

Gadolinium Retention Following Gadolinium Based Contrast Agents MRIs: Brain and Other Organs

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September 8, 2017

Why are we here?

To seek advice about gadolinium retention in the brain and other organs

What is retention? Persistence of gadolinium for a longer time than would be predicted from the acute time course of gadolinium leaving in the urine and feces

Where we need advice?

- Safety of gadolinium retention in the brain and other organs
- Interpretation of the scientific findings
- Possible clinical signals
- Recommendations for studies to fill the gaps in our knowledge
- Regulatory path forward to ensure safe use

Not for Today's Discussion

- We will not discuss the comparative efficacy of specific GBCAs
- We will not address other risks such as hypersensitivity reactions which are already included in the label

Today's Agenda

7:50 Fedowitz, FDA: Regulatory Safety Actions and Risk Mitigation

8:00 Guest speaker: Wagner, UT: Pathophysiology of GBCAs and the retention of gadolinium

8:30 Industry presentations: Bayer
Bracco
GE Healthcare
Guerbet

Today's Agenda

9:55 FDA presentations

Croteau: Adverse event reporting

Bird: Epidemiology

Greene: GBCA sales data

Bleich: Gadolinium retention

Fotenos: Endpoints in evaluation of safety



Overview of Today's Agenda

12:25 Open Public Hearing

1:55 Questions to the Committee

4:00 Adjournment

Background to Questions

1. We will summarize findings of gadolinium retention in the brain and other organs. We seek advice in interpreting this data in view of our previous evaluation of Nephrogenic Systemic Fibrosis (NSF).
2. We will present FAERS and other clinical adverse event reports related to GBCA exposure. Does the evidence support a causal relationship?

Background to Questions

3. Options to study the risk of retention will be presented. Some of the studies are ongoing. We seek advice on the design of studies to further evaluate the gaps in our knowledge
4. We plan to implement safety labeling changes. Is this approach consistent with the level of risk?

REGULATORY SAFETY ACTIONS & RISK MITIGATION

Michele Fedowitz, MD
Associate Director for Labeling, DMIP

Medical Imaging Drugs Advisory Committee
September 8, 2017

Overview

What is new safety information?

What are the sources of this information / FDA monitoring?

How does FDA address new safety information?

Labeling of safety information

A Review: Nephrogenic Systemic Fibrosis

Gadolinium Retention

What is New Safety Information?

New serious risk or unexpected serious risk associated with the use of the drug that FDA has become aware of the risk since the drug was approved

How does FDA become aware of new information?

- Reanalyze existing information
- New data (clinical trial, post-approval study, literature, active post-market safety surveillance)

Sources of New Safety Data

Clinical Trial/Post Approval Study

Pharmacovigilance

- FDA Adverse Event Reporting System (FAERS) Database (Medwatch and mandatory reporting by manufacturers)
- Post market risk identification and analysis system (active)

Peer-reviewed Literature

Regulatory Actions to Address New Safety Information

Withdrawal

Risk Evaluation and Mitigation Strategy (REMS)

Required Post Marketing Studies

Communication to the Public

Safety Labeling Changes

WITHDRAWAL

21 CFR §314.150

There is an imminent hazard to the public health

The drug is unsafe for use under the conditions of use upon the basis of which the drug was approved

REMS

Risk Evaluation and Mitigation Strategy

A Risk Evaluation and Mitigation Strategy (REMS) is a required risk management plan that uses risk minimization strategies beyond professional labeling and is necessary to ensure the benefits of a drug outweigh its risks.

- Medication Guide
- Patient package insert and/or
- Communication plan
- Elements to assure safe use (ETASU)



Safety Label Changes

Food and Drug Administration Amendments Act of 2007 Section 505(o)(4)

FDA received the authority to *require* safety label changes based on new safety information after the approval of a drug

Better define the risk benefit profile

Typically a safety label change will add or strengthen a contraindication or warning and precaution.

Useful if there are patients who benefit from the drug despite its risks.

Safety Label Changes

Boxed Warnings

Contraindications

Warnings and Precautions

Drug Interactions

Adverse Reactions

Indications and Usage

Dosage and Administration

Specific Populations

- Pregnancy
- Lactation
- Pediatric Use
- Geriatric Use
- Renal Impairment

Clinical Pharmacology

ADVERSE REACTIONS

21 CFR §201.57(c)(7) and Guidance

Undesirable effect, reasonably associated with
the drug

- Clinically meaningful information that is most important to health care practitioners' prescribing decisions
- Exhaustive lists of every reported adverse event should be avoided

WARNINGS AND PRECAUTIONS

21 CFR §201.57(c)(6) and Guidance

Clinically Significant Adverse Reactions

- Potentially Fatal/ Serious
- Can be prevented or mitigated through appropriate use of the drug

Potential safety hazard

- Anticipated adverse reactions (based on pharmacologic class)
- Anticipated serious risks in humans based upon toxicities seen in animal studies.

Outlines the risk and ways to minimize the risk

CONTRAINDICATIONS

21 CFR §201.57(c)(5)

Clinical Situations or Patients

The risk from use clearly outweighs any possible clinical benefit

BOXED WARNINGS

21 CFR §201.57(c)(1)

Highlight adverse reactions:

- May lead to death or serious injury
- So serious in proportion to the potential benefit from the drug that it is essential that it be considered in assessing the risks and benefits of using the drug
- Can be prevented or reduced in frequency or severity by appropriate use of the drug

Highlight Contraindications or Warning and Precaution

How Does FDA Evaluate a Safety Issue?

