DEPARTMENT OF VETERANS AFFAIRS
Veterans Health Administration
Washington, DC 20420

IL 10-2009-004
In Reply Refer To: 115

March 24, 2009

UNDER SECRETARY FOR HEALTH'S INFORMATION LETTER

GADOLINIUM USE IN PATIENTS WITH CHRONIC KIDNEY DISEASE

1. Introduction. This Veterans Health Administration (VHA) Information Letter provides information regarding gadolinium chelate use in patients with chronic kidney disease (CKD) within VHA facilities.

2. Background

a. Gadolinium-containing chelates (GCC) were first approved by the Food and Drug Administration (FDA) for use as contrast agents in the performance of magnetic resonance imaging in 1988. At present, five different chelates are FDA approved at a dose of 0.1 milli-mole per kilogram (mmol/kg) for this purpose. Although commonly used at higher doses for magnetic resonance angiography, arteriography and venography, these are not FDA-approved indications. Until recently, GCC were felt to have minimal toxicity. However, several recent studies showed that GCC, when used in patients with preexisting kidney disease, are associated with adverse clinical outcomes including acute kidney injury (AKI) and a rare disorder, predominantly affecting the skin, known as Nephrogenic Systemic Fibrosis (NSF). These agents have an excellent safety profile in patients with normal kidney function.

b. NSF was first observed in 1997 and reported in 2000 and initially named nephrogenic fibrosing dermopathy since its primary manifestations were in skin. With time it was recognized that other organ systems such as striated muscle, myocardium, pericardium and pleura were affected and the name was changed to NSF. The definitive diagnosis of NSF is established by skin biopsy and its characteristic skin presentation is well described in a number of reviews (see definitions below). To date, all patients with NSF have had advanced kidney disease. Although a variety of therapies have been attempted, largely in case reports, there is no convincing evidence that the disease can be reversed. There are many problems with the NSF treatment literature that make assessment of reported therapies difficult including: case reports or small series; the timing of therapy (early versus late); and the level of renal function (often fluctuating or not reported and most reports occurred before the association with gadolinium). There is little information regarding reexposure of affected patients. However, in situations where kidney function can improve, such as with recovery from acute kidney injury or after renal transplantation, skin lesions may stabilize or resolve.

c. In January of 2006, Grobner identified a group of five patients with metabolic acidosis on hemodialysis who developed NSF 2 to 4 weeks after exposure to the GCC gadodiamide. Since then several studies confirmed the association between exposure to GCC and the development of NSF. Three studies reported odds ratios for gadolinium association with NSF in the dialysis population of 8.97, 22.3, and 32.5; respectively. The International NSF Registry at Yale University has information on 239 patients with NSF worldwide. Approximately 95 percent of those for which adequate records could be obtained were exposed to GCC within 2 to 3 months prior to disease onset.

d. Approximately 90 percent of these cases were patients with end-stage renal disease treated with chronic dialysis. Further credence was lent to this association by the finding of Gadolinium (Gd^{3+}) deposition in affected skin of NSF patients using scanning electron microscopy and energy dispersive x-ray spectroscopy. The average concentration of gadolinium in NSF affected skin was 70 parts per million (ppm), range, 24.1-106.2 ppm, in comparison to 4.8 ppm in unaffected skin in an NSF patient.

e. Based on published data to date, the majority of NSF cases are associated with gadodiamide. As of October 30, 2007, according to the FDA's MedWatch program, 283 cases were associated with gadodiamide, 125 with gadopentetate, 20 with gadoversetamide, 10 with gadobenate dimeglumine and 9 with gadoteridol. Eight of the 10 cases associated with gadobenate dimeglumine, 8 of 9 cases associated with gadoteridol, and 12 of 20 cases associated with gadoversetamide had received other GCC. The Bayer Health Care Web site has stated that they are aware of 99 cases associated with gadopentetate dimeglumine exposure. Of the 195 biopsy-documented cases of NSF as of February 1, 2008, five cases had no documentable gadolinium exposure, 157 were associated with gadodiamide, eight with gadobenate dimeglumine, and three with gadoversetamide and in 18 cases the preparation was unknown. Deo *et al.* studied a group of patients in a dialysis practice in Bridgeport, Connecticut, and estimated the risk of developing NSF at 2.4 percent per gadolinium exposure. Two subsequent studies in hemodialysis patients have estimated the risk to be 1.1 percent and 3.99 percent per exposure. The risk may be higher in peritoneal dialysis patients.

