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Nephrogenic Systemic Fibrosis Risk After Liver Magnetic Resonance Imaging With Gadoxetate Disodium in Patients With Moderate to Severe Renal Impairment

Results of a Prospective, Open-Label, Multicenter Study

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Objective: The objective of this study was to assess the risk of gadoxetate disodium in liver imaging for the development of nephrogenic systemic fibrosis (NSF) in patients with moderate to severe renal impairment.

Materials and Methods: We performed a prospective, multicenter, nonrandomized, open-label phase 4 study in 35 centers from May 2009 to July 2013. The study population consisted of patients with moderate to severe renal impairment scheduled for liver imaging with gadoxetate disodium. All patients received a single intravenous bolus injection of 0.025-mmol/kg body weight of liver-specific gadoxetate disodium. The primary target variable was the number of patients who develop NSF within a 2-year follow-up period.

Results: A total of 357 patients were included, with 85 patients with severe and 193 patients with moderate renal impairment, which were the clinically most relevant groups. The mean time period from diagnosis of renal disease to liver magnetic resonance imaging (MRI) was 1.53 and 5.46 years in the moderate and severe renal impairment cohort, respectively. Overall, 101 patients (28%) underwent additional contrast-enhanced MRI with other gadolinium-based MRI contrast agents within 12 months before the start of the study or in the follow-up. No patient developed symptoms conclusive of NSF within the 2-year follow-up.

Conclusions: Gadoxetate disodium in patients with moderate to severe renal impairment did not raise any clinically significant safety concern. No NSF cases were observed.

Key Words: gadoxetate disodium, liver imaging, renal impairment, NSF

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Nephrogenic systemic fibrosis (NSF), formerly known as nephrogenic fibrosing dermopathy, was first described in the literature in 2000 with the first reports of cases dating back to 1997.[1] It is a very rare but serious disease, characterized by formation of connective tissue in the skin that becomes thickened, coarse, and hard, sometimes leading to contractures and joint immobility. Patients with NSF can also have involvement of other organs including the lungs, liver, muscles, and heart. The disease may develop for a period of a few days to several weeks or months.

To date, NSF has predominantly been reported in patients with severe renal impairment (estimated glomerular filtration rate [eGFR], <30 mL/min per 1.73 m^2) and those with acute renal injury. The etiology of NSF is still not fully understood but is likely to be multifactorial. A possible association between NSF and gadolinium (Gd)-based magnetic resonance imaging (MRI) contrast agents (GBCAs) was first described by Grobner et al[2] in 2006. Various other concomitant factors such as metabolic acidosis,[2] vascular surgery,[2] treatment with erythropoietin,[3] or systemic inflammation have also been discussed as possibly associated with the development of NSF. Histopathology of a skin biopsy specimen is necessary to establish a definitive diagnosis of NSF.[4]

One theory regarding Gd and NSF is that Gd^{3+} ions are released from the Gd-chelate and accumulate in tissue (predominantly skin), thereby triggering reactions involving induction of cytokine expression. Cytokines play a role in fibrosis or inflammation or function as chemoattractants for macrophages and monocytes.[5] The likelihood of a particular Gd-chelate to release Gd^{3+} ions seems to depend on that particular chelate's physicochemical properties, that is, particularly their kinetic and thermodynamic stability.[6] Risk for release may also be increased in cases of prolonged circulation of the Gd-chelate[7] such as in patients with severe renal impairment.

Gadoxetate disodium (gadoxetic acid, Primovist/Eovist) is a contrast agent specifically developed for the detection, localization, and characterization of liver lesions. It increased the frequency of correctly detected hepatic lesions versus spiral computed tomography by 10.4%. In particular, the highest rate of correctly detected lesions was for small hepatic lesions with a diameter less than1 cm.[8] Thus, gadoxetate disodium may improve diagnosis and assist surgical planning.[9,10]

Zech et al[11] have shown that the diagnostic performance of gadoxetate disodium MRI was better than that of contrast-enhanced computed tomography and MRI with extracellular contrast media as the

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initial imaging modality for the detection of liver metastases in patients with colorectal cancer. No further imaging was needed in the gadoxetate disodium MRI group, and comparison of efficacy parameters demonstrated diagnostic superiority in the gadoxetate disodium MRI group.

