Magnetic resonance (MR) imaging protocols used in daily radiology practice and in the context of clinical trials often require contrast enhancement by means of intravenous administration of gadolinium-based contrast agents (GBCAs). GBCAs have been believed to be exceedingly safe and have been administered more than 300 million times (1,2), with a very low frequency of acute adverse events.

In the past 2 years, concern has grown worldwide about the finding of gadolinium deposits in the brain in some patients undergoing GBCA-enhanced MR examinations, generating concerns in some patients, families, health institutions, regulatory agencies, and contrast media manufacturers. Since the first report on the association of high T1-weighted signal intensity in the dentate nucleus and globus pallidus in patients receiving repeated doses of GBCAs by Kanda et al (3) in Japan, several studies have explored this issue in patient cohorts and autopsy samples (3–20). Cornerstones of knowledge in this field were the report by Errante et al (4) from Italy on patients with normal renal function exposed to the linear agent gadodiamide, the one by McDonald et al (5) from the Mayo Clinic (Rochester, Minn) on the first demonstration of gadolinium in the extracellular neural tissue and within endothelial walls, and the back-to-back reports by Kanda et al (6) from Japan (gadopentetate dimeglumine vs gadoteridol) and Radbruch et al (7) from Germany (gadopentetate dimeglumine vs gadoterate meglumine) on the differential behavior of linear versus macrocyclic GBCAs. Subsequently, differences of behavior were demonstrated between two linear agents (nonionic gadodiamide vs ionic gadobenate dimeglumine) by Ramalho et al (10) from the United States, who suggested that the structure of the GBCA may indeed affect observed differences in signal intensity at sites of deposition. Even though there are differences in T1-weighted signal intensity behavior within the group of linear GBCAs, increased T1-weighted signal intensity in the dentate nucleus was observed after gadobenate dimeglumine when compared with the macrocyclic gadoterate meglumine (12). Indeed, Cao et al (19) confirmed that linear gadopentetate dimeglumine was associated with T1-weighted hyperintensities whereas the macrocyclic gadobutrol was not. At least two additional reports also showed that the macrocyclic gadobutrol was not associated with an enhanced high T1 signal intensity after multiple injected doses (14,20). Subsequently, studies in animal models (21–23) confirmed varying but higher rates of gadolinium retention in the deep nuclei of the cerebellum after repeated doses of various linear GBCAs in comparison with gadoterate, a macrocyclic agent. However, in these animal studies, which used macrocyclic agents, the intracranial gadolinium levels identified were higher than those in control animals given saline injections.

MR imaging is able to depict bilateral and symmetrical hyperintensity on T1-weighted images in the dentate nucleus of the cerebellum and the globus pallidus after more than four to six intravenous injections of linear GBCAs and in the thalamus, substantia nigra, red nucleus, cerebellar peduncles, and colliculi after more than 35 injections of linear GBCAs (24). This evidence confirms the brain distribution of gadolinium deposits that have been detected with analytical techniques. However, the sensitivity of MR imaging is lower than that of analytical techniques and the presence of insoluble gadolinium salts (eg, gadolinium phosphate, bicarbonate, citrate) that have little or no influence on the T1 and T2 relaxation times of protons may cause an
underestimation of the gadolinium content in the brain when estimated by evaluation of the signal intensity increase detected on unenhanced T1-weighted images. This mounting scientific evidence has generated an ethical conflict between the need to give patients crucial and life-saving information obtained with contrast material–enhanced MR imaging and the concerns generated by the appraisal of data regarding GBCA safety, as underlined by Kanal and Tweedle (25). In addition, safety alerts have developed among patients: For instance, “The Lighthouse Project” is aimed at shedding light on the effects of retained gadolinium from contrast-enhanced MR imaging (26). The first reported symptoms experienced by individuals after GBCA administration have been recently reported (27–29), albeit without comparison to proper control populations.

