Radiology

No Cases of Nephrogenic Systemic Fibrosis after Administration of Gadoxetic Acid

Jitka Starekova, MD • Richard J. Bruce, MD • Elizabeth A. Sadowski, MD • Scott B. Reeder, MD, PhD

From the Departments of Radiology (J.S., R.J.B., E.A.S., S.B.R.), Obstetrics and Gynecology (E.A.S.), Medical Physics (S.B.R.), Biomedical Engineering (S.B.R.), Medicine (S.B.R.), and Emergency Medicine (S.B.R.), University of Wisconsin, 600 Highland Ave, Madison, WI 53792. Received March 5, 2020; revision requested March 30; final revision received August 3; accepted August 14. **Address correspondence to** J.S. (e-mail: *starekova@wisc.edu*).

Conflicts of interest are listed at the end of this article.

See also the editorial by Davenport and Shankar in this issue.

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Background: Gadoxetic acid (GA) has distinctive pharmacokinetic properties with important applications in hepatobiliary imaging. However, there are limited data evaluating the safety of GA administration in patients with impaired kidney function and the incidence of nephrogenic systemic fibrosis (NSF).

Purpose: To evaluate safety of GA regarding risk of NSF in patients with impaired kidney function.

Materials and Methods: This retrospective study identified all GA-enhanced MRI (hereafter, GA MRI) examinations performed between July 2008 and December 2019 through a search of the electronic medical record. Serum creatinine values within 180 days or less of each GA MRI examination were retrieved and estimated glomerular filtration rate (eGFR) was calculated. The eGFR value nearest to each MRI examination was used. A separate search in the electronic medical record was also performed to identify patients with NSF. Dermatologists, nephrologists, and nephrologists at our institution were surveyed for any cases of NSF. In patients with NSF, all MRI examinations performed and contrast agents administered to these patients were recorded.

Results: Overall, 7820 GA MRI examinations were identified, performed in 5351 patients (3022 women and 2329 men). These included 299 examinations (242 patients) with eGFR of 30–44 mL/min/1.73 m^2 and 183 examinations (157 patients) with eGFR less than 30 mL/min/1.73 m^2. There were 109 examinations (in 94 patients) with eGFR of 15–29 mL/min/1.73 m^2, 40 examinations (in 39 patients) with eGFR less than 15 mL/min/1.73 m^2, and 34 examinations in 27 patients undergoing hemodialysis. Seventeen patients with eGFR less than 30 mL/min/1.73 m^2 or undergoing dialysis underwent GA MRI two or more times. Eighteen patients with biopsy-confirmed NSF were identified, none of whom were exposed to GA. The mean follow-up period for GA MRI examinations performed in patients with severe kidney impairment was 4.2 years (range, 0.2–11.3 years).

Conclusion: Gadoxetic acid may be safe with respect to nephrogenic systemic fibrosis in this patient population, although further studies are needed to confirm this.

Online supplemental material is available for this article.

Gadoxetic acid (GA; Eovist or Primovist; Bayer Healthcare Pharmaceuticals, Wayne, NJ) is a hepatobiliary gadolinium-based contrast agent (GBCA) (1–3). It is an ionic linear GBCA. We note that the chemical structure of GA is similar to gadopentetate dimeglumine (Magnevist; Bayer Healthcare Pharmaceuticals) based on the gadolinium-diethylenetriaminepentacetate backbone. GA has the same diethylenetriaminepentacetate backbone, but with a covalently bound ethoxybenzyl moiety, facilitating its uptake by hepatocytes via the organic anion transporting polypeptide pathway (3). Thus, compared with gadopentetate dimeglumine, GA is excreted by both the renal and hepatobiliary systems (2–5). It may be reasonable to speculate that the dual-excretion pathway of GA may confer a safety benefit in patients with kidney impairment. Gadobenate dimeglumine also has dual renal-hepatic excretion (6), which may also explain the absence of nephrogenic systemic fibrosis (NSF) cases associated with this agent. We also note that GA is administered at lower dose than other agents, which may provide an additional margin of safety. GA has proven use in the detection and characterization of focal liver lesions including hepatocellular carcinoma (2,3,7) and biliary abnormalities (7–9), and emerging work demonstrates potential to help quantify liver function (10).