Gadoxetate disodium belongs to the class of linear ionic GBCAs and features a high T1 relaxivity of 6.9 L $mmol^{-1}$ s^{-1} at 1.5 T (in plasma).[12] After intravenous application, gadoxetate disodium is first distributed in the extracellular space and then quickly taken up by the hepatocytes, thus providing both dynamic and hepatocyte-specific imaging. In healthy subjects, approximately 50% of the injected dose is excreted via the kidneys and 50% is excreted via the biliary system. Contrast enhancement of the liver parenchyma and liver-to-lesion contrast is highest at approximately 20 minutes after administration with a plateau lasting for at least to 45 minutes after injection.[13]

The excellent safety profile of gadoxetate disodium[8,14,15] has been demonstrated in several (controlled) clinical studies and in postmarketing experience. So far, since approval in March 2004, more than 2.2 million patients have been exposed to gadoxetate disodium worldwide and no case of NSF has been reported.[16]

We initiated this study titled "Prospective non-randomized cohort study (open-label, multicenter) to assess the magnitude of potential risk with the administration of Primovist/Eovist in patients with moderate to severe renal impairment for the development of nephrogenic systemic fibrosis (NSF) based on diagnostically specific clinical and histopathologic information" to meet a request from the United States Food and Drug Administration (FDA) in July 2008.[17] The aim of this study was to prospectively collect clinical data to assess the magnitude of risk for the development of NSF with gadoxetate disodium among patients with moderate (glomerular filtration rate [GFR], <60 mL/min per 1.73 m^2) to severe renal (GFR, <30 mL/min per 1.73 m^2) insufficiency.

MATERIALS AND METHODS

Study Design

We performed a prospective, nonrandomized, open-label phase 4 study in 35 centers (Australia [3 centers], Austria [1 center], Germany [9 centers], Italy [6 centers], Spain [1 center], South Korea [4 centers], United Kingdom [1 center], United States of America [7 centers], and Thailand [3 centers]). The enrollment period lasted from May 2009 to July 2013 (ClinicalTrials.gov Identifier: NCT00908596). The primary objective was to assess the magnitude of potential risk of gadoxetate disodium liver imaging in patients with moderate to severe renal impairment for the development of NSF.

This study was performed in compliance with International Conference on Harmonization Good Clinical Practice guidelines after approval by applicable ethics committees/institutional review boards.

Study Population

The study population consisted of patients with moderate to severe renal impairment scheduled for gadoxetate disodium-enhanced liver MRI within the approved indications and dose. Participating study sites checked whether patients scheduled for a liver MRI with gadoxetate disodium would potentially meet inclusion/exclusion criteria. After explaining the study details and obtaining informed consent, patients were included in the study.

The study was conducted in accordance with all guidelines set forth by the approving institutional review board. Informed consent was obtained before each examination.

The cohort with "severe" renal impairment was defined as patients with eGFR at less than 30 mL/min per 1.73 m^2 or on dialysis before gadoxetate injection. The cohort with "moderate" renal impairment consisted of patients with eGFR between 30 mL/min per 1.73 m^2 and 59 mL/min per 1.73 m^2. However, eGFR was assessed twice: once during screening/informed consent within 6 weeks before the contrast-enhanced MRI (at the local laboratory) and a second time at baseline (ie, 48 hours before gadoxetate disodium administration) (at a central laboratory). Consecutively, 2 additional cohorts were defined: an "extended moderate" renal impairment cohort presenting an eGFR of 59 mL/min per 1.73 m^2 or less at screening, but greater than 59 and less than 65 mL/min/1.73 m^2 at baseline. A "mild" renal impairment was defined for patients with an initial eGFR of 59 mL/min per 1.73 m^2 or less at screening, but an eGFR of greater than 65 mL/min per 1.73 m^2 at baseline (Table 1).

Treatment

All subjects received a single intravenous bolus injection of 0.025-mmol/kg (0.1 mL/kg) body weight of gadoxetate disodium (Primovist/Eovist/EOB-Primovist; Bayer HealthCare AG, D-51368 Leverkusen, Germany), followed by a 20-mL saline flush in the framework of the clinically routine diagnostic workup. For patients receiving hemodialysis, investigators were asked to consider prompt hemodialysis after Primovist/Eovist administration to enhance the contrast agent's elimination.

Gadoxetate disodium is marketed in all participating countries and was purchased locally by the centers at hospital pharmacies.