Regulatory agencies are currently investigating the health risks of gadolinium deposition in the brain after repeated use of GBCAs for MR imaging. On July 27, 2015, the National Center for Toxicological Research of the U.S. Food and Drug Administration (FDA) issued a safety announcement on GBCAs in which they reported that the risk to patients of brain gadolinium deposits following the repeated use of some type of GBCAs is under investigation and asked the research community to refer any adverse event related to the use of GBCAs (30). On March 18, 2016, the European Medicines Agency announced that they will “start a review of the risk of gadolinium deposition in brain tissue following the use of gadolinium contrast agents in patients having enhanced magnetic resonance imaging (MRI) scans” (31). The Pharmacovigilance Risk Assessment Committee of the European Medicines Agency is currently carrying out an Article 31 referral procedure (EMEA/II/A-31/1437) to review the risk of brain deposits and the issue of the overall safety of GBCAs (31). The issue of gadolinium deposits in the brain is, in this context, part of a systemic phenomenon as residual gadolinium is found in other body organs such as bone, skin, and liver in patients with normal renal function and in animal models after both linear and macrocyclic GBCAs (17,32–34). Indeed, the Drug Safety Communication from the FDA states that, despite reports that have been submitted to the FDA Adverse Event Reporting System database from patients describing pain or other symptoms after either a single administration or multiple administrations of GBCAs, to date there are no discernible clinical features that may be reasonably linked to gadolinium (30).

On this issue, the contrast media industry, referring physicians, and non–MR imaging imagers are to be considered crucial stakeholders, as nonevidence-based preconceptions may generate turf battles and squabbles and be harmful to the trust between patients and radiologists and to the development of a prudent risk-benefit analysis that can promote the health of patients.

Because there is evidence of an imaging sign of gadolinium accumulation (ie, hyperintensity on unenhanced T1-weighted images) after repetitive administration of GBCAs (especially linear), the informed consent document should include this information during the pre–MR imaging risk-benefit assessment and, according to known differences in stability, linear GBCAs should be used with caution. A reasonable guide to clinical practice using GBCAs might be the five-rule list of actions based on the “GBCAP” acronym that we have developed: (a) consider gadolinium deposits in the pre–MR imaging daily risk-benefit assessment, (b) apply body and/or brain gadolinium enhancement only if clinically indicated and appropriate, (c) macrocyclic GBCAs are more stable than linear GBCAs, (d) the amount of linear GBCA should be minimized if scientific evidence demonstrates diagnostic noninferiority of lower doses of GBCAs with high R1 relaxivity, and (e) suggest implementation of a patient-specific contrast medium passport to document and monitor type and amount of GBCA administered over time.

What is definitely known is that gadolinium is retained in the body and brain after intravenous GBCA injections, that retention is higher with linear than with macrocyclic compounds, and that retention is progressive with an increasing number of doses administered. Questions to be answered include the role of demographic, genetic, environmental, and clinical variables in the risk of gadolinium retention, the clinical consequences associated with gadolinium retention in the body and brain, and the form of gadolinium that is present in tissues, that is, the relative amount of gadolinium salts, transmetallation-induced macromolecular complexes, and the original intact GBCA compound.

On the basis of the levels of evidence classification of the Centre for Evidence-Based Medicine, Oxford, England (35), the currently available diagnostic studies may be classified as levels 3b, 4, and 5. Analyses of higher levels of evidence, such as meta-analyses or, at least, systematic reviews, currently are not feasible owing to variations in the degree of methodology and results among individual studies.

Data collection and/or methodology of available studies are flawed by several limitations, for example, retrospective design, selection bias, lack of randomization, small sample sizes, lack of good control populations, lack of longitudinal data, and mixed exposure to different GBCAs (both linear and macrocyclic), lumping together all linear and macrocyclic agents as if they all act similarly within each “class” (despite a growing body of evidence that this is not the case).

Knowledge Gaps and Expected Outcomes

As such, a number of very important safety questions are still open and need answers to guide recommendations on the safe use of GBCAs, including: (a) Is the gadolinium retention elsewhere in the body, where it seems to occur at significantly higher levels than intracranially, associated with symptoms or disease? (b) What is the epidemiologic burden of gadolinium deposits in the brain and other body tissues? (c) What is the form of the deposited gadolinium (chelated as initially administered
to the patient or in a new compound formed after transmetallation in the body? (d) Does gadolinium deposition have an influence on function of the tissues where it is deposited? (e) Is there a gadolinium deposition syndrome and, if so, is this dose dependent or are there no clinical consequences related to gadolinium deposition? (f) Is the gadolinium deposition in the brain one manifestation of a more complex gadolinium deposition syndrome that may also encompass nephrogenic systemic fibrosis?