All currently available GBCAs are generally regarded as safe (11). However, a link between GBCA exposure in patients with impaired kidney function and NSF has been reported. NSF is a rare but debilitating and potentially fatal disease, characterized by skin thickening, joint contractures, and general systemic fibrosis (12–14). NSF is not well understood and is likely a multifactorial disease occurring in patients with renal failure (13–15). Consequently, guidelines that recommend restricted use of GBCAs in patients with impaired kidney function have been released by the U.S. Food and Drug Administration and other medical societies (16–19). In addition, the European Medicines Agency defines some additional restrictions for linear GBCAs, including the limited use of GA and gadobenate dimeglumine for liver imaging only (19).

According to safety recommendations of the American College of Radiology, GBCAs are classified into three

Abbreviations

eGFR = estimated glomerular filtration rate, GA = gadoxetic acid, GBCA = gadolinium-based contrast agent, NSF = nephrogenic systemic fibrosis

Summary

Gadoxetic acid was not associated with the development of nephrogenic systemic fibrosis in this patient population, although further studies are needed to confirm these findings.

Key Results

- No cases of nephrogenic systemic fibrosis were detected among 383 patients with estimated glomerular filtration rate (eGFR) less than 45mL/min/1.73 m^2 who underwent 482 gadoxetic acid–enhanced MRI examinations.
- Given that no cases of nephrogenic systemic fibrosis were observed in patients with severe kidney impairment (eGFR <30 mL/min/1.73 m^2 and dialysis), the upper limit of the 95% confidence interval of incidence was 2.1%.
- At the authors' institution, 18 patients identified with nephrogenic systemic fibrosis had impaired kidney function and were exposed to a gadolinium-based contrast agent other than gadoxetic acid.

groups (17). Group 1 agents are those that should be avoided in the presence of acute kidney injury or severe chronic kidney disease where the estimated glomerular filtration rate (eGFR) is less than 30 mL/min/1.73 m^2 or in dialysis-dependent patients. Group 2 agents are those that are strongly preferred in patients with impaired kidney function who require a GBCA-enhanced MRI examination for their clinical care. Group 2 agents currently include one linear agent, gadobenate dimeglumine (MultiHance; Bracco Diagnostics, Princeton, NJ); and three macrocyclic agents, gadoteridol (ProHance; Bracco Diagnostics), gadoterate meglumine (Dotarem; Guerbet, Roissy, France and Clariscan; GE Healthcare, Norway), and gadobutrol (Gadavist, Gadovist; Bayer Healthcare Pharmaceuticals) (17). Group 3 agents are those that are generally regarded as safe, but with insufficient postapproval surveillance to conclusively determine the risk of NSF in patients with impaired kidney function. Therefore, screening of outpatients for potential kidney impairment and laboratory testing of outpatients with kidney impairment and all inpatients is recommended by the American College of Radiology, if a group 1 or 3 agent is considered (17). GA is currently the only group 3 agent that is commercially available.

Although to our knowledge no cases of NSF have been associated with GA (5,20), its continued status as a group 3 agent is likely related to its limited use in hepatobiliary MRI, its higher cost, and its introduction to the United States in 2008 shortly after NSF was initially reported and screening procedures for NSF had been widely implemented. GA has an important clinical role and because of its dual excretion (renal and biliary), there is a need for improved understanding of its safety profile in patients with kidney impairment. Therefore, the purpose of our study was to assess the incidence of NSF after GA administration in patients with impaired kidney function.

Materials and Methods

This retrospective Health Insurance Portability and Accountability Act–compliant study was approved by our local institutional review board. As part of this approval, written consent was waived.