Target Variables

The primary target variable was the number of patients with moderate to severe renal impairment who developed NSF, which was based on diagnostically specific clinical and histopathological information according to Girardi et al[4] during the 2-year follow-up period.

The secondary target variables included the following: (1) the number of patients in whom no biopsy was performed but who develop NSF-like symptoms based on diagnostically specific clinical information. Again, the clinical findings suggestive of NSF were also summarized by the clinical score according to Girardi et al[4]; and (2) the number and characteristics of adverse events reported in association with the administration of gadoxetate disodium.

Study Procedures

We designed the study in a way that a standardized diagnostic workup of potential NSF-related symptoms could be performed and comprehensive and reliable information could be collected under routine clinical conditions.

TABLE 1. Classification of Study Cohorts

		Moderate		
Renal Impairment	**Mild**	**Extended Moderate**	**Moderate**	**Severe (+ Dialysis)**
Screening/informed consent (6 weeks before MRI)	≤59	≤59	≤59	≤59
Baseline (48 hours before MRI)	>65	>59 and ≤65	≥30 and ≤59	<30

Renal impairment at screening and baseline according to eGFR (mL/min per 1.73 m^2).

MRI indicates magnetic resonance imaging.

A first blood sample to determine eGFR was drawn during screening/informed consent, at maximum 6 weeks before MRI and analyzed by the local laboratory. A second blood sample was drawn at baseline, that is, within 48 hours before gadoxetate disodium administration, and was analyzed by a central laboratory.

After gadoxetate disodium liver imaging, the patients were followed up according to a defined standardized protocol: visits at 12 and 24 months for clinical examination as well as review of source documents and telephone contacts at 1, 3, 6, and 18 months after injection. All patient contacts were performed by licensed health care professionals who had received study-specific training.

All skin findings potentially suggestive of NSF were clinically and, if indicated, histopathologically assessed. The criteria according to the study of Girardi et al[4]were applied. This approach ensured a high likelihood of potential NSF-related clinical outcomes to be adequately captured.

Statistics and Sample Size

Descriptive statistics including sample size, mean standard deviation, as well as minimum and maximum were calculated for quantitative variables. Frequency counts and percentages by category were made for qualitative data. Summaries are presented by renal status cohort (mild, extended moderate, moderate, and severe renal impairment) and overall study population. Outcome of NSF was reported individually.

As stipulated by the FDA (letter on May 22, 2007 for Gd-DTPA and July 7, 2008 for gadoxetate disodium[17]), initially, 1000 male and female patients aged 18 years or older were planned to be enrolled. This sample size suggestion was based on 1 retrospective study of 370 patients with severe renal insufficiency who received gadodiamide. The estimated risk for development of NSF was approximately 4%.[18] At least 400 patients with severe renal impairment (eGFR, <30 mL/min per 1.73 m^2) and 600 with moderate renal impairment (eGFR, 30–59 mL/min per 1.73 m^2) were targeted for enrollment. When the FDA released the pharmaceutical companies manufacturing GBCAs from completing their studies on June 2, 2011,[19] we stopped enrollment on August 1, 2011 but continued the 2-year follow-up for those patients already included according to the protocol.

RESULTS

We enrolled a total of 364 patients. Three-hundred fifty-seven patients completed the MRI examination and were included in the analysis set: 85 with severe, 193 with moderate, 32 with extended moderate, and 47 with mild renal impairment (Table 2). A total of 186 patients (52.1%) completed the 24-month follow-up. Demographics are shown in Table 2.

The mean age ranged from 58 years in the severe dialysis-dependent renal impairment cohort to 65 to 66 years in the other cohorts (overall range, 24–92 years). The majority of patients were men, ranging from 57% in the mild renal impairment cohort to 78% in the extended moderate renal impairment cohort. The majority of patients in the moderately severe and severe dialysis dependent renal impairment cohorts were white (52% to 87%), whereas the majority of patients in the mild and extended moderate renal impairment cohorts were Asian (57% and 50%, respectively; Table 2).