New Safety Issue

Nephrogenic Systemic Fibrosis (NSF)

- Debilitating fibrosis affecting the skin, muscle, and internal organs (sometimes fatal) related to GBCA exposure in patients with severe impairment in renal function
- Many patients and even many with renal insufficiency safely received the drug

Post Marketing Analysis: Sources of Evidence

Physiochemical Properties

- Structure
 - Linear – Gadolinium (Gd) linked to an open chain ligand
 - Macrocyclic – Gd linked to cyclic “cage” ligand

-Thermodynamic Stability (Binding strength of Gd to the ligand)
-Kinetic Stability/ (Rate of dissociation of Gd from the complex)

Pre-clinical Studies

Clinical (FAERS Database)

FDA analysis of Published Literature

ANALYSIS OF EVIDENCE FOR NSF



Tradename (Approved Agents)	Physiochemical Properties Log K_{therm} *	Nonclinical Studies^ Skin Lesions	Single Agent Domestic NSF cases since launch **	Total Volume sold 2005-2007** (liters X 1000)
Omniscan 1993	16.9	Yes	382	153
Optimark 1999	16.8	Yes	35	51
Magnevist 1988	22.5	NO	195	237
MultiHance 2004	22.6	NO	1	19
Prohance 1992	23.8	NO	0	23

*Frenzel, T., et al, *Invest. Radiology*, **43**, 817–828 (2008) and references cited within

^Data submitted to the NDA

** Gadolinium-Based Contrast Agents and Nephrogenic Systemic Fibrosis, FDA Briefing Document, Advisory Committee, December 8, 2009

Regulatory Actions

Risk Minimization Strategies

Communication to the Public

- Public Health Advisories
- Dear Healthcare Provider Letters

Increased Pharmacovigilance Efforts

- Required Expedited Reporting of Adverse Events
- Increased Frequency of Periodic Safety Reports

Clinical Data

- Required Post Marketing Studies

Regulatory Actions Following 2009 Advisory Committee

2010 Safety Label Changes

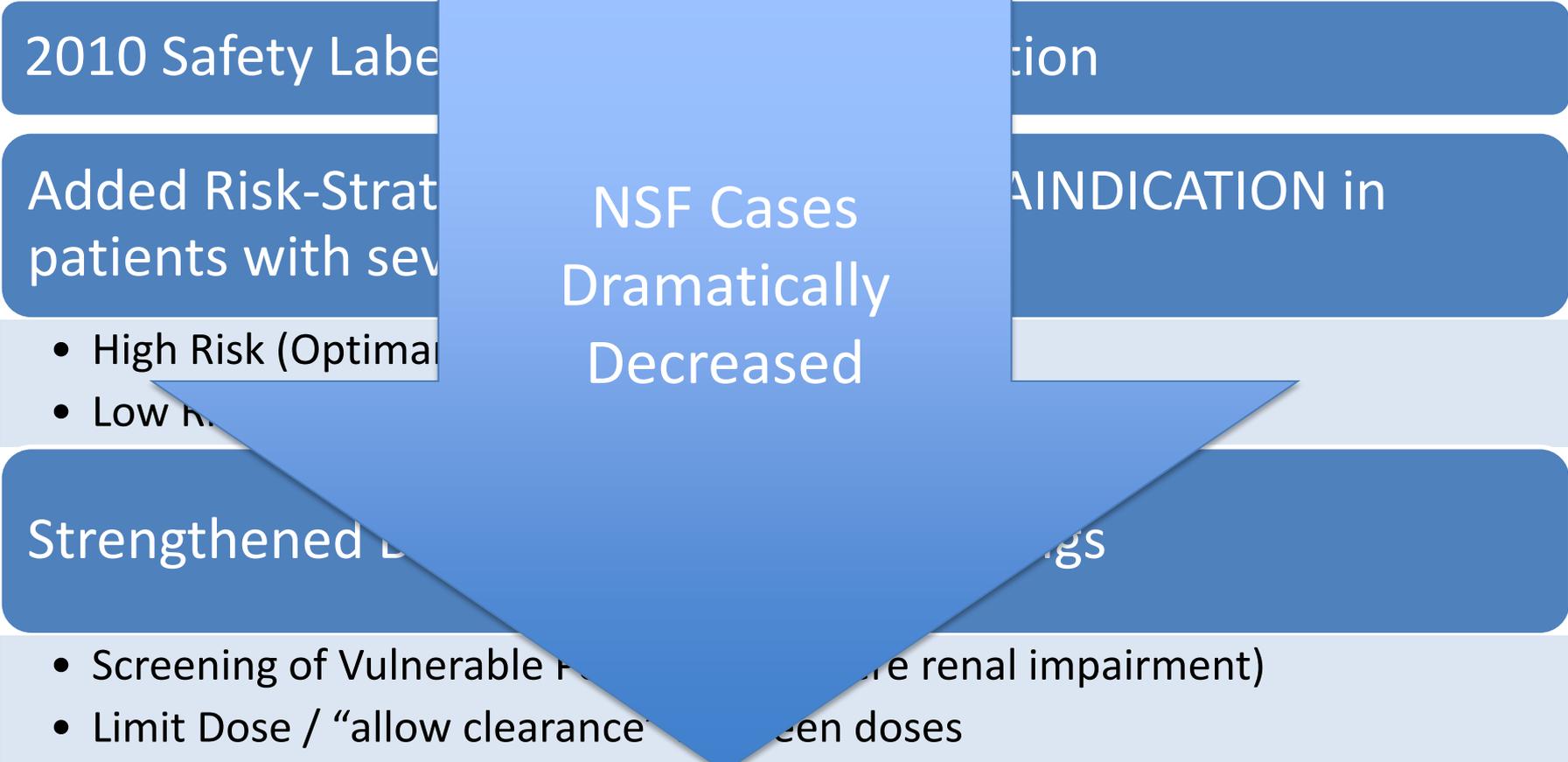
CONTRAINDICATION in patients with severe renal insufficiency
Differential Labeling / Differential Risk for GBCAs

- High Risk (Optimark, Omniscan, Magnevist)
- Low Risk (Multihance, Prohance, *Eovist*, *Gadavist*, *Dotarem*)

Strengthened Boxed Warning and Warnings and Precautions

- Screening of Vulnerable Population (severe renal impairment)
- Limit Dose / “allow clearance” between doses

Regulatory Actions Following 2009 Advisory Committee



New Safety Issue: Gadolinium Retention

Gadolinium noted in the brain, skin, bone and organs of patients receiving GBCAs with normal renal function.

