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-diethylenetriaminepentaacetic acid backbone. GA has the same diethylenetriaminepentaacetic acid 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
Gadoteric 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 45 mL/min/1.73 m² who underwent 482 gadoteric 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 m² 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 gadoteric acid.

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 Evist, Primovist, gadoteric 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 m² 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 m² 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 were 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
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Inpatients with a proinflammatory condition and eGFR less than 30 mL/min/1.73 m² 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 m² 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 m²), 540 examinations (453 patients) with mild to moderate kidney impairment (eGFR, 45–59 mL/min/1.73 m²), 299 examinations (242 patients) with moderate to severe kidney impairment (eGFR, 30–44 mL/min/1.73 m²), and 183 examinations (157 patients) with severe kidney impairment (eGFR, <30 mL/min/1.73 m² 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 m² 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 m² 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
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 GA 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 conclusion of the data collection period (January 21, 2020), for patients who were alive at the end of the study (n = 231), was 13.0 years (median, 5.3 years; range, 0–26.2 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).
No Cases of Nephrogenic Systemic Fibrosis after Administration of Gadoxetic Acid

Table 3: Documented Follow-up

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

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

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

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.

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.
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 m²] and 85 patients with severe kidney impairment [eGFR, < 30 mL/min/1.73 m²]). 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 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 m²) 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, gad ox etic 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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References


27. Fay MP, Britain EH, Proshan MA. Pointwise confidence intervals for a survival distribution with small samples or heavy censoring. Biostatistics 2013;14(4):723–736.


