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FULL PAPER

Advancing pharmacovigilance through academic–legal collaboration: the case of gadolinium-based contrast agents and nephrogenic systemic fibrosis—a research on adverse drug events and reports (RADAR) report

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Objective: To compare and contrast three databases, that is, The International Centre for Nephrogenic Systemic Fibrosis Registry (ICNSFR), the Food and Drug Administration Adverse Event Reporting System (FAERS) and a legal data set, through pharmacovigilance and to evaluate international nephrogenic systemic fibrosis (NSF) safety efforts.

Methods: The Research on Adverse Drug events And Reports methodology was used for assessment—the FAERS (through June 2009), ICNSFR and the legal data set (January 2002 to December 2010). Safety information was obtained from the European Medicines Agency, the Danish Medicine Agency and the Food and Drug Administration.

Results: The FAERS encompassed the largest number ($n = 1395$) of NSF reports. The ICNSFR contained the most complete ($n = 335$, 100%) histopathological data. A total of 382 individual biopsy-proven, product-specific NSF cases were analysed from the legal data set. 76.2% (291/382) identified exposure to gadodiamide, of which 67.7% (197/291) were unconfounded. Additionally, 40.1% (153/382) of cases involved gadopentetate dimeglumine, of which 48.4% (74/153) were unconfounded, while gadoversetamide was identified in 7.3% (28/382) of which 28.6% (8/28) were unconfounded. Some cases involved gadobenate dimeglumine or gadoteridol, 5.8% (22/382), all of which were confounded. The mean number of exposures to gadolinium-based contrast agents (GBCAs) was gadodiamide (3), gadopentetate dimeglumine (5) and gadoversetamide (2). Of the 279 unconfounded cases, all involved a linear-structured GBCA. 205 (73.5%) were a non-ionic GBCA while 74 (26.5%) were an ionic GBCA.

Conclusion: Clinical and legal databases exhibit unique characteristics that prove complementary in safety evaluations. Use of the legal data set allowed the identification of the most commonly implicated GBCA.

Advances in knowledge: This article is the first to demonstrate explicitly the utility of a legal data set to pharmacovigilance research.

Nephrogenic systemic fibrosis (NSF) induces cutaneous and subcutaneous "scleroderma-like" changes with acute-onset thickening and hardening of the skin.[1] This condition was first reported in 2000 as a debilitating disorder in persons with chronic kidney disease (CKD) who were on dialysis.[1–11] Although initially named "nephrogenic fibrosing dermopathy", since the condition seemed to be limited to the skin, it is now well documented that lesions extend beyond the dermis and can involve the joints, skeletal muscles, testes, kidney, myocardium and dura.[12–14] Currently, the diagnosis is made by clinicopathological correlation.[15] Major clinical diagnostic criteria include patterned plaques of bound-down skin, sometimes leading to a "peau d'orange" appearance, overlying hard subcutaneous tissue on the extremities, at times extending to the lower trunk and leading to joint contractures.[15,16] Histologically, dermal changes include increased cellularity with numerous spindle-shaped fibroblasts, $CD34^+$ tram tracks, thick collagen bundles with surrounding clefts, mucin deposition and retention of elastic fibres extending into widened subcutaneous septae. Electron microscopy has identified increased elastic fibres apposed to dendritic cell processes.[17] Although information regarding gadolinium exposure is not necessary for the diagnosis of NSF, it is highly recommend that this information be sought to better clarify the role of prior gadolinium exposure in the pathogenesis of NSF.[15] Cardiac, vascular and nervous system complications have been reported as NSF can have systemic fibrotic effects.[18–21]

Gadolinium-based contrast agents (GBCAs) are gadolinium chelates and may be divided into four classes: linear *vs* macrocyclic and ionic *vs* non-ionic. Linear, non-ionic GBCAs have predominantly been implicated in the development of NSF (Table 1). An association with the administration of gadodiamide (OmniScan®; GE Healthcare, Wauwatosa, WA), a linear non-ionic GBCA and NSF was reported in 2006.[16] In 2007, the European Medicines Agency (EMA) mandated that only protein-binding linear agents (intermediate risk group) and macrocyclic formulations be used in patients with Stage 4 or 5 CKD. In 2007, the Food and Drug Administration (FDA) required that a "boxed warning" be placed on each of the five FDA-approved GBCAs.[22] No differentiation was made between the various agents as to the strength of their associations with NSF. In one reported series of 36 patients, more than half of the patients with NSF died from NSF or underlying comorbidities within 18 months of diagnosis.[23]

The goal of this study was to compare the accuracy and completeness and the contradistinctions of the features of each of the safety databases. The International Centre for NSF Registry (ICNSFR), FDA-Adverse Event Reporting System (FAERS) and a publicly available legal data set were examined. We want to report on safety recommendations from the different national safety agencies such as the FDA and the EMA, among others. We also reviewed the international safety experience with NSF.