Identification of Patients Exposed to GA

First, a comprehensive list of all MRI performed with GA between July 3, 2008 (the date that GA was approved in the United States), through December 17, 2019, was obtained from our electronic medical record. Patients were included if an entry for administration of GA was present in the patient's medication administration record or if GA administration was recorded in the electronic medical record. Synonyms for GA used in the search included Eovist, Primovist, gadoxetic acid, gadoxetate disodium, and gadolinium ethoxybenzyl dimeglumine. The resulting list was then submitted to our institutional Information Technology Services to retrieve serum creatinine values within 180 days or less of GA-enhanced MRI (hereafter referred to as GA MRI) examinations, and also to identify all patients who underwent a GA MRI examination while undergoing hemodialysis or peritoneal dialysis. In addition, the time between each GA MRI examination and the conclusion of the data collection period (January 21, 2020) was calculated. Furthermore, for the patient population with eGFR less than 45 mL/min/1.73 m^2 or undergoing dialysis, the follow-up time between GA MRI examination and the last contact with our institution was recorded. Of all recorded serum creatinine values obtained, the value closest to (before or after) the GA MRI examination was used. Creatinine values were used to calculate the eGFR by using the Modification of Diet in Renal Disease study equation (17,21). Because eGFR is not a valid indicator of kidney function in patients undergoing dialysis, eGFR was not used in those patients undergoing dialysis (17). For the purposes of this study, patients undergoing dialysis were considered to be at potential risk for NSF, regardless of eGFR (17).

All GA MRI examinations were categorized into the six separate groups according the eGFR value or dialysis status nearest the time (before or after) of the GA MRI examination (Fig 1, Table 1). One additional group included GA MRI examinations wherein no recent eGFR values were available (serum creatinine was not available or was older than 180 days). Because we used the eGFR value obtained closest to the GA MRI examination, patients with multiple GA MRI examinations may be classified into different groups depending on their kidney function closest to the time of their GA MRI examination.

In all patients with eGFR less than 30 mL/min/1.73 m^2 or undergoing hemodialysis, the medical record for each patient was reviewed for a diagnosis of cirrhosis. Furthermore, the follow-up between GA MRI examination and the last contact with our institution was noted. In all patients with cirrhosis, the Child-Pugh class was recorded.

We note that our institutional guidelines for GBCA administration (including GA) have evolved over the years. On the basis of our prior data and experience with NSF (15), outpatients are not screened at our institution for renal failure before undergoing MRI. For inpatients, between November 2006 and December 2016, screening for renal failure was performed before any GBCA-enhanced MRI. Screening included eGFR and the presence of a major proinflammatory condition including major

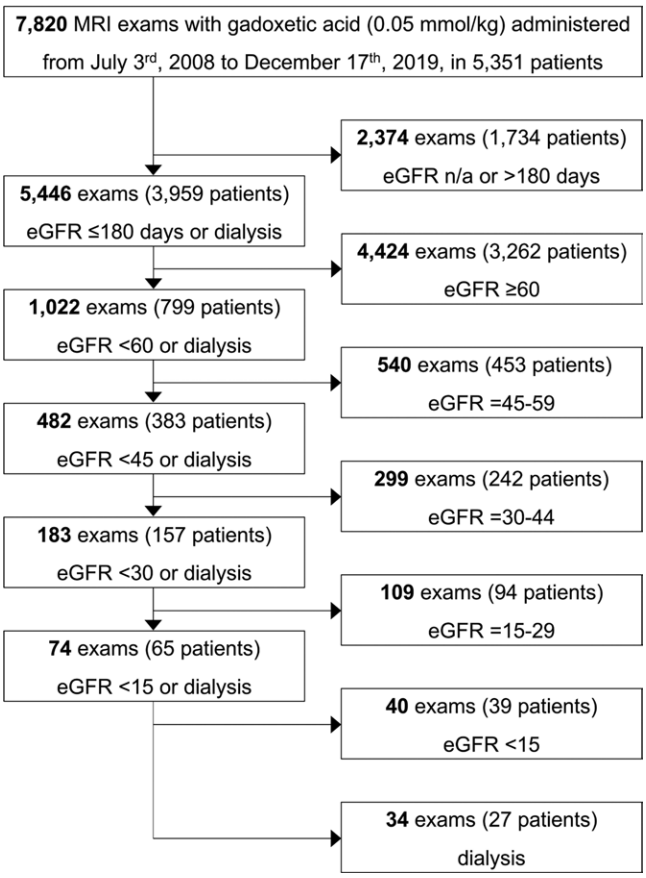

Figure 1: Flow diagram of enrolled study population. Gadoxetic acid–enhanced MRI examinations were categorized into groups (boxes on the right) based on estimated glomerular filtration rate (eGFR; in milliliters per minute per 1.73 m^2). Dialysis-dependent patients and patients in whom eGFR was not available within less than or equal to180 days of the MRI examination were grouped separately.