The time period since diagnosis of renal disease increased with severity of renal impairment, ranging from 0.54 years in the mild renal impairment cohort to 5.46 years in the severe renal impairment cohort (overall range, <0.1–29.5 years). Hypertension and diabetes were the most frequently reported causes of renal disease, 49.4% and 38.8%, respectively. A total of 39 patients (10.9%) were dependent on dialysis and were thus assigned to the severe renal impairment cohort. Vascular injuries were reported by 35 patients (41%) in the severe renal impairment cohort and by 50 patients (26%) in the moderate cohort. A total of 30 patients (8.4%) had a history of organ transplant surgery (Table 3).

Liver cirrhosis was recorded for 129 patients (36%). Benign and malignant liver lesions were recorded for 77 (22%) and 113 patients (32%), respectively (Table 4).

Overall, 101 patients (28%) underwent contrast-enhanced MRI with another GBCA within 12 months before the start of the study or in the follow-up. Thirty-one patients (8.7%) were exposed to a GBCA before the start of the study and 82 patients (23.0%) received additional GBCAs during follow-up, that is, after gadoxetate disodium administration at baseline. The number of GBCA administrations ranged from 1 for most patients (51 patients, 14%) to more than 5 (10 patients, 3%). Two patients received 9 injections. Of the 10 patients with more than 5 injections, 9 had moderate renal impairment and 1 had severe renal impairment (Table 5).

TABLE 2. Demographic and Baseline Characteristics by Degree of Renal Impairment (Full-Analysis Set)

	Renal Impairment	Mild		Moderate: Extended Moderate		Moderate: Moderate		Severe		Severe + Dialysis		Overall	
		n = 47		n = 32		n = 193		n = 46		n = 39		n = 357	
Age, y	Mean ± SD	65.3 ± 9.6		65.3 ± 12.0		65.5 ± 10.9		65.8 ± 11.7		57.9 ± 14.5		64.7 ± 11.6	
Age group, n (%)													
	<65 y	21	(44.7)	16	(50.0)	87	(45.1)	16	(34.8)	26	(66.7)	166	(46.5)
	≥65 y	26	(55.3)	16	(50.0)	106	(54.9)	30	(65.2)	13	(33.3)	191	(53.5)
Sex, n (%)													
	Male	27	(57.4)	25	(78.1)	147	(76.2)	27	(58.7)	28	(71.8)	254	(71.1)
	Female	20	(42.6)	7	(21.9)	46	(23.8)	19	(41.3)	11	(28.2)	103	(28.9)
Ethnic group, n (%)													
	White	15	(31.9)	9	(28.1)	101	(52.3)	29	(63.0)	34	(87.2)	188	(52.7)
	Black	2	(4.3)	1	(3.1)	6	(3.1)	1	(2.2)	1	(2.6)	11	(3.1)
	Hispanic	0		1	(3.1)	3	(1.6)	0		0		4	(1.1)
	Asian	27	(57.4)	16	(50.0)	56	(29.0)	7	(15.2)	1	(2.6)	107	(30.0)
	Other	3	(6.4)	5	(15.6)	27	(14.0)	9	(19.6)	3	(7.7)	47	(13.2)
Weight, kg													
	Mean ± SD	69.4 ± 19.1		73.0 ± 18.5*		73.3 ± 17.4*		74.9 ± 19.2		74.4 ± 14.1		73.1 ± 17.6*	

*Weight - extended moderate cohort, n = 31; moderate cohort, n = 191; total, 354.

TABLE 3. History of Renal Disease by Degree of Renal Impairment (FAS)