What is retention? Persistence of Gd for a longer time than would be predicted from the acute time course of Gd leaving the body in urine & feces

Gadolinium Retention

Moving Forward

EVIDENCE

Chemistry

Preclinical Studies

Clinical Studies

- Safety Data
- Epidemiologic studies
- Ongoing studies

Literature

Gadolinium Retention Regulatory Options

What is the risk?

How can we minimize the risk?

Communication / Education

Labeling

Increase Pharmacovigilance

Additional Clinical / Preclinical Studies



Adverse Events with Gadolinium Retention after Gadolinium-Based Contrast Agent Exposure: FAERS and Medical Literature Review

**David Croteau MD, FRCPC
Medical Officer
Division of Pharmacovigilance
Office of Surveillance and Epidemiology
U.S. Food and Drug Administration**

September 8, 2017

Medical Imaging Drugs Advisory Committee Meeting

Outline

- Purpose of the review
- Methods
 - FAERS database
 - FAERS search
 - Medical literature review
- Results
 - FAERS case reports
 - Medical literature
 - Case reports and case series
- Discussion
- Summary

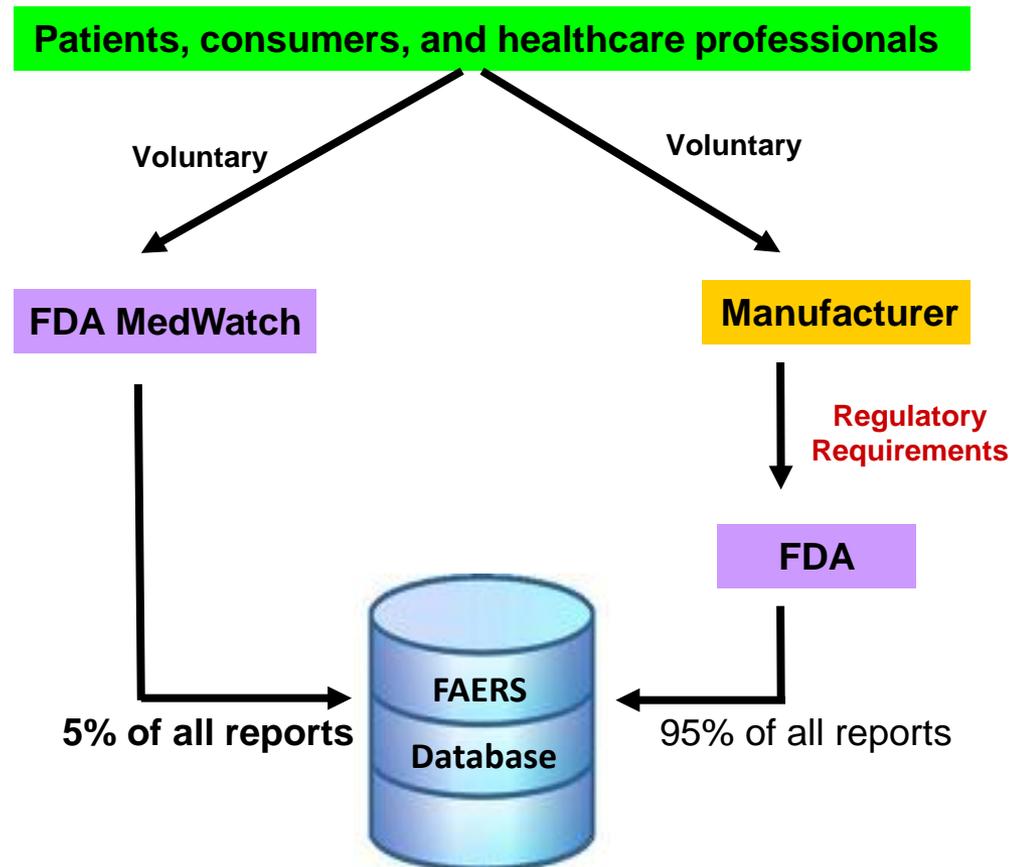
Purpose of the Review

- To identify and describe clinical adverse events in patients with gadolinium retention after gadolinium-based contrast agent (GBCA) exposure without reported renal impairment
- To evaluate the supporting medical literature available on gadolinium retention
- Nephrogenic systemic fibrosis and hypersensitivity reactions are not addressed as they are well-characterized in the various GBCA labels

FDA Adverse Event Reporting System



- Computer database of spontaneous reports for human drugs and biologics
 - Mandatory reporting by manufacturers
 - Voluntary reporting by healthcare professionals, patients, and the general public
- > 14 million reports since 1968
 - Over 1.6 million new reports in 2016



FAERS Strengths

- Computerized database
- Includes all U.S. marketed products
- Includes all uses (both approved and off-label use)
- Includes broad patient populations:
 - elderly, children, pregnant women, co-morbidities
- Simple, relatively inexpensive reporting system

- **Detection of events with low background rate**
- **Detection of clinically serious events**
- **Useful for events that occur shortly after exposure and early in postmarketing phase**
- Useful for events highly attributable to drugs
- Identification of possible risk factors, and other clinically significant emerging safety concerns

FAERS Limitations

- **Variable report quality**
- **Reporting biases**
- **Confounding effect of intended drug indication**
- Underreporting – not every adverse event is reported (passive surveillance)
- Difficult to attribute events with high background rates or long latency periods after exposure

- **Causal relationship between a product and an event is not required for reporting to the FDA**
- FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population
- Comparison of drugs difficult