METHODS AND MATERIALS

Previously described Research on Adverse Drug events And Reports methods were used.[24] These included a systematic literature review from Medline, PubMed, EMBASE (search period from 1 January 1997 to 30 June 2011), and searches of regulatory agency databases (FAERS and EMA), a publicly available legal data set and the ICNSFR registry. MeSH search terms included nephrogenic systemic fibrosis; nephrogenic fibrosing dermopathy; all GBCAs, including generic and brand names; renal failure; and systemic fibrosis. Sources included safety reports obtained through the Freedom of Information Act (USA) from FAERS, EMA and the Danish Medicine Agency (DMA),[25] as well as from an independent investigation conducted under the auspices of the Danish Parliament. Data were obtained from conference proceedings[26] and from individual cases' product-specific identification legal data set.[27]

Case definition included prior GBCA exposure and the previously outlined clinicopathological criteria.[28] Data reviewed included specific GBCA product, date of administration, renal function, skin biopsy, diagnosis date and report date. Databases were dated from 1 January 2002 to December 2010. Data extraction was conducted on a standardized case report form. Data items included product identification of concurrent GBCA used, stage of CKD, clinical manifestations, comorbidities and medications.

The legal data set was created through collaborative efforts of law firms representing the manufacturers and the patients following an assessment of applicable records. Within the legal data set, cases were characterized as unconfounded, if it was

Table 1. Identification of the different gadolinium-based contrast agents

Structural aspect	Ionic	Non-ionic
Linear	Ablavar (gadofosveset trisodium)	OmniScan® (gadodiamide, Gd-DTPA-BMA)
	Eovist® (gadoxetate disodium)	OptiMARK™ (gadoversetamide, Gd-DTPA-BMEA)
	Magnevist® (gadopentetate, Gd-DTPA)	
	MultiHance® (gadobenate, Gd-BOPTA)	
Cyclic	DOTAREM® (gadoterate, Gd-DOTA)	GADAVIST® (USA)/GADOVIST (Europe, Canada) (gadobutrol, Gd-BT-DO3A)
		ProHance® (gadoteridol, Gd-HP-DO3A)

DOTA: 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid.
DOTAREM, Guerbet, Bloomington, IN; Eovist, Bayer, Whippany, NJ; GADAVIST, Bayer; Magnevist, Bayer; MultiHance, Bracco, Singen, Germany; OmniScan, GE Healthcare; Wauwatosa, WA; OptiMARK, Mallinckrodt Inc., St Louis, MO; ProHance, Bracco.

documented that the individual was exposed to only one GBCA prior to NSF diagnosis, and as confounded, if there was documentation of exposure to two or more GBCAs. Data were analysed only in cases that were reported by the patient's law firm as biopsy proven. All cases analysed had GBCA exposure and were positively identified as linked to a specific product. The FDA requested this data set, which is publicly available.[27] Available patient variables and citation history were used in an effort to eliminate redundant reports. As with most registries, it is difficult to be certain that all cases were truly collected. Certainly in the beginning of the NSF issue, cases would have gone unnoticed and unreported, and, as they are usually retrospective data, those with non-disabling disease are especially unreported.

RESULTS

Safety databases

As of 30 June 2009, the FAERS data set included 1395 NSF cases in the USA and Europe. Of these, 960 (68.8%) cases were reported between 1 January 2008 and 30 June 2009. 692 (49.6%, 692/1395) reports listed only 1 product. 74% (511/692) of these identified gadodiamide, 23% (162/692) gadopentetate dimeglumine and 2% (16/692) gadoversetamide.