			Moderate					
	Mild		Extended Moderate		Moderate		Severe + Dialysis		Overall	
Renal Impairment	**n = 47**		**n = 32**		**n = 193**		**n = 85**		**n = 357**	
Years since renal diagnosis										
N*	27		19		85		19		150	
Mean	0.54 ± 1.76		0.93 ± 1.64		1.53 ± 2.74		5.46 ± 7.79		1.78 ± 3.82	
Cause of renal disease, n (%)										
Diabetes	8	(17.0)	7	(21.9)	72	(37.3)	33	(38.8)	120	(33.6)
Glomerulonephritis	0		2	(6.3)	5	(2.6)	16	(18.8)	23	(6.4)
Collagen disease	1	(2.1)	0		1	(0.5)	0		2	(0.6)
Hypertension	16	(34.0)	12	(37.5)	85	(44.0)	42	(49.4)	155	(43.4)
Polycystic kidney disease	1	(2.1)	0		5	(2.6)	8	(9.4)	14	(3.9)
Other	25	(53.2)	17	(53.1)	105	(54.4)	30	(35.3)	177	(49.6)
Receiving dialysis, n (%)										
Any	0		0		0		39	(45.9)	39	(10.9)
Peritoneal dialysis	0		0		0		1	(1.2)	1	(0.3)
Hemodialysis	0		0		0		38	(44.7)	38	(10.6)
Vascular injuries, n (%)†										
Any injury	5	(10.6)	7	(21.9)	50	(25.9)	35	(41.2)	97	(27.2)
Shunt surgery/repair	2	(4.3)	0		5	(2.6)	12	(14.1)	19	(5.3)
Organ transplant surgery	3	(6.4)	4	(12.5)	14	(7.3)	9	(10.6)	30	(8.4)
Thrombotic events	0		1	(3.1)	13	(6.7)	9	(10.6)	23	(6.4)
Other surgeries	3	(6.4)	3	(9.4)	23	(11.9)	11	(12.9)	40	(11.2)
Other non specified	1	(2.1)	2	(6.3)	12	(6.2)	4	(4.7)	19	(5.3)

*Number of patients with information available.

†Patients reporting more than 1 injury per injury type were counted only once for each type.

FAS indicates full-analysis set.

Three patients experienced drug-related adverse events (AEs) immediately after gadoxetate disodium administration and before leaving the MRI facility: generalized pruritus and respiratory distress were reported in 1 subject, and pruritus and vomiting were reported in 2 subjects. No AE was considered life-threatening.

During the 24-month follow-up, AE reporting was limited to skin-related findings and other findings suggestive of NSF. The patients with mild renal impairment were not included in the follow-up. No subject developed symptoms conclusive of NSF. Nineteen (9.8%) and 7 (8.2%) patients reported skin-related findings in the moderate

TABLE 4. History of Liver Disease Requiring MRI by Degree of Renal Impairment (FAS)

			Moderate					
	Mild		Extended Moderate		Moderate		Severe + Dialysis		Overall	
Renal Impairment	**n = 47**		**n = 32**		**n = 193**		**n = 85**		**n = 357**	
Patients with diffuse liver disease, n (%)										
Liver cirrhosis	14	(29.8)	13	(40.6)	81	(42.0)	21	(24.7)	129	(36.1)
Fatty infiltration	2	(4.3)	4	(12.5)	19	(9.8)	9	(10.6)	34	(9.5)
Diffuse liver fibrosis	4	(8.5)	5	(15.6)	15	(7.8)	7	(8.2)	31	(8.7)
Other liver diseases	11	(23.4)	5	(15.6)	22	(11.4)	8	(9.4)	46	(12.9)
Patients with focal liver lesions, n (%)										
Benign	9	(19.1)	7	(21.9)	44	(22.8)	17	(20.0)	77	(21.6)
Malignant	16	(34.0)	13	(40.6)	59	(30.6)	25	(29.4)	113	(31.7)
Not assessable	6	(12.8)	5	(15.6)	36	(18.7)	32	(37.6)	79	(22.1)

Patients with multiple diseases were counted just once in each group (diffuse disease or lesion-type disease).

FAS indicates full-analysis set; MRI, magnetic resonance imaging.

TABLE 5. Patients With and Number of GBCA Injections From 12 Months Before Start of the Study (Gadoxetate Disodium Administration) and During Follow-Up (FAS)

			Moderate							
	Mild		Extended Moderate		Moderate		Severe + Dialysis		Overall	
Renal Impairment	n = 47		n = 32		n = 193		n = 85		n = 357	
No. patients with GBCA injections, n (%)										
Overall*	5	(10.6)	11	(34.4)	70	(36.3)	15	(17.6)	101	(28.3)
Before start of the study	5	(10.6)	4	(12.5)	19	(9.8)	3	(3.5)	31	(8.7)
During follow-up	0		8	(25.0)	60	(31.1)	14	(16.5)	82	(23.0)
No. GBCA injections, n (%)†										
1	4	(8.5)	7	(21.9)	33	(17.1)	7	(8.2)	51	(14.3)
2	0		1	(3.1)	16	(8.3)	3	(3.5)	20	(5.6)
3	1	(2.1)	1	(3.1)	11	(5.7)	1	(1.2)	14	(3.9)
4	0		1	(3.1)	0		1	(1.2)	2	(0.6)
5	0		1	(3.1)	1	(0.5)	2	(2.4)	4	(1.1)
>5	0		0		9	(4.7)	1	(1.2)	10	(2.8)

*Includes patients who had GBCA injections before the start of study and during follow-up.