Methods

FAERS

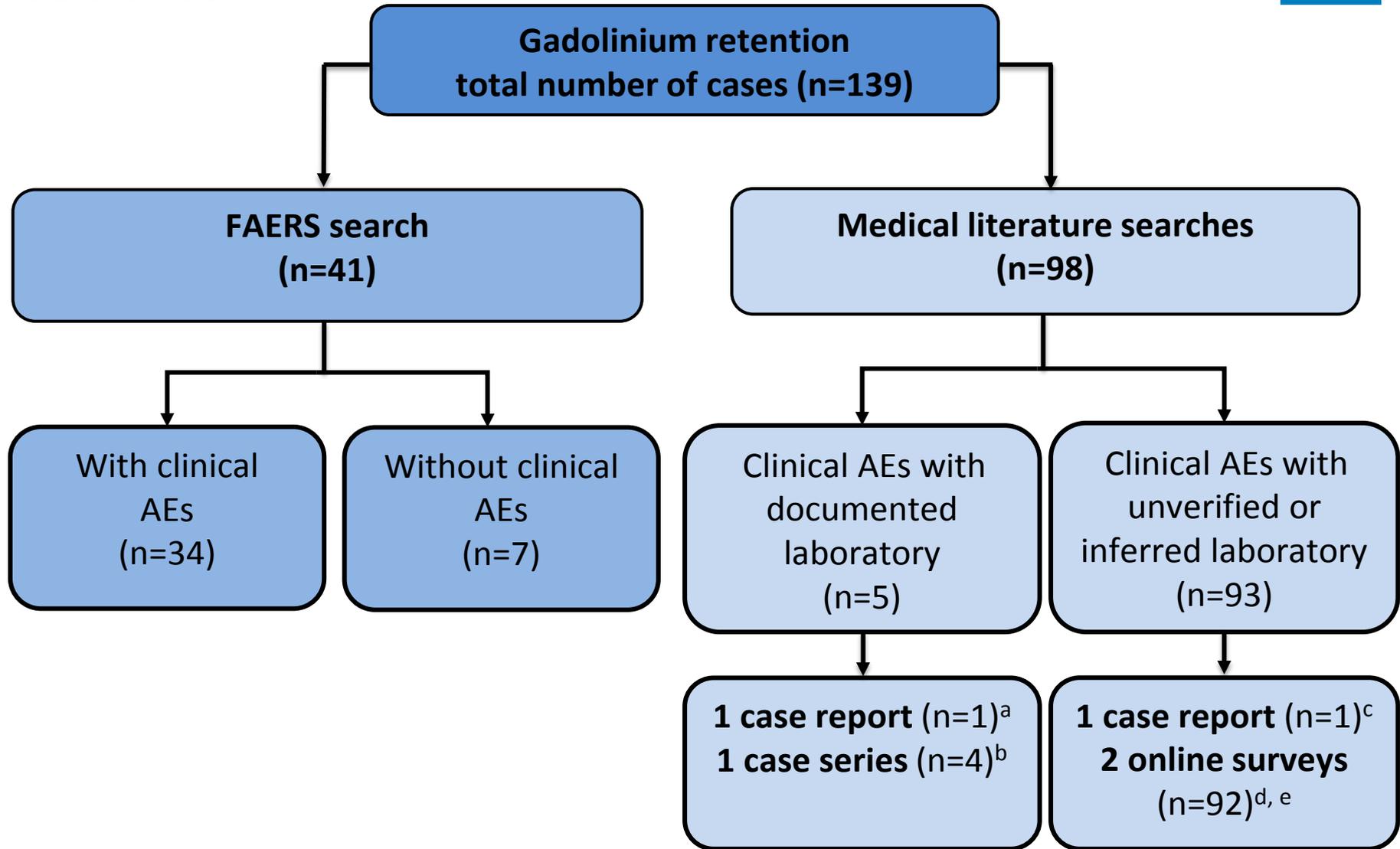
- Cases reporting gadolinium retention, with or without clinical adverse events
- Gadolinium retention evidence*
 - Any body fluid or tissue, without required quantitative data
 - Inferred based on specific brain MRI abnormalities

*≥4 weeks after GBCA exposure

Medical Literature

- PubMed and EMBASE search engines
- Search strategies included key words relating to
 - Clinical manifestations associated with gadolinium retention already published in the medical literature
 - Hypothetical clinical manifestations based on brain retention patterns

Results



^aRoberts 2016; ^bSemelka 2016a; ^cMiller 2015; ^dBurke 2016; ^eSemelka 2016b

Case Characteristics

Characteristic	Number of Cases (N=139)	
Country of reporter (n=139)	USA	132
	Foreign	7
Year of initial report (n=139)	2007-2014	12
	2015	15
	2016	9 (98 literature cases)
	2017	5
Reporter type (n=138)	Consumer	27
	Physician/other HCP	13
	Publication	98
Age (years) (n=85)	Range	7-81
	Median	49
Sex (n=87)	Female	65
	Male	22
Race/ethnicity (n=64)	Caucasian	61
	Hispanic	3