f. Gadodiamide is a nonionic linear chelate and has the lowest stability constant and highest dissociation rate of the five FDA-approved GCC. Due to these factors, the Gd^{3+} ion is more likely to dissociate from the stabilizing chelate moiety. Gd^{3+} is bound more tightly to macrocyclic rather than linear chelates, and more tightly to ionic rather than nonionic chelates. Therefore, binding would be most avid to an ionic cyclic chelate. The stability constant of gadoversetamide, the other FDA-approved linear non-ionic GCC, is slightly higher than gadodiamide. Stability constants are much higher for gadoteridol, a macrocyclic chelate. However, the stability constant of gadopentetate is much higher than gadodiamide and gadoversetamide, yet gadopentetate is currently the second most common GCC associated with NSF. Taken together these data suggest that the stability of Gd^{3+} binding to the chelate cannot be the sole factor involved in the association of GCC with NSF.

g. Market share likely plays a role in the number of affected patients with each of the five GCC. The market share for the Department of Veterans Affairs (VA) Health Care System was calculated by analyzing the purchasing records for GCC between July 1, 2005, and September 30, 2007. There is no national contract for GCC and each individual facility chooses its own GCC. Because of the nationwide distribution of VA medical centers, the VA market share is a reasonable estimate of the Unites States market share for GCC. The total volume of each GCC purchased over this time period was calculated and then expressed as a percentage compared to the other GCC agents. The largest share of GCC purchased during this time period was gadopentetate dimeglumine at 53.9 percent. Gadodiamide had the second highest share at 25.6 percent followed by gadoteridol, gadoversetamide, and gadobenate dimeglumine at 11.1 percent, 6.1 percent and 3.2 percent, respectively. Since gadodiamide does not have the majority of the market share, this cannot be used to explain the overwhelming majority of reported cases associated with its use. The market share data increases the significance of the gadoversetamide cases given that it has such a low market share. Data obtained from each company's website lists worldwide administrations as follows: gadopentetate dimeglumine 79.7 million; gadodiamide 36.5 million; gadoteridol 12.5 million; gadobenate dimeglumine 2.1 million; and gadoversetamide 1.5 million. The FDA has warned that all GCC carry the potential risk of NSF.

h. The dose of GCC administered is also associated with the frequency of NSF. A typical Magnetic Resonance Imaging (MRI) exam employs a dose of 0.1 mmol/kg, while an Magnetic Resonance Angiogram is often done using doses of 0.3-0.6 mmol/kg or higher. These higher doses are not FDA approved. In one study, the odds ratio of developing NSF at a gadodiamide dose of 0.2 versus. 0.1 mmol/kg was 12.1. The International NSF registry confirms this association in that the majority of patients that developed NSF were exposed to high doses of GCC (less than 0.2 mmol/kg) and were often exposed on multiple occasions.

3. <u>Definitions</u>

a. **Nephrogenic Systemic Fibrosis (NSF).** NSF is a biopsy of affected skin revealing haphazardly arranged dermal collagen bundles with increased numbers of plump fibroblasts and mucin deposition. The histology is similar to that of a healing wound. There is extensive symmetrical waxy hardening and thickening of the skin of the extremities and trunk. The lower extremities are affected in more than 95 percent of cases from ankles to mid thigh. The upper extremities are involved in approximately 75 percent of patients, most commonly from the wrist to mid upper arm. The neck and face are generally spared with the exception of the sclera where yellow plaques have been described. Progressive fibrosis often results in severe joint contractures. A small subset of patients has rapid progression to a wheelchair or bed bound state.

b. **Chronic Kidney Disease (CKD).** CKD is defined as either kidney damage or decreased kidney function (decreased Glomerluar Filtration Rate (GFR)) for three or more months. Kidney damage may be either a structural or functional abnormality of the kidney that persists for at least 3 months that can impair kidney function. An estimated GFR of less than 60 milliliters per

minute per 1.73 square meter (m^2) is considered a priori evidence of CKD. Five stages of CKD have been defined; they are:

(1) Stage 1. There is kidney damage with normal or increased GFR (more than 90 ml per min per 1.73 m^2);

(2) Stage 2. There is a mild decrease in GFR defined as kidney damage with a GFR from 60-89 ml/min per 1.73 m^2;

(3) Stage 3. Stage 3 has GFR from 30-59 mL/min per 1.73 m^2;

(4) Stage 4. Stage 4 has GFR from 15-29 mL/min per 1.73 m^2; and

(5) Stage 5. Stage 5 has GFR ≤15 mL/min per 1.73 m^2 or dialysis.