†Includes all GBCA injections from 12 months before and during follow-up.

FAS indicates full-analysis set; GBCA, gadolinium-based magnetic resonance imaging contrast agent.

(n = 193) and severe (n = 85) renal impairment cohort, respectively. Of these patients, 3 had a clinical NSF score according to the study of Girardi et al[4] of higher than 0.

One subject in the severe renal impairment cohort was diagnosed with basal cell carcinoma, which was considered as not drug-related. The patients in the extended moderate cohort had no skin-related findings at all.

No patient developed symptoms conclusive of NSF. There were 3 patients with a clinical score of higher than 0 owing to skin-related findings. One dialysis-dependent patient in the severe renal impairment cohort experienced a mild extremity contracture 5 days after the administration of gadoxetate disodium. This event fulfilled one of the major clinical criteria for NSF and was therefore given a clinical score of 3 (ie, clinically consistent with NSF). Because no skin findings suggestive of NSF (eg, patterned plaques, cobblestoning, marked induration/peau d'orange, superficial patches/plaques, dermal papules) were detected, a skin biopsy was not indicated. The contracture was resolved at the follow-up 6 months later.

One patient with severe renal impairment had had a skin rash 3 months after administration of gadoxetate disodium, and 1 patient with moderate renal impairment developed a macule on the right calf 6 months after administration of gadoxetate disodium. Both of these patients were given a clinical score of 1 (ie, inconsistent with NSF). Biopsies were not performed for these patients.

None of the subjects with skin-related findings died. The frequency of deaths during the follow-up period was related to the severity of renal impairment, with 15.6%, 29.5%, and 37.6% of patients in the cohorts with extended moderate, moderate, and severe renal impairment, respectively. Progression of study disease was the most frequent cause of death.

DISCUSSION

After an FDA request, dated July 2008,[17] we performed a prospective, nonrandomized multicenter study in 357 patients with various degrees of renal impairment. Our objective was to assess the NSF risk of gadoxetate disodium in liver MRI. After 2 years of follow-up, no case of NSF was detected.

To the best of our knowledge, this is the first time that such prospective data on gadoxetate disodium have been published. So far, only 2 similar studies have been reported. One study by Amet et al[20] investigated 268 patients on dialysis undergoing contrast-enhanced MRI mainly with gadoteric acid. Another study by Smorodinsky et al[21] retrospectively looked at 1167 patients with chronic liver disease; thereof, 72% had also some degree of renal insufficiency. The GBCAs applied were gadobenate dimeglumine, gadoversetamide, and gadopentetate dimeglumine. None of their patients developed NSF.

We stopped this study prematurely after inclusion of roughly one third of our target following the FDA's decision to release manufactures of GBCAs from completing enrollment (letter from June 2, 2011). At this time, the FDA concluded that the NSF incidence estimate based on postmarketing surveillance reports was lower than the original literature-based estimate.[19] As a consequence, the predefined sample size became inadequate to address the study's objective. In addition, the enrollment quota became unrealistic, owing to new labeling (FDA's black-box warning for application in patients with chronic, severe kidney disease) and changes in clinical practice. Therefore, enrollment was prematurely stopped in December 2011, but follow-up was continued for 2 years as defined in the protocol.

Thus, our study population consisted of 357 patients. A total of 85 patients had severe and 193 had moderate renal impairment, which was the target population requested by the FDA. In several patients, the 2 eGFR determinations (1 at screening and 1 immediately before the MRI/baseline) resulted in different patient classifications on the basis of the cutoff values for mild, moderate, or severe renal impairment; that is, patients who originally fulfilled the criterion for moderate renal impairment at the time of screening actually showed improved renal function at the time of contrast injection. To reflect a kind of worst-case scenario, we subsumed those patients still in the category moderate, which also allowed us to perform the 2-year follow-up; however, to be fully transparent, we defined a subgroup of the so-called extended moderate (screening, ≤59 mL/min; baseline, >59 and ≤65 mL/min). For the patients in the mild renal disease group, an elevated NSF

risk has not been established,[22] so follow-up was waived according to protocol.