infection, thrombosis, recent major surgery, or multiorgan system failure. Inpatients with a proinflammatory condition and eGFR less than 30 mL/min/1.73 m^2 were considered to be at risk for NSF. For these inpatients, before administration of GBCA, a discussion took place between a radiologist and the ordering physician regarding the risk versus benefit specific to that patient (15). Alternative diagnostic methods including other imaging methods were considered. However, if GA MRI was considered necessary for diagnosis and subsequent treatment of the patient, the GA MRI examination was performed. On the basis of the lack of any reported cases of NSF associated with GA in nearly a decade, screening for kidney impairment in patients scheduled to undergo GA MRI was discontinued on January 1, 2017.

Finally, at our institution the standard dose for GA was 0.05 mmol/kg (0.2 mL/kg) (twice the recommended dose) to achieve more consistent arterial phase enhancement (22–25). On September 1, 2017, a maximum dose of 20 mL was set.

Identification of Patients with NSF

We performed a search in our entire electronic medical record to identify patients at our institution with NSF. We included all records from 1994 through January 21, 2020. Keywords used in the search query included nephrogenic systemic fibrosis, NSF, nephrogenic fibrosing dermopathy, NFD, and fibrosing dermopathy. Coding, billing, and patient problem list entries were also included. In addition to the electronic medical record, a letter was sent to all dermatologists, nephrologists, and hepatologists at our institution asking them to contact the study investigators if they were aware of any confirmed or suspected cases of NSF. All patients identified with known or suspected NSF were then investigated with an in-depth manual review of the patient's chart in the electronic medical record. A patient was considered positive for NSF if they had undergone evaluation by a board-certified dermatologist and NSF was confirmed by deep skin biopsy after interpretation by a board-certified dermatopathologist. Conversely, patients were not considered positive for NSF if NSF was only mentioned in the patient's record as a differential diagnosis consideration or potential diagnosis without biopsy.

Statistical Analysis

Descriptive data and statistical analyses were performed with GraphPad Prism (version 5.0; GraphPad Software, San Diego, Calif) and Excel (version 16.30; Microsoft, Redmond, Wash). For the patients with eGFR less than 30 mL/min/1.73 m^2 and who were undergoing dialysis, risk of NSF with the upper bound of two-sided 95% confidence interval by using the Wilson score without continuity correction (26) and a time-to-event analysis by using the β product confidence procedure (27) was calculated.

Results

Patients Exposed to GA

A total of 7820 GA MRI examinations were identified and performed in 5351 patients between July 2008 and December 2019. Details of these patients and number of GA MRI examinations are summarized in Figure 1. The average age of the patients at the time of GA MRI was 53 years (range, 0–101 years). There were 3022 female patients and 2329 male patients. In 2374 GA MRI examinations, the eGFR was not available because serum creatinine was not obtained within the defined time frame (≤180 days from performed GA MRI examination).

The remaining 5446 GA MRI examinations included 4424 examinations (3262 patients) with normal or mildly decreased kidney function (eGFR, ≥60 mL/min/1.73 m^2), 540 examinations (453 patients) with mild to moderate kidney impairment (eGFR, 45–59 mL/min/1.73 m^2), 299 examinations (242 patients) with moderate to severe kidney impairment (eGFR, 30–44 mL/min/1.73 m^2), and 183 examinations (157 patients) with severe kidney impairment (eGFR, <30 mL/min/1.73 m^2 or dependent on dialysis). As shown in Figure 1, there were 40 GA MRI examinations (39 patients) with eGFR less than 15 mL/min/1.73 m^2 and 34 GA MRI examinations (27 patients) in patients undergoing hemodialysis. There were no patients who underwent GA MRI who were undergoing peritoneal dialysis. These results are summarized in Figure 1, and the demographics of these patients are shown in Table 1.

