controller General of India requested the MAHs to update the product package inserts with regards to brain deposition of Gd and to conduct human studies to further assess this risk.

Latin America

A few countries have requested some regulatory actions. In May 2018, the product information was updated following a request of the health authorities in Costa Rica. An educational brochure on the risks of using GBCAs was also elaborated. In June 2018, an information note was created by the health authorities in Chile. Updates of risk management plans were also requested to the MAHs to reflect the current knowledge on the associated risks. In October 2018, an update of the product monograph to include information about Gd retention in the brain was triggered by the health authorities in Colombia.

Middle East and Africa

In November 2017, the Ministry of Health and Prevention in the United Arab Emirates took the decision to withdraw the marketing authorizations of the linear GBCAs and to request batch recalls from the MAHs. A similar process occurred in Jordan in March 2018 and in the Kingdom of Saudi Arabia in June 2018.

In February 2018, the Ministry of Health in Israel requested an update of the leaflets of the GBCAs. In parallel, the Saudi Food and Drug Authority in the Kingdom of Saudi Arabia requested a DHPC on the risks of using GBCAs. In November 2018, the Ministry of Health and Population in Egypt validated the proposed DHPC.

PRACTICAL CONSEQUENCES FOR GBCA USERS

The main practical consequence for radiologists is to use the lowest dose that provides sufficient enhancement for diagnosis. The lowest dose is the dose that is written in the “posology” section of the SmPC. Its efficacy and safety were established during phase 2 and phase 3 clinical trials. It is the “approved dose” for a specific indication and a specific population. Injecting more than the approved dose (overdosing) and injecting less than the approved dose (underdosing) are both “special situations,” which must be collected by MAHs because they are associated with safety issues, that is, toxicity and lack of efficacy, respectively.

CONCLUSIONS—HAS THE STORY ENDED?

Compared with NSF, the regulatory agencies managed faster the Gd retention issue. After the first reported case of NSF, it took 14 years to publish the risk classification for NSF with low-, intermediate-, and high-risk GBCAs, including 9 years to establish the relationship between Gd and NSF symptoms in patients with impaired renal function.²³ As for the Gd retention issue, it took 3 years between the first publication by Kanda and colleagues and the first regulatory decisions.

The MAHs of GBCAs had to face different situations according to the countries, due to the different positions and expectations from institutions and regulatory agencies. With the same amount of preclinical and clinical evidence in adults and children, those agencies came up to different conclusions and decisions:

- Suspension of the marketing authorizations of the linear GBCAs with the possibility to reverse the decision if new clinical studies provide compelling evidence of a positive benefit-risk balance (EU);
- No suspension or withdrawal of any product but clear changes in the labeling of the GBCAs mentioning a difference of Gd retention between linear and macrocyclic agents (Japan, South Korea, China, etc);
- No suspension or withdrawal of any product but identical changes in the labeling of all GBCAs, plus a request for additional preclinical and clinical studies whose results will be available in several years from now (United States).

Although different in nature, all stakeholders have had concerns and duties regarding this Gd retention issue:

- Regulatory agencies have requested evidence of Gd accumulation, made their decision on the benefit-risk balance of the GBCAs, and finally conducted a clear communication to healthcare professionals.
- MAHs have adapted their responses to the different positions of the regulatory agencies and conducted specific preclinical and clinical investigations to provide the expected evidence. It is also their responsibility to continuously monitor the benefit-risk balance of the products and to propose risk minimization measures to the regulatory agencies.
- Healthcare professionals had to adapt their practice with the use of GBCAs. They also play a major role in the collection and analysis of clinical data on the safety and efficacy of the products.
- Finally, the patients should receive GBCAs with a favorable benefit-risk balance, especially if repeated injections are needed for diagnosis or follow-up purposes.