A total of 382 individual biopsy-proven, product-specific NSF cases were analysed from the legal data set. 76.2% (291/382) identified exposure to gadodiamide, of which 67.7% (197/291) were unconfounded. Additionally, 40.1% (153/382) of cases involved gadopentetate dimeglumine, of which 48.4% (74/153) were unconfounded, while gadoversetamide was identified in 7.3% (28/382) of which 28.6% (8/28) were unconfounded. Some cases involved gadobenate dimeglumine or gadoteridol, 5.8% (22/382) all of which were confounded. The mean number of exposures to GBCA was gadodiamide (3), gadopentetate dimeglumine (5) and gadoversetamide (2). Of the 279 unconfounded cases, all involved a linear-structured GBCA. 205 (73.5%) were a non-ionic GBCA, while 74 (26.5%) were an ionic GBCA (Figure 1). The ICNSFR included 335 biopsy-proven cases collected since 1997.[29] Almost all patients had CKD and were receiving or had received haemodialysis (HD); 98% had undergone vascular surgical procedures and 12% exhibited hypercoagulability.[2]

The EMA database included 104 cases between 1997 and 30 June 2009. Databases maintained by manufacturers of gadodiamide and gadopentetate dimeglumine contained 340 and 64 cases, respectively.[30,31]

Comparison of databases

Commonalities among the databases included de-identification and some inconsistent reporting on comorbidities, drugs and laboratory tests (Table 2). The legal database was the most useful related to its extensive assessment for unique GBCAs (unconfounded cases with good faith substantiation), thus allowing for the identification of gadodiamide as the GBCA most commonly associated with NSF. The ICNSFR contained the most completely authenticated clinicopathological collection of cases, while the FAERS contained the largest number of reports. Case reports from the FAERS also identified gadodiamide as the most commonly associated GBCA, but because databases are de-identified, it was not possible to ascertain redundant reporting.

The Danish experience

In March 2008, the Minister for Heath and Prevention requested that the DMA prepare a report on gadodiamide and NSF. However, by February 2009, public concern related to the report motivated the parliament to commission an independent investigation. The investigation identified deficits in the regulatory actions of the DMA relating to GBCAs, in particular removal of contraindications related to CKD (1998), and a delay in case reporting (2006). It was considered that the delayed reporting contributed to further NSF occurrence in Denmark and other European nations[25] (Table 2).

Epidemiology

The first case of NSF was published in 2001.[17] In 2006, an association was described with GBCA-enhanced MRI.[14,32] A Centers for Disease Control study identified GBCA exposure as a risk factor in early 2007.[33] Girardi et al,[15] have provided

Figure 1. Breakdown of nephrogenic systemic fibrosis cases by associated contrast agent, confounding status in legal data set. GBCAs, gadolinium-based contrast agents.

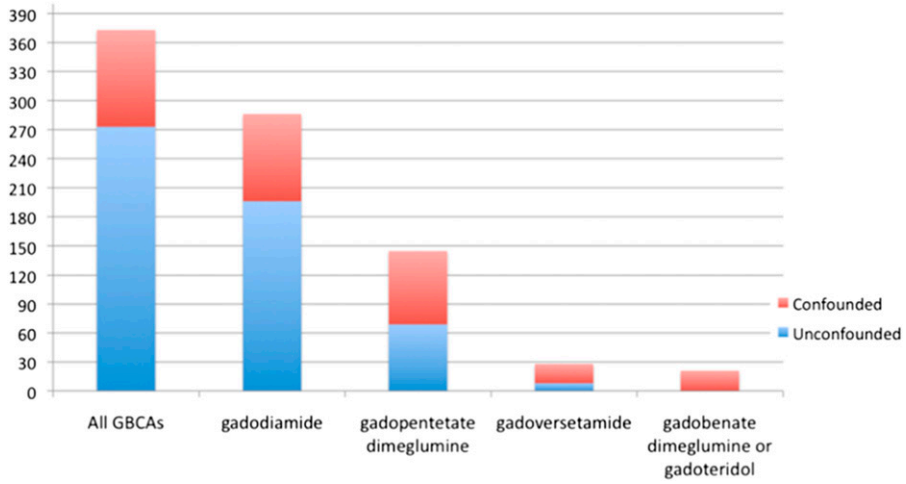

Table 2. Strengths and limitations of pharmacovigilance databases

Database	Strengths	Limitations	Skin biopsy
Food and Drug Administration Adverse Event Reporting System	Largest number of reports	Possible redundancy Freedom of information act Inconsistent reporting of comorbidities, medications and laboratory tests	Variable
International Centre for NSF Research Registry	No redundancy Clinicopathological evidence	De-identified Comorbidities, medications and laboratory testing not reported	100%
Legal data set	No redundancy Medical and billing record review about GBCA Allowed identification of GBCA agent most associated with NSF	Court must authorize the release of database Comorbidities, medications and laboratory testing not reported	75%