Case Characteristics

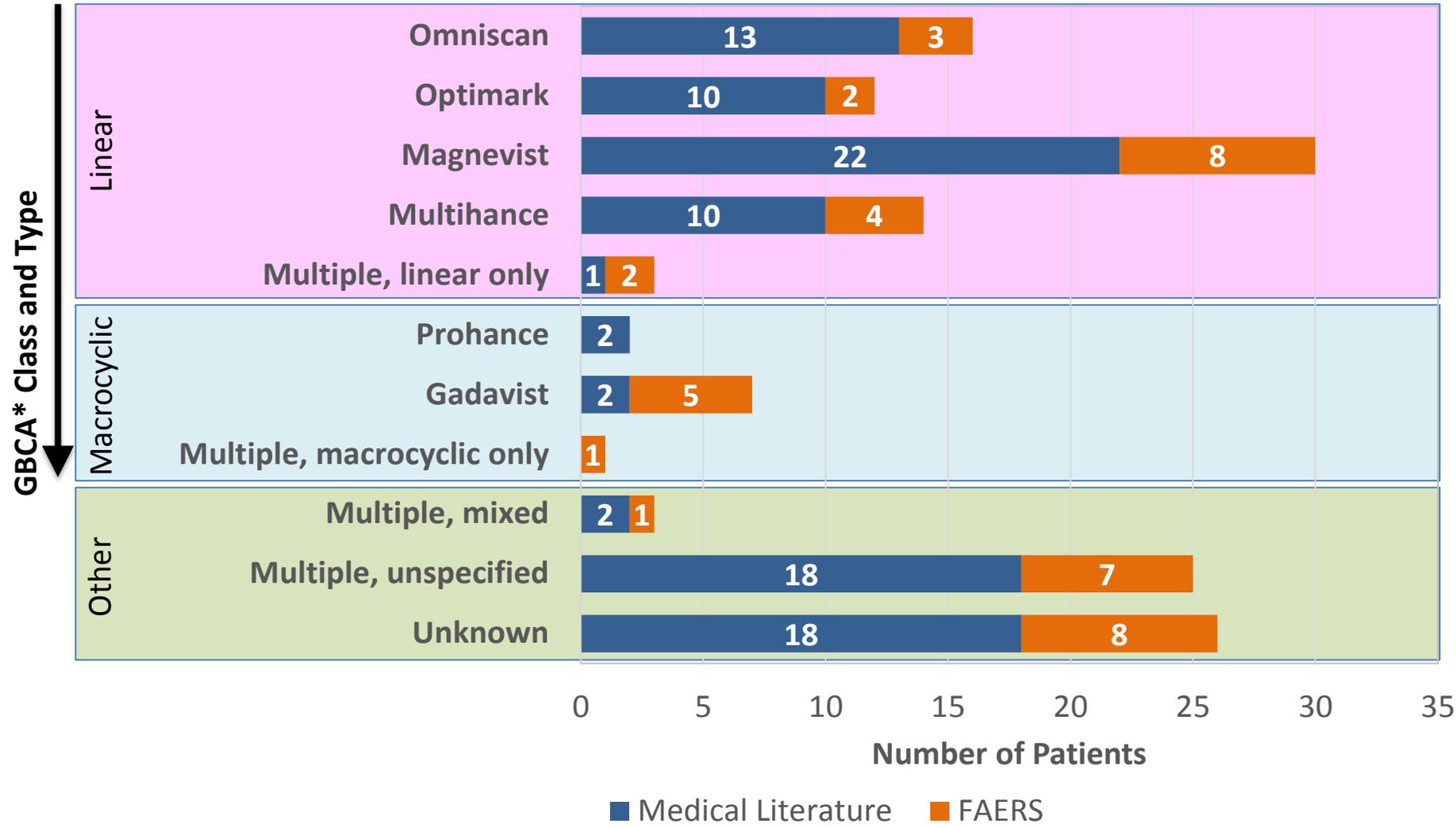
Characteristic	Number of Cases (N=139)	
Body region imaged* (n=39)	Brain/cranium	20
	Abdomen/pelvis	10
	Breast	5
	Spine	5
	Cardiac	3
	Limb	3
	Unknown	100
GBCA indications* (n=32)	Neoplasm/screening	12
	Trauma	3
	Tachycardia	2
	Other	13
	Unknown	107
Gadolinium retention evidence* (n=137)	Urine	104
	Serum	19
	Hair	12
	Skin	7
	Other	13

*A patient may have more than one body region imaged, more than one GBCA indication, and more than one body fluid/tissue tested

Case Characteristics

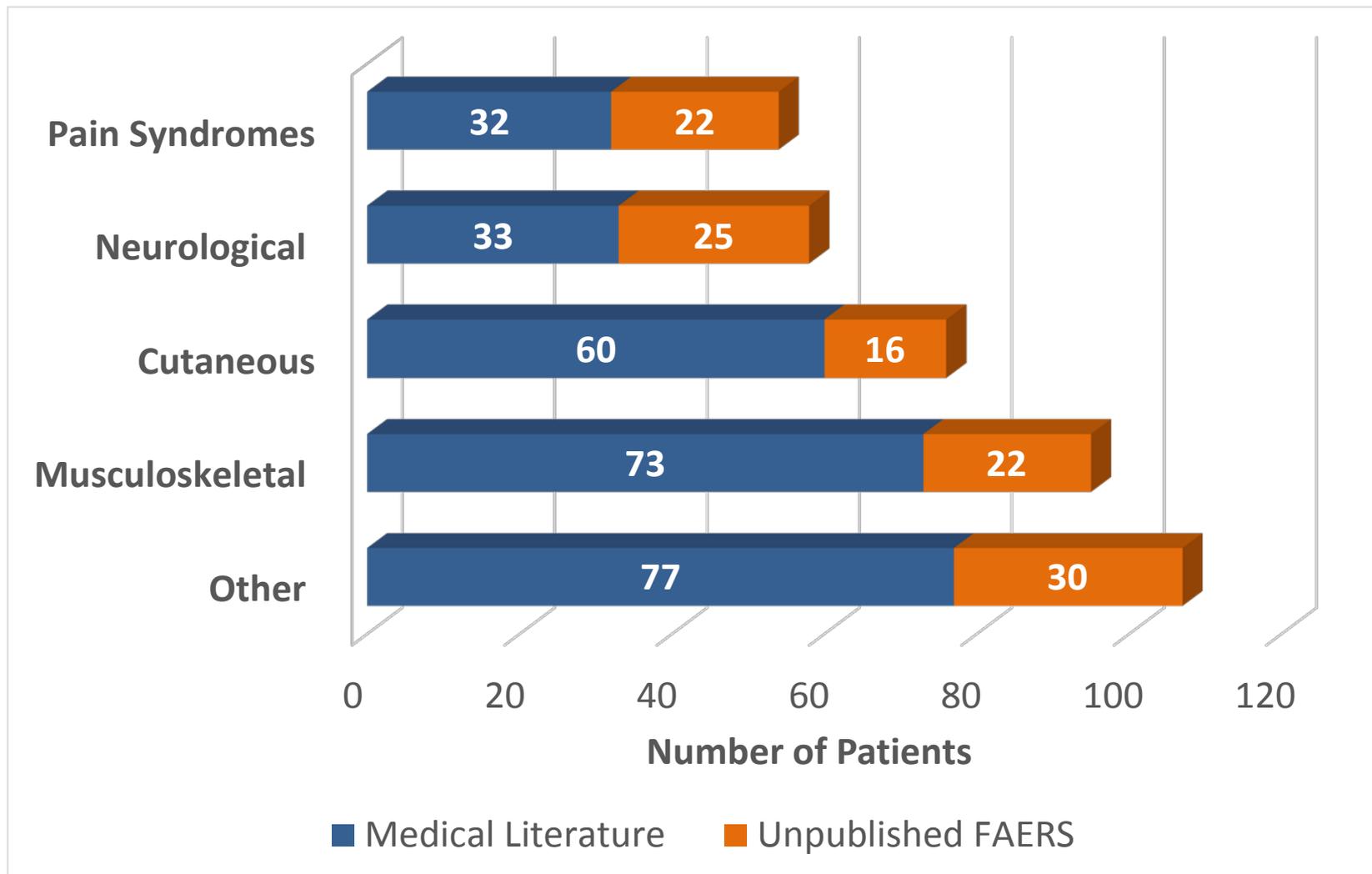
Characteristic	Number of Cases (N=139)	
Number of adverse events per patient (n=40)	1	4
	2	1
	3	3
	4	5
	5-10	16
	>10	11
	Range	1-39
	Median	7
Adverse event onset after GBCA exposure (n=80)	Immediately	37
	≤ 24 hours	11
	>24h - 6 weeks	29
	>6 weeks	3
Adverse event duration at the time of report (n=35)	1-≤3 months	10
	3-≤6 months	9
	6-≤12 months	3
	>12 months	13
	Range	1 month – 9 years
	Median	5 months