We note that 17 patients with eGFR less than 30 mL/min/1.73 m^2 or who were undergoing hemodialysis underwent two or more GA MRI examinations when having the same degree of kidney function impairment (Table 2). Two of the

Table 1: Demographic Characteristics of Patients

Parameter	No. of Patients	Mean Age (y)	No. of Women/Men*	Mean Follow-up (y)†
Kidney function				
eGFR not available	1734	51.5 ± 16.2 (0.2–89.9)	1058/676 (61/39)	3.0 ± 2.5 (0.1–11.3)
eGFR, ≥60 mL/min/1.73 m^2	3262	52.1 ± 16.8 (0.0–100.7)	1801/1461 (55/45)	4.6 ± 2.8 (0.1–11.3)
eGFR, 45–59 mL/min/1.73 m^2	453	64.3 ± 12.7 (19.9–95.8)	246/207 (54/46)	4.9 ± 2.8 (0.2–11.3)
eGFR, 30–44 mL/min/1.73 m^2	242	62.9 ± 12.7 (16.0–98.7)	137/105 (57/43)	4.8 ± 2.8 (0.1–10.8)
eGFR, 15–29 mL/min/1.73 m^2	94	62.5 ± 14.4 (25.2–92.7)	47/47 (50/50)	4.8 ± 3.4 (0.2–11.3)
eGFR, <15 mL/min/1.73 m^2	39	61.1 ± 12.3 (34.2–84.4)	21/18 (54/46)	3.4 ± 2.7 (0.3–10.4)
Hemodialysis	27	52.8 ± 15.2 (19.6–74.1)	11/16 (41/59)	3.4 ± 2.3 (0.2–8.8)

Note.—Mean data are ± standard deviation. Data in parentheses are ranges unless otherwise noted. eGFR = estimated glomerular filtration rate, GA = gadoxetic acid.

* Data in parentheses are percentages of women/men.

† Time between GA-enhanced MRI and conclusion of the data collection period (January 21, 2020).

Table 2: Number of Patients with Severe Kidney Impairment Who Underwent One or More Gadoxetic Acid–enhanced MRI Examinations

	No. of GA MRI Examinations				
Parameter	1	2	3	4	≥5
Kidney function					
eGFR, 15–29 mL/min/1.73 m^2	82	9	3	0	0
eGFR, <15 mL/min/1.73 m^2	38	1	0	0	0
Hemodialysis	23	2	1	1	0

Note.—eGFR = estimated glomerular filtration rate (in milliters per minute per 1.73 m^2), GA = gadoxetic acid.

patients undergoing hemodialysis underwent two GA MRI examinations, one underwent three GA MRI examinations, and one patient underwent four GA MRI examinations (Table 2).

In patients with eGFR less than 30 mL/min/1.73 m^2 or patients who were undergoing hemodialysis, 98 examinations (81 patients) were performed before and 85 examinations (79 patients) were performed after January 1, 2017 (ie, the date of the change to our institutional guidelines for GBCA administration).

For the patients with eGFR less than 30 mL/min/1.73 m^2, the median time between the eGFR before or after the GA MRI was 5 days (average, 21 days; range, 0–170 days). A survival analysis that used the β product confidence procedure determined that the lower 95% confidence interval on the probability of NSF not occurring dropped below 50% after 7.5 years.

The mean follow-up period for all GA MRI examinations performed at our institution was 4.2 years (range, 0.1–11.3 years). The mean follow-up period for the 183 GA MRI examinations performed in 157 patients with eGFR less than 30 mL/min/1.73 m^2 or in patients undergoing dialysis was 4.2 years (range, 0.2–11.3 years).

The mean follow-up time between the GA MRI examination and the last clinic or hospital visit that included a physical examination of the integument in patients with eGFR less than 45 mL/min/1.73 m^2 was 1.7 years (range, 0.03–9.3 years) for deceased patients (n = 152) and 3.3 years (range, 0–10.7 years) for patients who were alive at the end of the study (n = 231). Subgroups are shown in Table 3. There were three patients with eGFR of 30–44 mL/min/1.73 m^2 and one patient with eGFR less than 30 mL/min/1.73 m^2 without follow-up, and these accounted for having 0 years of follow-up (Table 3).