4. Other recommendations

a. The FDA, Danish Medicines Association (DMA), United Kingdom Medicines and Healthcare Products Regulatory Agency (MHRA), and the American College of Radiology (ACR) have all developed recommendations for gadolinium use in patients with renal impairment. These were summarized in a recent review and are excerpted here. Regarding specific gadolinium preparations, the FDA is the only agency to suggest that all Gd^{3+} chelates are potentially linked to NSF. The other three organizations specifically implicate gadodiamide as carrying the highest risk for NSF based on the fact that the majority of cases are associated with this preparation. The DMA and MHRA view gadodiamide as contraindicated in patients with a GFR of <30/ml/min per 1.73m^2, while the ACR recommends avoiding gadodiamide in patients with any degree of renal disease. Although the FDA does not state that a specific preparation is contraindicated, it does recommend that physicians carefully consider the need for any GCC in those with moderate to end-stage renal disease. Gadopentetate dimeglumine was approved for use in Europe on July 23, 2007. The European Public Assessment Report for this GCC stated that it is contraindicated in patients with an epidermal growth factor receptor (eGFR) (see Web site at: http://vaww.oqp.med.va.gov/CPGintra/cpg/ckd/GOL.htm

NOTE: *This is an internal VA link not available to the public*. Less than 30 ml/min per 1.73m^2 is similar to the contraindication for gadodiamide. The ACR views gadopentetate dimeglumine as carrying an increased risk, but no contraindication to its use is specifically stated. Both the ACR and MHRA warn that gadoversetamide has an increased risk over the remaining GCC. The MHRA states that a serum creatinine concentration should be measured prior to GCC administration while the ACR does not and recommends relying on information provided by the referring physician or patient regarding kidney disease determined from a questionnaire. The MHRA recommends that standard doses not be exceeded and repeat doses not be given in less than 1 week; and that gadodiamide should be avoided in patients that have had or are undergoing a liver transplant with renal dysfunction. The ACR recommends considering postponing the study in patients with AKI until renal function has recovered.

b. Perhaps the most controversial area of recommendations involves the need for hemodialysis. There is a significant difference of opinion among these groups regarding the necessity of hemodialysis after GCC exposure. The FDA states that it may be prudent to initiate prompt hemodialysis after GCC administration in patients with advanced kidney dysfunction (stage 5 CKD or ESRD). The term "prompt" is not defined in the recommendation. The ACR advocates hemodialysis within 2 hours of GCC administration in patients already on hemodialysis. There is as of yet no evidence to support this recommendation. The MHRA does not consider hemodialysis indicated due to a lack of evidence regarding its efficacy. The MHRA is correct that there is no evidence that hemodialysis prevents NSF. Based on data reported by Broome where four patients with AKI secondary to hepatorenal syndrome developed NSF despite three consecutive daily hemodialysis sessions, it is clear that NSF can still occur despite aggressive hemodialysis. The first dialysis session in each of these patients was initiated 9, 17, 18, and 21 hours after exposure. Data regarding GCC removal from the body based on plasma concentration decay curves may overestimate GCC removal by hemodialysis.

c. The risk of NSF in patients with stage 3 to 5 CKD after GCC exposure is unknown, but appears to be less than the 2.5 to 4 percent postulated in the End Stage Renal Disease (ESRD) population. NSF was reported in two patients with stage 3 CKD. This report needs to be interpreted with caution, however, since one patient had a renal transplant and the other a liver transplant and GFR was declining in both at the time of multiple gadolinium exposures. It is likely that the true GFR of both patients was lower than estimated using the Modification of Diet in Renal Disease (MDRD) equation. The MDRD equation should not be used to estimate GFR in the setting of acute kidney injury. Five patients with stage 4 CKD have developed NSF after GCC administration. All had multiple GCC exposures. One patient had a renal transplant, two a liver transplant, and two advanced stage 4 CKD (GFR 17 and 18 ml/min per $1.73m^2$). Taken together, these data would indicate that subgroups of stage 4 CKD patients may be at increased risk for NSF including: those with multiple GCC exposures; post liver transplantation; and patients where the MDRD equation may overestimate the true GFR, such as organ transplant recipients and those with AKI superimposed on CKD. It would seem intuitive that the risk of NSF increases as GFR declines through stages 4 and 5 to ESRD. The risk appears to be very low in stage 4 CKD, approximately 2.5 percent per exposure with ESRD, and intermediate risk in stage 5 CKD prior to renal replacement therapy.

d. Decisions regarding hemodialysis are difficult in the peritoneal dialysis (PD) patient. GCC clearance appears to be low with PD. It should be pointed out, however, that this is based on older chronic ambulatory peritoneal dialysis regimens. Improved clearance may be obtainable with more aggressive cycler-based regimens; that said, data from the Centers for Disease Control Morbidity and Mortality Weekly Report suggesting that the NSF attack rate in GCC-exposed PD patients is 7.5 times higher than hemodialysis patients is alarming and warrants caution.