One important aspect is that many patients in our study population did not receive only gadoxetate disodium. A total of 101 patients (28%) received other, additional GBCA administrations before the study or during follow-up. Although this does confound our primary study objective, we included all these patients in our analysis. Taking the most conservative approach, we report the full-analysis data set that includes all patients who have got at least 1 dose of gadoxetate disodium and disregarded the per-protocol set, which would be cleaned for those protocol violators. Thus, we are confident that our study population reflects the clinical reality of this particular patient group. In addition, because the number and dose of GBCA administrations may impact the likelihood of NSF development, it might be reassuring that, even in these cases, no NSF has been detected.

We think that our study provides sufficiently detailed data on medical history, showing that most patients had renal disease caused by hypertension or diabetes, which are both very common in the modern Western world.[23,24] The most frequent reasons for liver imaging were liver cirrhosis (36%) and malignant liver tumors (32%), which are the 2 most relevant diagnoses for liver imaging.[25]

Interestingly, a study by Gschwend et al[15] showed that, in humans with moderate renal impairment and mild-to-moderate hepatic impairment, no relevant changes were observed in pharmacokinetic parameters. This was considered a result of increased renal excretion to compensate in cases of hepatic impairment, or increased hepatic elimination in cases of renal impairment. Gschwend et al[15] concluded that there is no need for dose adjustment of gadoxetate disodium.

Today, gadoxetate disodium is used in more than 50 countries worldwide, including the extended European Union, Switzerland, Australia, the United States, Canada, Japan, and China. Since its introduction to the market in 2004, until May 14, 2014, the cumulative patient exposure is estimated to be more than 2.2 million patients (NSF Annual Surveillance Report, Data on File). No case of NSF has been reported to any regulatory authority in any country where gadoxetate disodium is marketed (evidence level C, derived from registries[26]). However, it is reasonable to assume that only a nonspecified minority of these patients was in the high-risk group for NSF, that is, in the group with moderate to severe renal impairment as our study cohort.

Eventually, no new safety concerns surfaced in our study. Neither drug-related AEs nor clinically significant changes in any of the safety variables (laboratory values, vital signs, electrocardiograms, cardiac rhythm, oxygen saturation, findings on physical examination) were found during the study. Mean serum creatinine values were stable throughout the study, except for dialysis-dependent changes.[15]

Finally, it is important to note that the FDA[27] and the European Medicines Agency[28] have defined risk categories for GBCAs. In addition, the European Society of Urogenital Radiology followed those categories in their recommendation.[26] Certain linear molecules have been identified as GBCAs with the highest risk potential for NSF. In addition, European Medicines Agency and the European Society of Urogenital Radiology defined a subclass, linear ionic agents. Accordingly, gadoxetate disodium was assigned to that intermediate risk group. The GBCAs of this intermediate risk group should be used with caution in patients with chronic kidney disease stages 4 and 5 (GFR, <30 mL/min per 1.73 m^2), and there should be at least 7 days between injections. Use in pregnant women should only be considered in case essential information is expected. However, laboratory testing of renal function (eGFR) is not mandatory.[26] In the United States, however, the FDA has mandated a new boxed warning on the product labelling of all GBCAs.[29]

As previously mentioned already, the major limitation of our study is the limited sample size. Even with an NSF incidence of 0.1% to 1% for Gd-DTPA in the at-risk population as mentioned by Thomsen et al,[26] a confirmative study might hardly be possible. Another limitation may be related to the fact that some patients also received other Gd-based contrast agents before the study or even during follow-up. However, none of these patients developed signs of NSF. In addition, all patients received the approved standard dose of 0.025-mmol/kg body weight. A number of institutions, however, routinely administer a dose of 10 mL in all patients instead of weight-based dosing. Thus, this study might not reflect the situation in all centers. Finally, it is unclear whether the medical background of the cohort with severe renal impairment matches the medical background of the group of GBCA-induced NSF cases worldwide because this kind of analysis is, to our knowledge, not published yet.

As triggered by the FDA request, a number of similar studies with other GBCAs have been initiated. We hope that, when all studies have been evaluated, a better assessment on the impact of GBCA administration on NSF development might be possible.

CONCLUSIONS

Gadoxetate disodium in patients with moderate to severe renal impairment did not raise any clinically significant safety concern. No NSF case was observed with gadoxetate disodium in this study.

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