GBCA, gadolinium-based contrast agent; NSF, nephrogenic systemic fibrosis.

a clinicopathological definition of NSF that includes clinical and pathological scoring of visual standards and a diagnostic grid to lead to a final diagnosis. Overall, 1280 GBCA-associated NSF cases were described in the literature by December 2009. Three-quarters reported CKD Stages 4 or 5 at the time of exposure. The odds of developing NSF were 7- and 45-fold greater among patients during HD with single and multiple gadolinium exposures, respectively.[34] Others identified the incidence as 4.3 patients per 1000 CKD patient-years, with each GBCA-enhanced procedure presenting a 2.4% risk.[29] Investigators found a NSF risk of 0.01% in its population after GBCA exposure, a risk of 1.0% for patients on HD, 0.8% for patients undergoing renal transplantion and 0% for patients undergoing liver transplantation, in the USA.[35] A retrospective study in the USA reported no NSF cases among 308 patients with CKD, of whom 53.6% had Stage 5 CKD and 75% had received GBCA.[36] Between 2003 and 2006, the incidence of NSF was 36.5 cases per 100,000 gadolinium-enhanced MRI procedures at the Johns Hopkins University in Baltimore, MA, USA and fell to four cases per 100,000 during 2007 and 2008 after the initiation of risk factor screening.[37] In a retrospective cohort study on individuals on HD in the west of Scotland, 14 of 1826 patients had a diagnosis of NSF. Mortality was similar for affected and non-affected patients. 13 (92.9%) of 14 patients with NSF had undergone gadolinium-enhanced MRI compared with 408 (22.5%) of 1812 non-affected patients ($p < 0.001$). Patients with NSF received a higher median cumulative dose of gadodiamide (0.39 *vs* 0.23 mmol per kilogram of body weight; $p = 0.008$) and underwent more gadolinium-enhanced MRI than their non-affected gadolinium-exposed counterparts. The data support a positive association between the administration of GBCAs and the development of NSF in the established patient population with renal failure; in addition, there is a positive association between the cumulative dose of gadodiamide used and dosing events.[38]

Regulatory and manufacturer notifications

The DMA reported an association between NSF and GBCAs on 29 May 2006, based on 25 patients who received gadodiamide and developed NSF. Owing to high variability in reporting requirements, the reported risk of NSF after GBCA exposure ranges widely from 0% to 55%.[39] In 2010, public concerns motivated the Danish Parliament to order an independent investigation (Table 3). On 8 June 2006, the FDA advisory recommended that GBCAs should only be used in Stage 5 CKD if absolutely necessary. An updated advisory on 22 December 2006 reported 90 patients with Stage 4 or 5 CKD who had developed NSF from 2 days to 18 months after MRI or MR angiography scans with GBCAs.[40]

Following the 23 May 2007 mandated "boxed warning" about the use of GBCA in individuals with Stage 4 or 5 CKD or acute kidney injury (AKI), on 9 September 2010, the FDA disallowed the use of gadopentetate dimeglumine, gadodiamide and gadoversetamide in patients with Stage 4 and 5 CKD and AKI. All GBCA labels had to emphasize screening for renal insufficiency (CKD) prior to administration. For patients over 60 years of age or with hypertension or diabetes mellitus, a point of service creatinine measurement and calculation of an estimated glomerular filtration rate (eGFR) were recommended. Multiple GBCA administrations were discouraged, and the prior high dose approval of gadodiamide was removed.[41]

On 7 February 2007, the EMA announced that gadodiamide was contraindicated among all those with AKI, Stage 4 and 5 CKD and in those under consideration for liver transplantation. This same notification advised caution when administering other EMA-approved GBCAs to CKD patients. In June 2007, the UK Commission on Human Medicines and the European Pharmacovigilance Working Party of the Committee on Medicinal Products for Human Use recommended against the use of gadodiamide and gadopentetate dimeglumine in patients with Stage 4 and 5 CKD as well as careful consideration prior to the use of other GBCAs. During the same month, gadoversetamide was approved, with a similar contraindication. Caution was advised when using these three agents in people with lesser degrees of renal failure. In the spring of 2008, the EMA classified GBCAs as high-, medium- or low-risk agents related to causing NSF.[42–44] Gadodiamide, gadoversetamide and gadopentetate dimeglumine were defined as high risk, the macrocyclic agents (gadoteridol, gadobutrol and gadoterate meglumine) as low risk and the remaining linear agents (gadobenate dimeglumine, gadoxetic acid disodium salt and gadofosveset trisodium) as