Many of the challenges in monitoring the safety of contrast media stem from the limited amount of information available from clinical trials at the time of drug approval. Regulators have to strike a balance between making promising new medicines available for use in patients as early as possible and waiting until sufficient information on a product’s quality, safety, and efficacy is known. Patients in phase II–IV clinical trials are selected carefully and followed up very closely under controlled conditions. After approval, however, the results of controlled clinical trials are verified by the real-world use and the large number of individuals exposed to contrast media compounds. Despite a very low rate of adverse events based on spontaneous reporting (36,37) and postmarketing surveillance (38), some side effects may only start to emerge once a contrast agent has been in use for a long time, as has happened in the case of the scientific reports on gadolinium deposition in the brain. Thus, regulators must continue to protect the public from newly identified safety issues with phase IV postauthorization surveillance trials. Currently, several cohorts are followed up with frequent contrast-enhanced MR examinations, such as patients with multiple sclerosis and other central nervous system chronic inflammatory demyelinating diseases, children with neurofibromatosis, young patients with chronic inflammatory bowel disease, patients with primary sclerosing cholangitis, and women with high genetic risk of breast cancer undergoing breast MR imaging surveillance. To evaluate the risk of gadolinium-related clinical consequences, systematic data collection and analysis from individuals in these cohorts will allow correction for clinical confounding variables and different technical parameters of MR image acquisition and pave the way to risk-stratification strategies.

Research Cooperation: Gadolinium Retention Evaluation Consortia

To improve the quality and speed of the efforts underway and contemplated, we believe that the integration of cohorts (“big data projects”) is needed, as this approach would minimize duplication of efforts from single institutions, free up resources by rationalizing and simplifying reporting on safety issues, and help establish a clear legal framework for postauthorization monitoring. A joint international initiative named the International Gadolinium Retention Evaluation Consortium has been established. This joint initiative started from an idea of the authors of this opinion and has so far involved 25 scientists from eight countries across Europe and the United States. The International Gadolinium Retention Evaluation Consortium is currently made up of investigators who have contributed to the scientific knowledge on gadolinium deposition in the brain and well-known experts in the field of MR contrast media and MR safety across the world, supported by a team of consultants from the contrast media industry. Its members are currently searching for funding, with the goal to be a gateway to the optimal exploitation of single-institution resources, to underpin confounding variables, and to have an impact on regulatory agency decisions on the use of GBCAs in MR imaging. Members from the European branch participated in a kick-off meeting in Europe (Naples, Italy) on November 4–6, 2016, to gather and develop strategies of collaboration. Investigators across the world who are willing to collaborate are welcome to contact the authors of this opinion and will receive updates on the initiatives as well as modalities of participation.

The mission of this international strategy of cooperation is to create a big data web-based infrastructure on large populations exposed to commercially available GBCAs, where local inhomogeneous retrospectively collected data are made available for big data mining. Also, homogeneous prospective data with harmonized protocols can be obtained to give answers to open questions. The infrastructure will play as a multicenter MR image and clinical data repository and GBCA and demographic registry. The systematic and harmonized collection of data on exposure to GBCA type and amount, demographic variables, MR imaging techniques and measures, clinical symptoms, and neuropsychologic testing would need to be launched. In addition, biobanking repositories of tissue samples would allow centralized chemical, biochemical, and genetic analyses. All institutions involved in the consortium will share competence and knowledge, harmonize research protocols, and ensure hypothesis- and data-driven research from shared databases. Centralized data collection and analysis will need expertise from contrast media physicochemistry, major clinical specialties (like neurology and neurosurgery, dermatology, rheumatology, radiology, pathology), analytical chemistry, information technology, and biostatistics. On the basis of the results obtained, multidisciplinary guidelines and consensus statements will be made available to the clinical community and to the regulatory agencies. The search for funding is currently active, as financial support is welcome from organizational, governmental, and transnational entities.

It is now roughly 3 decades since GBCAs were first introduced into the clinical arena. These unexpected pharmacokinetic findings of long-term gadolinium deposition in patients receiving GBCAs seemingly has caught the world off guard and unprepared to respond to determine what, if any, the clinical significance of these findings may be. We owe it to our patients at this point to gather, organize, and consolidate our international resources to reliably answer some of these pressing clinical
questions in as timely a manner as possible. Researchers with a track record in any of the above-mentioned fields who wish to actively join us in this regard are encouraged to contact us for further information as to how to collectively and efficiently proceed toward answering the question of the clinical relevance, if any, of human retention of gadolinium, be it intra- or extracranial in nature.

Disclosures of Conflicts of Interest: C.C.Q. disclosed no relevant relationships. A.J.v.d.M. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: received a speakers fee from GE Healthcare, Bayer Healthcare, and Bracco Imaging; received a chairman fee from Guerbet; received a fee for educational material to the present article: received a speakers fee no relevant relationships. Activities related to the present article: disclosed no relevant relationships.

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