Number of Patients by GBCA Type (N=139)



*GBCAs thermodynamic stability based on Ramalho J, et al. Am J Neuroradiol. 2016;37(7):1192-1198

Number of Patients by Adverse Event Clinical Category (N=132)



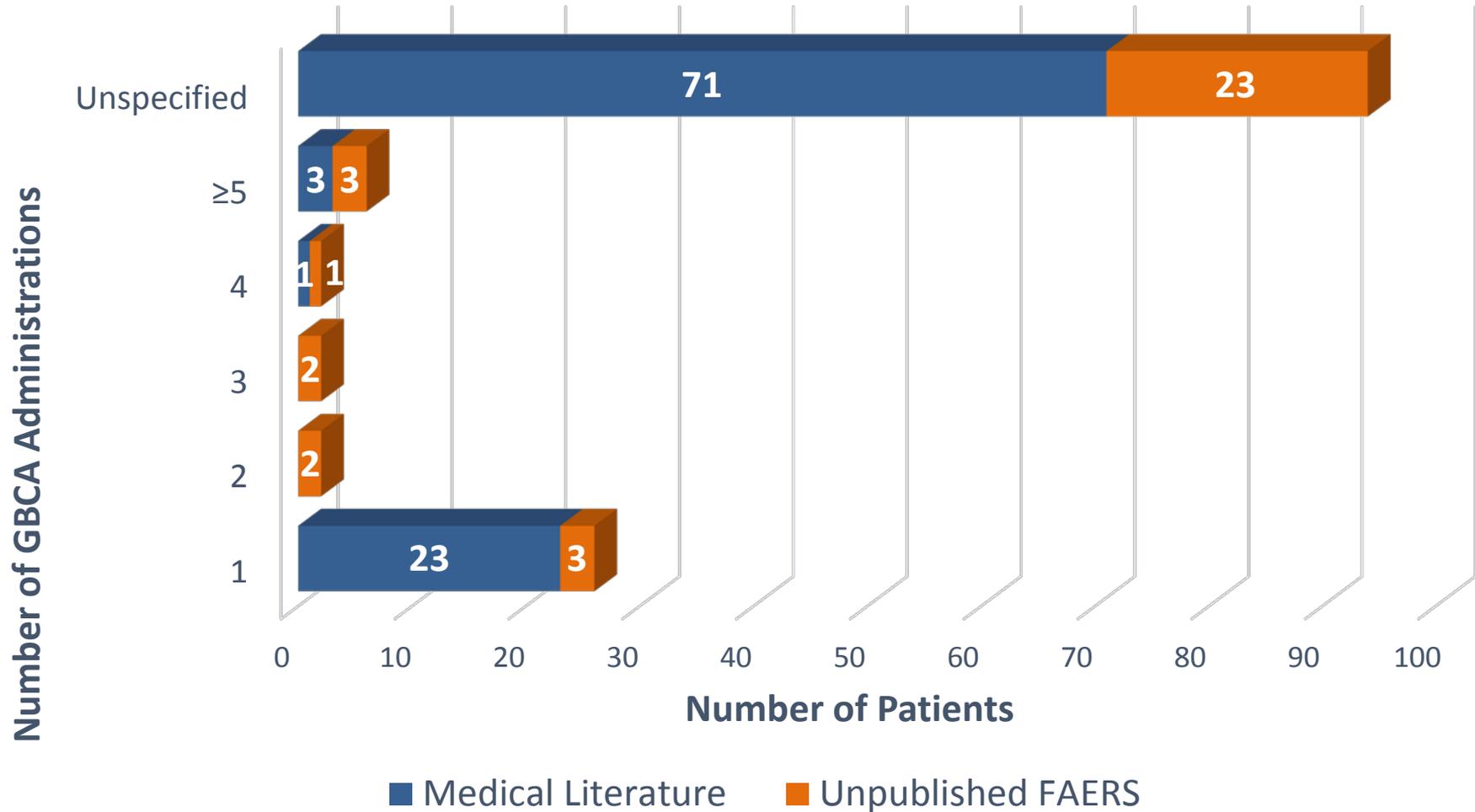
Adverse Events Reported by Clinical Category (N=132)