Table 3. Independent investigations regarding regulatory activity in gadolinium-based contrast agents (GBCAs) and nephrogenic systemic fibrosis (NSF) in Denmark[25]

Events	Date	Safety measures	Independent investigation
Approval of gadodiamide	18 January 1994	Contraindications: "Hypersensitivity for OmniScan®. Diminished kidney function. Must not be given to patients under 18 years old." Pre-clinical study identifying greater liver (11%) and kidney (14%) content after OmniScan than after Magnevist® (0.03%, 0.06%) MRI in Mosby Year Book 1992; 14 days after GBCA administration, there are 10-fold greater concentrations of OmniScan than ProHance®, DOTAREM® or Magnevist	There is no cause to express critique of the National Health Board medicines department in connection with the approval of OmniScan in 1994
Change of indication	22 July 1994	Nycomed imaging AS requested amongst others to change the contraindication from "kidney reduction" to "severe kidney insufficiency (eGFR $<30\,ml\,min^{-1}$)" together with particular warnings: "hypersensitivity reactions can occur in rare instances" Additionally, contraindications with regard to persons under 18 years were added "as experience with OmniScan does not exist amongst this patient group"	
Dosage change from 0.1 to 0.3 mmol per kilogram of body weight	9 August 1995	Nycomed imaging AS applied on 6 December 1994 to expand the dosage recommendation for OmniScan of 0.1 mmol per kilogram of body weight to include 0.3 mmol per kilogram of body weight for imaging of brain metastasis The Health Committee approved the dosage change, as well as an expansion of the indication for children over 6 months of age	
Change of indication to general MRI	31 July 1996	Nycomed imaging AS applied for the expansion of the previously approved indication for OmniScan to include "general MRI".	
Change of contraindication	30 March 1998	Nycomed imaging AS applied for approval of changes in the product summary of OmniScan. "It is documented that gadodiamide injection at a dosage of 0.1 mmol per kilogram of body weight is safe and well tolerated in patients with severely reduced renal function (eGFR $<30\,ml\,min^{-1}$) or with end-stage renal failure treated with dialysis" Nycomed imaging AS requested to add new warnings about anaphylactic shock and problems with the use of OmniScan in patients with severely decreased kidney function Contraindications: hypersensitivity to OmniScan. Severe kidney insufficiency (eGFR	The Medicines Agency accepted all the changes The case has not been handled in a professionally correct manner. There was no professional review: the change was not submitted to the Registration Committee the officer in charge prepares a very brief presentation of the case

(Continued)

Table 3. (Continued)

Events	Date	Safety measures	Independent investigation
		$<30\ ml\ min^{-1}$) was crossed out. In the medical voting minutes, it is noted that the text was accepted The contraindication for kidney patients was not only removed in Denmark, but also in Belgium, Finland, France, Israel, Iceland, Netherlands, Norway, UK, Switzerland, Sweden, Germany and Austria	
Expansion of use side effects	17 August 1999	Nycomed imaging AS applied for the use of OmniScan to cover central nervous system examinations in children under 6 months of age In the product summary dated 17 August 1999, the age restriction for use of OmniScan in children was partially removed	
Expansion of indication	1 August 2005	Amersham Health AS applied for an indication for myocardial perfusion MRI (stress/rest and late examinations), detection and localization of coronary arterial disease	
Reintroduction of contraindication	5 February 2007	Changes occurred in the product summary for OmniScan based on events surrounding reports of NSF. Urgent Safety Restriction procedure was finalized on 2 February 2007: product summary for OmniScan was edited and a contraindication for kidney patients was inserted "Gadodiamide™ is contraindicated in patients with severe renal failure (eGFR $<30\ ml\ min^{-1}$ per $1.73\ m^2$), and in patients who have received or will receive liver transplantation" The PhVWP concluded that there was a strong indication for a causal association between gadodiamide and NSF in patients with severe renal failure. The PhVWP noted that there were relatively few spontaneous reports on NSF associated with other GBCAs. There were differences in stability of the gadolinium complex of the different substances that might impact the propensity to trigger NSF	The PhVWP was concerned about the delays in competent authorities having access to case reports that were being discussed within the professional community
PSURs		21 PSURs concerning OmniScan administration prior to the presentation of NSF were submitted	
PSURs	After February 2006	26 NFD/NSF cases in Denmark, Austria and the USA. Two NFD/NSF cases in Germany and Denmark with some consistent symptoms, but the diagnosis of NFD/NSF was not established. The FDA, DMA and GE Healthcare decided to inform radiologists, nephrologists and dermatologists, directly through their professional societies, by a Dear Healthcare	