Among patients with eGFR less than 30 mL/min/1.73 m^2 and patients undergoing hemodialysis, of all 183 examinations (157 patients), 38 examinations (34 patients) were performed in patients with cirrhosis (Table 4). The mean follow-up times between the GA MRI examination and the last hospital visit in patients with eGFR less than 30 mL/min/1.73 m^2 or undergoing hemodialysis and concomitant liver cirrhosis were as follows: Child-Pugh A, 3.6 years ± 3.5 (standard deviation; range, 0.5–7.8 years); Child-Pugh B, 1.6 years ± 2.1 (range, 0.1–5.7 years); and Child-Pugh C, 2.2 years ± 3.4 (range, 0.02–10.7 years).

The incidence of NSF in the high-risk patient population (<30 mL/min/1.73 m^2 or patients undergoing hemodialysis) was 0 of 183 examinations (0%). The upper bound of the two-sided 95% confidence interval estimated risk of 2.1%. Figure 2 shows the results of the time-to-event analysis over the full range of follow-up times. The analysis determined that the cumulative probability of an occurrence of NSF in a patient between administration of GA and follow-up within approximately 11 years was 0% (Fig 2). However, the calculated 95% confidence interval ranged from 2% to 100% over the same 11-year interval (Fig 2).

Patients with NSF

We identified 18 patients with a biopsy-confirmed diagnosis of NSF (Fig 3, Table E1 [online]). The average age at the time of diagnosis was 53 years (range, 18–73 years; 12 men and six women). All 18 patients had acute or chronic renal disease, with severe kidney impairment (eGFR, <30 mL/min/1.73 m^2) or were undergoing dialysis (Table E1 [online]). Among these patients, 17 were diagnosed before the availability of GA in the United States (ie, before U.S. Food and Drug Administration approval on July 3, 2008). We note that 14 of these cases are the same as those previously reported by our institution in 2007 and 2016 (15,28).

Table 3: Documented Follow-up

	eGFR, 30–44 mL/min/1.73 m²		eGFR, <29 mL/min/1.73 m²		Hemodialysis	
Parameter	No. of Patients	Mean Follow-up (y)*	No. of Patients	Mean Follow-up (y)*	No. of Patients	Mean Follow-up (y)*
Alive	151	3.7 ± 2.7 (0–9.6)	70	2.4 ± 2.5 (0–10.7)	21	3.0 ± 2.3 (0.04–7.8)
Deceased	91	1.9 ± 2.2 (0.003–9.3)	61	1.3 ± 1.8 (0.003–6.1)	6	2.0 ± 3.0 (0.07–8.7)

Note.—Mean data are ± standard deviation. Data in parentheses are ranges. Follow-up is in patients with estimated glomerular filtration rate (eGFR) less than 45 mL/min/1.73 m² and undergoing dialysis (482 examinations in 383 patients) as defined by the last contact between the patient and a provider at our institution, which included a physical examination of the integument. GA = gadoxetic acid.

* Time between GA-enhanced MRI examination and last hospital or clinic visit.

Table 4: Child-Pugh Class, Gadoxetic Acid–enhanced MRI Examinations, and Mean Follow-up

Liver Cirrhosis Child-Pugh Class	No. of GA MRI Examinations	No. of Patients	Mean Follow-up (y) *
A	6	5	3.6 ± 3.5 (0.5–7.8)
B	13	11	1.6 ± 2.1 (0.1–5.7)
C	19	19	2.2 ± 3.4 (0.02–10.7)

Note.—Mean data are ± standard deviation. Data in parentheses are ranges. Gadoxetic acid (GA)–enhanced MRI examinations were in patients with estimated glomerular filtration rate less than 30 mL/min/1.73 m² and who had concomitant liver cirrhosis.

* Time between GA-enhanced MRI examination and last hospital or clinic visit.