REFERENCES

1. Kanda T, Ishii K, Kawaguchi H, et al. High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images: relationship with increasing cumulative dose of a gadolinium-based contrast material. *Radiology*. 2014;270:834–841.
2. Errante Y, Cirimele V, Mallio CA, et al. Progressive increase of T1 signal intensity of the dentate nucleus on unenhanced magnetic resonance images is associated with cumulative doses of intravenously administered gadodiamide in patients with normal renal function, suggesting dechelation. *Invest Radiol*. 2014;49:685–690.
3. Quattrocchi CC, Mallio CA, Errante Y, et al. Gadodiamide and dentate nucleus T1 hyperintensity in patients with meningioma evaluated by multiple follow-up contrast-enhanced magnetic resonance examinations with no systemic interval therapy. *Invest Radiol*. 2015;50:470–472.
4. 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;276:28–32.
5. McDonald RJ, McDonald JS, Kallmes DF, et al. Intracranial gadolinium deposition after contrast-enhanced MR imaging. *Radiology*. 2015;275:772–782.
6. Robert P, Lehericy S, Grand S, et al. T1-weighted hypersignal in the deep cerebellar nuclei after repeated administrations of gadolinium-based contrast agents in healthy rats: difference between linear and macrocyclic agents. *Invest Radiol*. 2015;50:473–480.
7. Kanda T, Osawa M, Oba H, et al. High signal intensity in dentate nucleus on unenhanced T1-weighted MR images: association with linear versus macrocyclic gadolinium chelate administration. *Radiology*. 2015;275:803–809.
8. Radbruch A, Weberling LD, Kieslich PJ, et al. Gadolinium retention in the dentate nucleus and globus pallidus is dependent on the class of contrast agent. *Radiology*. 2015;275:783–791.
9. Weberling LD, Kieslich PJ, Kickingreder P, et al. Increased signal intensity in the dentate nucleus on unenhanced T1-weighted images after gadobenate dimeglumine administration. *Invest Radiol*. 2015;50:743–748.
10. Runge VM. Macrocyclic versus linear gadolinium chelates. *Invest Radiol*. 2015;50:811.
11. Lancelot E. Revisiting the pharmacokinetic profiles of gadolinium-based contrast agents: differences in long-term biodistribution and excretion. *Invest Radiol*. 2016;51:691–700.
12. Robert P, Frenzel T, Factor C, et al. Methodological aspects for preclinical evaluation of gadolinium presence in brain tissue: critical appraisal and suggestions for harmonization—A joint initiative. *Invest Radiol*. 2018;53:499–517.
13. Quattrocchi CC, Ramalho J, Van der Molen AJ, et al. GREC, European Gadolinium Retention Evaluation Consortium and the ESNR, European Society of Neuroradiology. Standardized assessment of the signal intensity increase on unenhanced T1-weighted images in the brain: the European Gadolinium Retention Evaluation Consortium (GREC) task force position statement. *Eur Radiol*. 2019;29:3959–3967.
14. Fretellier N, Granottier A, Rasschaert M, et al. Does age interfere with gadolinium toxicity and presence in brain and bone tissues?: A comparative gadoterate versus gadodiamide study in juvenile and adult rats. *Invest Radiol*. 2019;54:61–71.
15. Roberts DR, Chatterjee AR. The critical need for pediatric and juvenile animal research addressing gadolinium retention in the developing body. *Invest Radiol*. 2019;54:72–75.
16. Frenzel T, Apte C, Jost G, et al. Quantification and assessment of the chemical form of residual gadolinium in the brain after repeated administration of gadolinium-based contrast agents: comparative study in rats. *Invest Radiol*. 2017;52:396–404.
17. Robert P, Fingerhut S, Factor C, et al. One-year retention of gadolinium in the brain: comparison of gadodiamide and gadoterate meglumine in a rodent model. *Radiology*. 2018;288:424–433.
18. Radbruch A. Gadolinium deposition in the brain: we need to differentiate between chelated and dechelated gadolinium. *Radiology*. 2018;288:434–435.
19. FDA evaluating the risk of brain deposits with repeated use of gadolinium-based contrast agents for magnetic resonance imaging (MRI). Safety Announcement [7–27-2015]. Available at: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-evaluating-risk-brain-deposits-repeated-use-gadolinium-based>. Accessed May 17, 2019.
20. FDA identifies no harmful effects to date with brain retention of gadolinium-based contrast agents for MRIs; review to continue. Safety Announcement [5–22-2017]. Available at: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-identifies-no-harmful-effects-date-brain-retention-gadolinium>. Accessed May 17, 2019.
21. 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.
22. Kanda T. The new restrictions on the use of linear gadolinium-based contrast agents in Japan. *Magn Reson Med Sci*. 2019;18:1–3.
23. Hazelton JM, Chiu MK, Abujudeh HH. Nephrogenic systemic fibrosis: a review of history, pathophysiology, and current guidelines. *Curr Radiol Rep*. 2019;7.