Adverse Events by Clinical Category Occurring in ≥10 Cases

Pain Syndromes (N=54)	Neurological (N=58)	Cutaneous (N=76)	Musculoskeletal (N=95)	Other (N=107)
limb or central torso nociceptive paresthesias/dysesthesias (53) headache (37) unspecified pain (10)	clouded mentation (31) non-nociceptive paresthesias/dysesthesias (14) cognitive impairment (13)	skin discoloration (30) skin changes (29) skin thickening (25) rash/erythema (14)	bone pain (40) bone/joint pain (38) muscle spasms (36) joint stiffness (33) arthralgia (12) muscular weakness (10)	fatigue/asthenia (51) head & neck including headache, vision changes, and hearing changes (38) other unspecified (37) generalized whole body symptoms (30) digestive symptoms including nausea, vomiting, and diarrhea (27) chest symptoms/dyspnea (26) buzzing sensation (24) metallic taste (20)

Number of GBCA Administrations Before Onset of Reported AE (N=132)



Case Report: FAERS

- FAERS #11805981, reported by consumer, 2015
- 53-year-old Caucasian woman with normal renal function and reportedly unremarkable past medical history
- GBCA exposure
 - 6 contrast-enhanced MRIs over 9 months with Gadavist (4), Multihance (1), and Magnevist (1) for transverse myelitis indication
 - 3 contrast-enhanced MRIs with unspecified GBCA and indications over the preceding 9 years
- Symptoms developed 2 months after first of 6 most recent contrast-enhanced MRIs and included
 - Bone pain
 - Generalized muscle tightening
 - Weakness
 - Fatigue
 - Other unspecified symptoms

Case Report: FAERS

- Investigation: 24-hour urine gadolinium measurements revealed
 - One month before last MRI: 17 mcg/specimen (reference range, <0.6 mcg/specimen)
 - Two months after last MRI: 6.9 mcg/specimen (reference range, 0.0 – 0.4 mcg/specimen)

Case Report: Medical Literature



- 29-year-old Caucasian woman with normal renal function and past medical history significant for medullary sponge kidney
- GBCA exposure
 - One contrast-enhanced MRI with Magnevist (20 mL) for suspected complex renal cysts indication observed on ultrasonography
- Symptoms developed within 24 hours of the contrast-enhanced MRI and included
 - Flu-like body aches
 - Nociceptive paresthesias/dysesthesias (burning, sharp pins and needles) involving central torso and all 4 limbs
 - Clouded mentation
 - Headaches
 - Arthralgias

Case Report: Medical Literature



- Investigation (1 month later)
 - Blood gadolinium: 0.7 ng/mL (reference range, <0.5 ng/mL)
 - 24-hour urine gadolinium: 18 mcg/specimen (reference range, 0.0 – 0.4 mcg/specimen)
- Physical examination unremarkable (2 months later)
- Outcome (2 months)
 - Progression over days with subsequent gradual diminution of symptoms
 - Sporadic nociceptive paresthesias/dysesthesias
 - Persistent clouded mentation, headaches, and arthralgias

Specific Populations

- Pediatric (≤ 18 years old) (n=2)
- Geriatric (≥ 65 years old) (n=3)
- Pregnancy/lactation (n=0)
- Hepatic insufficiency (n=0)
- Pre-existing systemic inflammatory conditions (n=1)
 - Pelvic skin graft rejection, idiopathic thrombocytopenic purpura (ITP), rheumatoid arthritis, unspecified autoimmune symptoms
- Pre-existing neurological inflammatory conditions (n=1)
 - Encephalitis not otherwise specified

Discussion

- Despite clustering around certain clinical categories, the marked heterogeneity of clinical adverse reported makes interpretation challenging
- Unverified self-reported information in most reports
 - Assessment of clinical adverse events by HCP
 - Laboratory results supporting gadolinium retention
 - Originates from published online surveys (n=92) (Semelka 2016b; Burke 2016) and FAERS consumer reports (n=27)

Discussion

- Alternative etiology investigation not provided
- Symptoms related to MRI study indication
- Discordant site of gadolinium measurement and symptomatic body region(s)
- Internet websites and social media with interest in gadolinium retention may lead in reporting stimulation
- Challenging recognition of clinical manifestations with insidious or delayed onset, and non-specific features

Summary

- Evidence of growing concern for untoward effects of retained gadolinium, within both the lay public and the medical community
- Despite lacking consistent phenotype, some clustering of clinical adverse events around certain clinical categories (pain syndromes, neurological, cutaneous, and musculoskeletal) was observed
- At this juncture, a causal association between reported clinical adverse events and GBCA exposure cannot be determined





Epidemiologic Studies on the Safety of Gadolinium-Based Contrast Agents

Steven T Bird, PhD, PharmD
Division of Epidemiology I
Office of Surveillance and Epidemiology
CDER / FDA

Welk 2016: Association Between Gadolinium Contrast Exposure and the Risk of Parkinsonism



- Retrospective Cohort Study using Administrative Databases in Ontario
- Patients >66 years of age without parkinsonism between 2003-2013
- MRI with gadolinium (n=99,739) and MRI without Gadolinium (n=146,818); excluding brain or spine MRI
- Rate of parkinsonism
 - ≥ 1 Contrast MRI: 3.17 / 1,000 person-years
 - Only Non-Contrast MRI: 2.71 / 1,000 person-years
- Relative Risk = 1.04 (0.98 – 1.09) per Contrast MRI
- While a well done study, its average four year follow-up per patient may not be sufficient for evaluating parkinsonism

Welk B et al. *JAMA* 2016;316(1):98-8

Ray 2016: Child and Infant Outcomes Following Gadolinium Contrast Exposure during Pregnancy