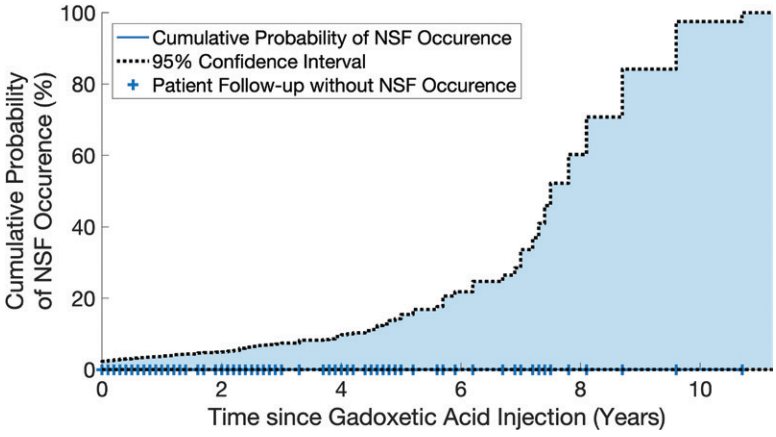

Figure 2: The time-to-event analysis plot shows the probability and 95% confidence intervals of a patient having had an occurrence of nephrogenic systemic fibrosis (NSF) as a function of time since injection of gadoxetic acid. Because no cases of NSF were detected at any follow-up, the cumulative probability of NSF occurrence is 0% and overlaps the lower 95% confidence interval at all studied follow-up times since gadoxetic acid injection. The time-to-event analysis was calculated by using the β product confidence procedure during all follow-up times for all patients with estimated glomerular filtration rate less than 30 mL/min/1.73 m². The β product confidence procedure is a method robust to follow-ups without event occurrence.

Only one patient was diagnosed with NSF after July 3, 2008 (Fig 3). This patient was formally diagnosed in 2019, although he had reported many years of thickened skin. This patient had multiple documented exposures to gadodiamide (Omniscan; GE Healthcare) in 1995–2000 and no documented exposures to GA (Fig 3, Table E1 [online]). Furthermore, this patient did not have a history of liver disease or focal liver lesions and therefore was unlikely to have undergone GA MRI at an outside institution.

The identity of the GBCA used in one patient with NSF could not be ascertained because the MRI was performed at an outside institution and the identity of the GBCA was not documented (Table E1 [online]). However, the GBCA-enhanced MRI examination was performed in 2006, before U.S. Food and Drug Administration approval of GA. All other patients were documented to have been administered one or more doses of gadodiamide (Omniscan; GE Healthcare). One patient who was administered gadodiamide was also administered gadobenate dimeglumine (MultiHance; Bracco Diagnostics), as previously reported (28). On the basis of our investigation, none of the 18 patients diagnosed with NSF were administered GA.

Discussion

We evaluated the incidence of nephrogenic systemic fibrosis (NSF) in patients with kidney impairment who were exposed to gadoxetic acid (GA) at our institution, where GA has been used routinely since 2008. No cases of NSF were identified, despite the administration of 0.05 mmol/kg of GA in 157 patients with severe kidney impairment (estimated glomerular filtration rate [eGFR], <30 mL/min/1.73 m²) or who were undergoing dialysis, who underwent a total of 183 independent GA-enhanced MRI examinations (hereafter, GA MRI), and a mean follow-up of 4 years.

GA is a widely used GBCA with important applications in hepatobiliary imaging. It is particularly valuable for characterization of and discrimination between focal nodular hyperplasia and adenoma, dysplastic nodules, and hepatocellular carcinoma; detection of metastatic disease to the liver; and anatomic and functional evaluation of the bile ducts (2,7–9,29). Although GA has not been associated with NSF, the current American College of Radiology classification of GA as a group 3 agent led to continued uncertainty about the safety of GA, specifically the need to screen for kidney impairment in patients considered for GA MRI. For this reason, there is a need for studies that evaluate the risk of NSF in patients administered GA.