(Continued)

Table 3. (Continued)

Events	Date	Safety measures	Independent investigation
		Professional letter. Patient Insurance Association, 1 September 2006; all specialists who handle OmniScan should be aware that OmniScan should not be used in patients with kidney disease. Therefore, any use of OmniScan in patients with kidney disease after this date will, as a rule, in the eyes of the patient Insurance Association constitute a breach of the best specialist standard Contrasting the fact that the DMA at the same time in September, 2006, in the Council of Side Effects, comments that it is a problem that doctors are ceasing to use OmniScan in patients with kidney disease	
Contacting the MAH	7 April 2006	The DMA forwarded the reports of side effects that they received from the Herlev Hospital. MAH sent a warning to the DMA and similar agencies worldwide about a possible side effect of OmniScan in the form of NSF Physician letter: we think that there is a possible causal relationship between gadolinium-containing contrast agents and the development of NSF/NFD, a potentially life threatening condition due to following factors: we have only seen NSF/NFD to date when we have two coincident conditions: (i) renal failure (ii) gadolinium-containing contrast administration	The DMA upon receipt of the many adverse reaction reports should at once review the entire agency's action regarding the approval of subsequent changes to OmniScan. Since adverse reaction reports referred to patients with kidney disease, there was particular interest in why the contraindication for patients with kidney disease was revoked in 1998 If the DMA in March 2006 had undertaken a thorough review of the files concerning OmniScan, an independent investigator suggested that the DMA would have found that revoking the contraindication in 1998 was based on a mistake and could have taken the appropriate precautions The DMA does not mention that the warning in May 2006 was largely influenced by the FDA publication of a warning about the use of OmniScan for patients with kidney disease
EU Side Effects Committee	29 June 2006	There was skepticism on one side regarding a correlation between gadolinium chelate use and NSF, and a push on the other side for a closer study In June 2006, at the EU level, there was a consensus that there was no basis for a regulatory measure	Mention of OmniScan was not documented at other Side Effects Council meetings, only at the meeting in September 2006 At this meeting, the DMA stated that it would be problematic to advise against the use of OmniScan based upon the available evidence
EU Side Effects Committee	January 2007	Dissuade use of OmniScan in persons with reduced kidney function. After that the SPC for these medicines were changed and adapted to the new knowledge. In the SPC, under special warnings and precautions regarding use, it is, among other things, noted that OmniScan is not for use in patients with significant kidney failure or patients with liver transplant	
Parliament question	27 February 2008	What comments does the minister have with regard to the article in Dagens Medicin, entitled "At least 60 Danes	The DMA did not mention in their statement regarding question S 1188 on February 16. 2009 that the agency had

(Continued)

Table 3. (Continued)

Events	Date	Safety measures	Independent investigation
		have become invalids or have died after contrast agent", and does the minister think that the DMA acted swiftly enough when suspicions arose regarding the contrast agent? The minister is asked to explain if he finds it satisfactory that the DMA in 1997 and 1998 did not make a specific assessment of the manufacturer's desire to have the contraindication regarding patients with kidney disease removed, despite earlier studies from 1992 clearly showing that patients with kidney disease were far more often exposed than healthy patients. Independent investigation is commissioned	already, on 12 February 2009, discovered that there was no professional evaluation of the application to revoke the contraindication in 1997. At the same time, the DMA refers to the expert report that was attached to the application in 1997, despite that there was no professional evaluation of the said report during the processing of the application The Minister did not know the truth about the proceedings of the removal of the contraindication in 1998