5. <u>Recommendations.</u> After careful literature review, VHA has developed the following recommendations:

a. Identify patients with a known diagnosis of NSF or where there is strong clinical suspicion of NSF to prevent further exposure to any GCC.

b. Identify patients who appear to have an increased risk for developing NSF following exposure to GCC. These include the following levels of kidney disease:

(1) ESRD patients on either hemodialysis or peritoneal dialysis (highest risk).

(2) Patients with an eGFR <30 ml/min/1.73m^2 not receiving dialysis. ***NOTE:*** *The issue of whether all patients receiving GCC should have measurement of a serum creatinine concentration prior to the procedure is controversial. At a minimu,m it is recommended that all patients be asked if they have kidney disease and, if they answer yes, a serum creatinine concentration be obtained within 3 months prior to the procedure.*

(3) Patients with acute kidney injury, especially with associated liver disease.

(4) Patients with kidney or liver transplants.

c. The electronic ordering form in CPRS that the referring clinicians must complete when ordering an MR exam includes the following types of questions:

(1) Does the patient have ESRD?

(2) Does the patient have an eGFR < 30/ml/min/1.73m^2?

(3) Does the patient have acute kidney injury and/or significant liver disease?

(4) Does the patient have a liver or kidney transplant?

d. Once a patient with potential risk is identified, if possible, avoid administration of all types of GCC and employ an alternative form of imaging. This needs to take place in consultation with the ordering physician, radiologist, and nephrologist to discuss alternatives that may provide the requested clinical diagnostic information at lower potential risk. If an iodinated radiocontrast Computerized Tomography scan is considered, a risk-benefit assessment is required to evaluate the benefit gained from iodinated radiocontrast administration (avoiding NSF) versus the risks of developing radiocontrast nephropathy and performance of hemodialysis (in some cases). The risk of radiocontrast nephropathy is less important in ESRD patients, but is particularly significant in advanced stage 4 and stage 5 CKD patients.

e. If administration of a GCC is deemed necessary in a patient with a risk profile as described in the preceding paragraph, the patient needs to be informed of the benefits, risks, and alternatives of gadolinium-contrast exposure (based on currently available information). This disclosure and the informed consent needs to be documented in the chart. When using a GCC, the following guides might be employed:

(1) Avoid high doses, since higher doses of GCC (> 0.1 mmol/kg) appear to be a risk factor for development of NSF. The lowest dose required to provide the diagnostic information being

clinically sought should be employed. The appropriate dose needs to be determined in consultation with the ordering physician and radiologist.

(2) Gadodiamide and gadopentetate dimeglumine are the two GCC most frequently associated with NSF and these agents need to be avoided in at risk patients with kidney disease. They are both linear chelates and whether this recommendation should extend to the other available linear GCC (gadoversetamide, gadobenate dimeglumine) is unclear. Some authorities have suggested that, for patients at risk who must receive a GCC, the macrocyclic chelates may be safer. Gadoteridol is the only FDA-approved macrocyclic chelate available in the United States.

(3) Avoid multiple exposures to gadolinium in a short period (1 week or less).

(4) Every attempt needs to be made to avoid gadolinium exposure in the patient with acute kidney injury until renal function has recovered.

f. Based on the proposed theory that NSF is caused by gadolinium deposition in tissues and that GCC is removed with hemodialysis, several authors have recommended immediate and intensive dialysis to prevent NSF in patients at risk. However, most of the studies documenting the removal of GCC by hemodialysis have used blood-based rather than dialysate-based clearance measures and do not account for potential tissue deposition. Furthermore, there is not a randomized trial or clinical report to provide evidence that hemodialysis is effective in preventing NSF. In contrast, there are four cases of NSF reported even with daily hemodialysis beginning on the same day as the administration of a GCC. Therefore, the following guidelines regarding the use of hemodialysis are recommended.