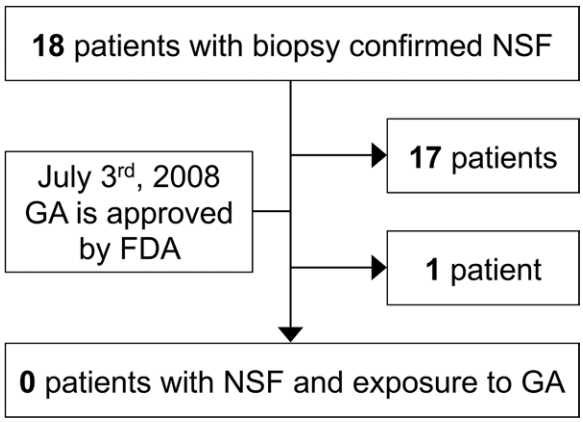

Figure 3: Timeline of patients diagnosed with nephrogenic systemic fibrosis (NSF). We identified 18 patients at our institution with a confirmed diagnosis of NSF. Seventeen patients were diagnosed before gadoxetic acid (GA) was approved for use in the United States by the Food and Drug Administration (FDA). One patient was formally diagnosed with NSF in 2019 but had last documented exposure to a gadolinium-based contrast agent (gadodiamide) in 2000. This patient had also reported many years of thickened skin. All 18 patients who were identified with NSF were associated with injection of gadodiamide (17 patients) or an unidentified contrast agent (one patient), all before 2008. None of these patients were exposed to GA.

To the best of our knowledge, there are no previous reports of NSF cases in patients exposed to GA (4,5,12,20) and a limited number of studies evaluating the risk of NSF in patients with kidney impairment. So far, the largest available database of 1989 patients exposed to GA was reported by the manufacturer of GA (Bayer Healthcare Pharmaceuticals) by using clinical phase II–IV studies and after marketing surveillance (4). In the prospective multicenter clinical phase IV study reported by Lauenstein et al (20), the authors evaluated 357 patients who underwent a single GA MRI examination (193 patients with moderate kidney impairment [eGFR, 30–59 mL/min/1.73 m^2] and 85 patients with severe kidney impairment [eGFR, <30 mL/min/1.73 m^2]). During a 24-month follow-up period, no cases of NSF were identified. Compared with our study, Lauenstein et al used a single dose of GA (0.025 mmol/kg), which is lower compared with our local standard of care. Furthermore, the number of patients with severe kidney impairment was lower (n = 85).

Regarding the risk of nephrogenic systemic fibrosis from GA, the incidence of NSF in patients with severe kidney impairment was 0 of 183 examinations (0%). The upper bound of the two-sided 95% confidence interval, calculated by using the Wilson score method without continuity correction, estimated risk at 2.1%. The upper limit of the confidence interval is higher compared with group 2 GBCAs (0.07%) (30). Although no NSF events occurred, the calculated risk may not represent the true risk of NSF. Because NSF is considered a rare disease (31), a much larger sample size would be needed to determine the true risk of NSF after administration of GA in patients with kidney impairment. Furthermore, because there is a longitudinal aspect to the data, we performed a time-to-event analysis by using the β product confidence procedure described by Fay et al (27) to determine the upper 95% confidence interval for the probability of NSF occurring in patients at risk (<30 mL/min/1.73 m^2) over time.

A limitation of our study was that creatinine values contemporaneous to the GA MRI examinations were not available in all patients. Similarly, same-day creatinine values were not available in many patients, and it is possible that acute renal failure may have been overlooked in some patients. However, without these limitations, this would only increase the number of patients identified to be at potential risk of NSF (ie, with kidney impairment), and would not impact the number of patients with confirmed NSF, which was determined separately.

Furthermore, our institutional guidelines for GBCA administration in inpatients with kidney impairment may have led to additional sources of bias. Specifically, from 2008 until the end of 2016, GA MRI was performed in inpatients with kidney impairment only after careful consideration of the risk and benefit for each individual patient. Therefore, potential exclusion of patients at high risk may have led to possible selection bias during this period. Another potential limitation was the identification of those patients with kidney impairment who were exposed to GA but were lost to follow-up, died prior to potentially developing NSF, or may yet develop NSF after the completion of this study from past exposure to GA. It is possible that we were unable to contact dermatologists, nephrologists, and hepatologists who may have retired or left our health care system, potentially missing known cases of NSF. The possibility of missing any cases of NSF as a result was considered highly unlikely, however, given the comprehensive nature of the electronic medical record search for cases of NSF. We also note that all but one patient identified to have NSF at our institution was diagnosed before the availability of GA in the United States. Finally, our study was limited by its single-center nature.

In conclusion, gadoxetic acid was not associated with the development of nephrogenic systemic fibrosis in patients with kidney impairment in this population; however, further studies with larger cohorts are needed to confirm the safety of gadoxetic acid.

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