DMA, Danish Medicine Agency; EU, European Union; eGFR, estimated glomerular filtration rate; FDA, Food and Drug Administration; GE, General Electric; MAH, marketing authorization holder; NFD, nephrogenic fibrosing dermopathy; PhVWP, Pharmacovigilance Working Party; PSUR, periodical safety update report; SPC, summary of product characteristic.
DOTAREM®, gadoteric acid; GADOVIST®, gadobutrol; Magnevist®, gadopentetate dimeglumine; Omniscan™, gadodiamide; ProHance®, gadoteridol. DOTAREM, Guerbet, Bloomington, IN; GADOVIST, Bayer, Whippany, NJ; Magnevist, Bayer; OmniScan, GE Healthcare; Wauwatosa, WA; ProHance, Bracco, Singen, Germany.

medium risk. High-risk agents were contraindicated in Stages 4–5 CKD, around the time of liver transplantation and in infants. A warning was added to the prescribing information for medium- and low-risk agents about their use in CKD, liver transplantion and infants. A mandatory minimum 7-day waiting period between repeat GBCA administrations was instituted. For medium- and low-risk agents, only the minimum recommended dose of GBCA was to be used in Stage 4 or 5 CKD, around the time of liver transplantation and in neonates and infants. Laboratory screening for renal disease was recommended but not mandated for medium- and low-risk agents.[45] The American College of Radiology (ACR) MR Safety Committee and the ACR Committee on Drugs and Contrast Media updated their NSF-related recommendations on 14 June 2010 (10th edition of the ACR Manual on Contrast Media v. 7, 2010). GBCAs were divided into three groups: Group I: high-risk GBCAs, gadodiamide, gadoversetamide and gadopentetate dimeglumine, to be avoided in patients with AKI or CKD Stage 3b or lower (*i.e.* eGFR of $<45\,ml\,min^{-1}$ per $1.73\,m^2$); and for those with CKD Stage 3a (*i.e.* GFR of $>45\,ml\,min^{-1}$ per $1.73\,m^2$ and $<60\,ml\,min^{-1}$ per $1.73\,m^2$) use the lowest possible dose after appropriate risk–benefit assessment. Group II: gadobenate dimeglumine, gadoteridol (FDA approved) and gadoterate meglumine, for those with AKI or Stage 3b or lower CKD (eGFR $<45\,ml\,min^{-1}$ per $1.73\,m^2$) to avoid re-administration until any previous dose has cleared (days to weeks) and if the patient is on HD, dialysis should follow promptly after GBCA administration. For Stage 3a CKD, use only the lowest dose required for diagnosis. Group III: gadofosveset trisodium and gadoxetic acid disodium salt, limited data are available, with few, if any, associated unconfounded NSF cases having been reported.[45,46]

DISCUSSION

Each database used for this analysis has unique characteristics, strengths and limitations. While the FAERS had the largest number of case reports, reporting is often incomplete and variable; in only half of the reports is the name of the GBCA noted. Case reports may lag by 6–12 months, and notable is the possibility of reclassification of cases, possibly leading to enhanced reporting after national safety warnings in 2008. Assessing a legal data set for pharmacovigilance is also unique. Obtaining the data set was complicated, as it required court approval prior to public release, delaying the investigation. These data do corroborate FDA findings that gadodiamide was the most commonly NSF-associated GBCA. The ICNSFR provides comprehensive dermatopathological assessment but variable clinical data. In all three data sets, additional clinical information such as comorbidities and concomitant medications are not available. Case reports are de-identified, so it was not possible to determine duplicate reporting. These data sets have allowed for pharmacovigilance analysis, identification of safety signals and specific GBCA attribution. Nevertheless, a clinical data set would be useful to calculate incidence rates and risk factors.

A confluence of factors related to diagnostic imaging may account for the occurrence of GBCA-associated NSF. The initial approval for gadodiamide in the 1980s included a $0.1\,mmol\,kg^{-1}$ dose recommendation and advice not to use it in persons with renal insufficiency. In 1995, gadodiamide administration was approved at a higher dose ($0.3\,mmol\,kg^{-1}$) for evaluation of suspected brain metastases. In 1996, $0.3\,mmol\,kg^{-1}$ dosage was approved for use in MR angiography in Europe. In 1998, the regulatory contraindication to administering gadodiamide in renal insufficiency was eliminated both for single dose (0.1) and triple (0.3) doses despite the application not containing studies of patients with poor renal function having 0.3. There was no documentation for the safe use of 0.3 in patients with poor renal function. Nevertheless DMA granted the marketing authorization holder marketing permission. Because of concerns over iodine-induced nephrotoxicity, radiologists shifted from performing contrast-