(1) Hemodialysis should not be considered an effective measure to make the administration of GCC safe.

(2) There is insufficient evidence to recommend the routine use of hemodialysis after the administration of GCC in CKD or hemodialysis patients.

g. ESRD patients on peritoneal dialysis that are exposed to GCC are a more complex situation. In the absence of residual renal function, peritoneal dialysis clearance of GCC is very poor. Every possible attempt needs to be made to avoid GCC in patients on peritoneal dialysis. In patients on peritoneal dialysis who must receive a GCC, the following are recommended:

(1) To optimize clearance (based on no data) it may be prudent to avoid a dry abdomen (dry day) and perform either frequent manual exchanges or increase the automated peritoneal dialysis prescription for at least 48 hours after GCC administration.

(2) However, since hemodialysis clears gadolinium-based contrast more effectively than does peritoneal dialysis, consider utilizing hemodialysis for ESRD patients undergoing peritoneal dialysis with the following:

(a) Patients with a functional vascular access for hemodialysis.

(b) Patients exposed to high dose or multiple exposures.

(c) Patients who have other risk factors for NSF such as infection, recent surgery, or other sources of inflammation.

h. Stage 4 and 5 CKD patients (not on chronic maintenance dialysis), as well as patients with AKI (not requiring dialysis) who are exposed to GCC, present the most challenging situation. Insufficient data exist to estimate the risk of developing NSF in relationship to the underlying GFR in patients with CKD or AKI. Furthermore, the use of alternative imaging procedures using iodinated contrast material may result in contrast induced nephrotoxicity. As discussed, the use of hemodialysis has not been shown to prevent NSF and initiating hemodialysis as a means of preventing NSF in patients with CKD not yet on dialysis who receive GCC is not recommended. The choice of imaging procedure and contrast agent needs to be individualized based on discussions with the radiologist, nephrologist and patient.

7. References

a. Cowper, S. (2003) Nephrogenic fibrosing dermopathy: the first 6 years. Current Opinions in Rheumatology (Curr Opin Rheumatol) 15:785-790.

b. Grobner, T. (2006) Gadolinium--a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? Nephrology Dialysis in Transplantation (Nephrol Dial Transplant) 21:1104-1108.

c. Perazella, Reilly R., MA (2008) Nephrogenic systemic fibrosis: recommendations for gadolinium-based contrast use in patients with kidney disease. Seminars in Dialysis (Semin Dial) 21:171-173.

d. Food and Drug Administration (October 23, 2007) Adverse Event Reporting System. Rockville, MD Department of Health and Human Services

e. Magnevist Safety Information: NSF/NFD Update. Available at http://www.imaging.bayerhealthcare.com/html/magnevist/nsf_nfd.html?WT.mc_id=berleximaging.com.

f. Perazella, Reilly R., MA (2002) Chronic kidney disease: a new approach to an old problem. Connecticut Medicine (Conn Med) 66:579-583.

g. Danish Medicines Agency (online 29 May 2006) Investigation of the safety of MRI contrast medium Omniscan [press release]. [http://www.dkma.dk/1024/visUKLSArtikel.asp?artikelID=8931]

h. Medicines and Healthcare products Regulatory Agency (online 7 February 2007) Public assessment report: increased risk of nephrogenic fibrosing dermopathy/nephrogenic systemic fibrosis and gadolinium containing MRI contrast agents. [http://www.mhra.gov. uk/home/idcplg?IdcService=SS_GET_PAGE&ssDocName=CON2030229&ssSourceNodeId=221&ssTargetNodeId=221]

i. Kanal E, Barkovich AJ, Bell C, et al. (2007) ACR guidance document for safe MR practices: 2007. American Journal of Roentgenology (AJR)188:1447-1474.

j. Penfield J, Reilly R, (2007) What nephrologists need to know about gadolinium. Nature Clinical Practice Nephrology 3:654-668.

k. European Medicines Agency (online 23 July 2007) EPARs for authorized medicinal products for human use: Optimark Product Information. [http://wwwemeaeuropaeu/humandocs/PDFs/EPAR/optimark/H-745-PI-en.pdf]

8. Questions. Questions may be addressed to Robert Reilly at (214) 857-1908 or Jeffrey Penfield at (214) 857-1593.

Michael J. Kussman, MD, MS, MACP
Under Secretary for Health

DISTRIBUTION: E-mailed to the VHA Publication Distribution List 3/25/09