enhanced CT examinations to GBCA-enhanced MRI whenever possible. Gradually, higher doses of GBCAs were administered to improve vascular visualization in MR angiography. CE-MR angiography was revolutionary as a non-invasive substitute for the more invasive conventional angiography. The original implementation mandated higher doses for the required acquisition times and multiple stations to cover the vasculature. Lower dosages of contrast are now required owing to higher signal–noise ratio using phased array coils and faster acquisition times with improved gradient performance, moving tables and parallel imaging.[47] The occurrence of NSF has resulted in modification of imaging protocols and point of service renal function assessment. Policy-wide, safety notifications have been circulated by international safety agencies. Greater clinician and public awareness is evident.

It is clear that there is an association between GBCA and NSF. The incidence of biopsy-proven NSF cases dropped significantly after the FDA, EMA and other international regulatory bodies' warnings.

There is a discrepancy between the numbers of FAERS reports and GBCA manufacturers' reports. Although at least one GBCA manufacturer had noted fewer new NSF cases,[30] the FAERS received >900 reports between 1 January 2008 and 20 June 2009. The majority of reports did not have an event date during this same period. We suggest that the discrepancy is attributable to delayed provider reporting or reclassification of earlier cases or follow-up reports.[48]

The Danish investigation into NSF and the disappointing DMA performance highlight two issues. First, the public can exert considerable influence on the government when public health is at risk, and thus does have the power to enhance general safety. Second, it is not clear that a government regulatory agency can operate in a self-disclosing fashion compared with an independent investigatory body.

The risk of NSF with GBCA-MRI is low when compared with the risks of acute renal failure associated with iodinated contrast agents when used appropriately, especially with the use of low-dose macrocyclic compounds. In people with CKD, iodinated contrast agents can lead to loss of residual renal function, precipitating dialysis or transplantation. Interestingly, the concern about NSF has masked worries about other GBCA-related adverse effects.[49,50] The current NSF discussion also fails to address the risk of making an incorrect diagnosis because of the failure to employ gadolinium-based diagnostic modalities.[51] The failure to detect cancer or another life-threatening disease may far outweigh the risk of acquiring NSF through the use of gadolinium-based modalities.

The comprehensive documentation of legal cases contributed significantly to the completeness of data. In particular, the collaborative efforts exploring unconfounded cases allowed the specific association with each GBCA. This data-quality contrasts with the FAERS incomplete reporting. Future projects analysing such legal data sets will likely be instrumental in the advancement of pharmacovigilance. Additionally, it is essential to note that the Parliament-commissioned independent Danish investigation highlighted underlying deficits in pharmacovigilance at a regulatory level and underscores the profound impact that these failures can exert on international safety measures.

Some limitations of this report should be noted. The FAERS database contains reports on specific products, symptom onset, report date and country, but data are highly variable owing to self-reporting and redaction. This complicated the identification of duplicate cases. Case series in the literature may represent publication bias or selective reporting. Reports included in some manufacturer's databases included clinical and pathologically diagnosed patients, whereas others included only pathologically confirmed cases. Cases in the ICNSFR registry were pathologically confirmed by a single dermatopathologist, but lack product-specific information and outcome data. The publicly available legal data set include information on specific GBCA products for biopsy-proven NSF cases; however, clinical and outcomes data are not available. Database reconciliation would facilitate estimation of the international burden of NSF. Finally, knowing market share offers an additional and valuable perspective. Gadopentetate dimeglumine has the largest market share (approved in 100 countries with an estimated 95 million administered doses), whereas gadodiamide reported the second largest market share (approved in 93 countries with 40 million administered doses). In the USA, both agents dominated the market with a combined share of nearly 80% during the time of this investigation.[52] In addition, US renal dialysis programmes are more likely to be colocated with academic institutions, and presumably more likely to use gadodiamide.

CONCLUSION

The use of multiple databases, and particularly a legal data set, in pharmacovigilance activities is advantageous and provides independent confirmation of product-specific adverse event association, complementary clinical and histopathological findings, as well as concordance with the timeline of the adverse event occurrence.

CONFLICTS OF INTEREST

Dr Restaino represented patients diagnosed with Nephrogenic Systemic Fibrosis in Federal Litigation. The NIH did not have any role in study design, collection, analysis or interpretation of data or the decision to publish this manuscript.

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