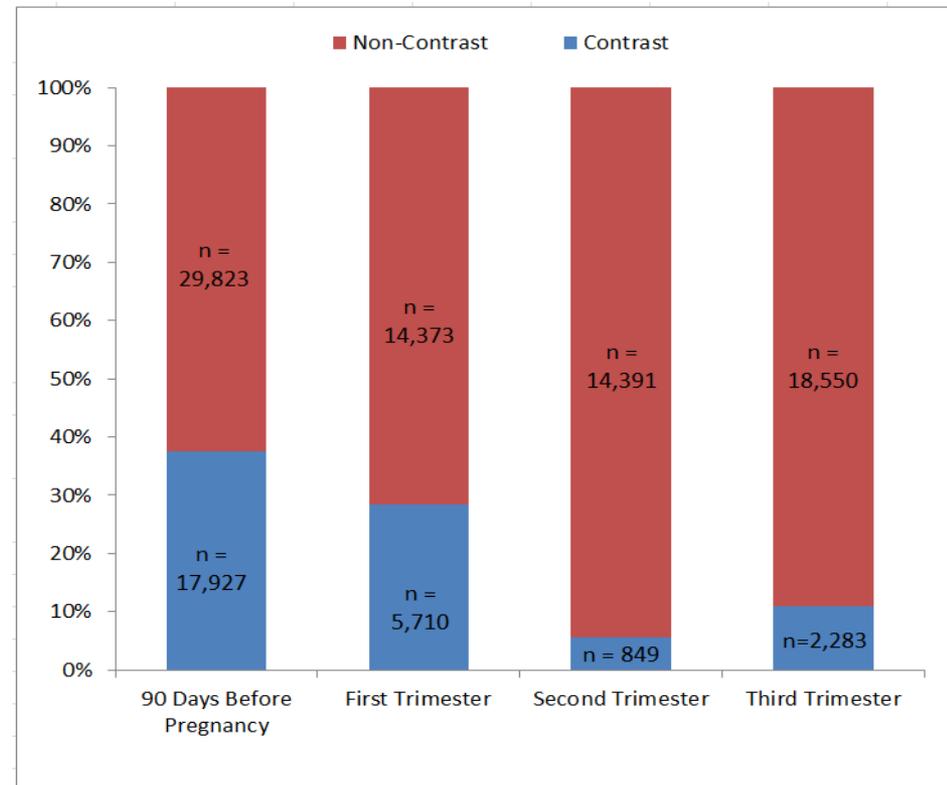


- Retrospective cohort study in administrative database in Ontario (2003-2015)
- A sample of 1,424,105 linked mothers and infants
- Contrast MRI anytime during pregnancy (n=397)
- Rate of stillbirth or neonatal death
 - Contrast MRI: 7 outcomes in 397 women (17.6 / 1000 person-years)
 - No MRI: 9,844 outcomes / 1,418,451 women (6.9 / 1000 person-years)
- Relative Risk for stillbirth and neonatal death = 3.70 (1.55 to 8.85)
- While a well done study, it had a small number of outcomes, was not powered for a comparison of contrast MRI versus non-contrast MRI, and needs replication.

Utilization of Gadolinium During Pregnancy in the United States



- An internal FDA evaluation in a sample of 3,726,555 pregnancies from the Sentinel Distributed Database observed 8,842 gadolinium MRI during pregnancy (2008-2015)
 - 1 in 421 US pregnancies
- The majority of exposures in the first trimester
- 8-fold greater use of gadolinium pregnancy in this US study Canadian study by Ray et al
- FDA is evaluating the feasibility of replicating the Ray study



High Level Considerations when Evaluating Adverse Effects of Gadolinium Exposure

- All tissues could potentially retain gadolinium
 - This leads to a large number of potential adverse effects
 - Focus Groups, case reports, and historical datasets may inform outcomes to study
- Number of Exposures and Dosage Matters
 - Focus on identifying patients receiving multiple MRIs for conditions unrelated to the adverse effects being studied
- Dose Exposure (i.e. retention) Varies
 - The extent of retention varies with time, by tissue, and by agent
- Follow-up Time
 - Latency of outcomes is unknown and studies with long follow-up are required to assess risk

Challenges in Epidemiological Assessment of the Risk Due to GBCA Deposits in the Body



Study Characteristics	Suggestions and rationale	Challenges
<i>Study Population</i>		
Administrative Databases (e.g. claims data or electronic medical record)	<ul style="list-style-type: none"> - Cohorts including millions of exposures can be identified - Historical datasets of patients with CKD who received gadolinium may be informative - Mother-baby linkages available to study exposures during pregnancy 	<ul style="list-style-type: none"> - Most outcomes are not captured - Outcome of interest may be unpredictable - Patients with ≥ 4 exposures are less common - Follow-up time is limited
Ongoing prospective observational studies	<ul style="list-style-type: none"> - These studies typically have long follow-up and high quality data on patient comorbidity 	<ul style="list-style-type: none"> - Pertinent outcomes may not have been captured - Lower exposure levels - Loss to follow-up is an issue
New Prospective observational studies	<ul style="list-style-type: none"> - Prospective observational studies can be tailored to a specific clinical concern - Parallel arms can be conducted by each sponsor 	<ul style="list-style-type: none"> - These studies take a long time to conduct - May be expensive - Loss to follow-up is an issue
Randomized Clinical Trials	<ul style="list-style-type: none"> - Gold Standard 	<ul style="list-style-type: none"> - Ethical and feasibility requirements need to be taken into consideration

Key Messages

- Epidemiologic studies on the safety of gadolinium contrast in patients without chronic kidney disease are sparse
- Focus groups with highly-exposed patients and review of case reports may inform avenues for further research
- Vulnerable populations and pregnant women need special attention
- Studies must be carefully evaluated for quality attributes such as outcome identification and length of patient follow-up
- A multitude of studies are likely required to address current concerns with gadolinium retention
- There is no guarantee of definitive answers in the near term



Gadolinium-Based Contrast Agents

U.S. Sales Data

2006-2016

Patty Greene, PharmD
Drug Utilization Analyst
Division of Epidemiology II
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

September 8, 2017

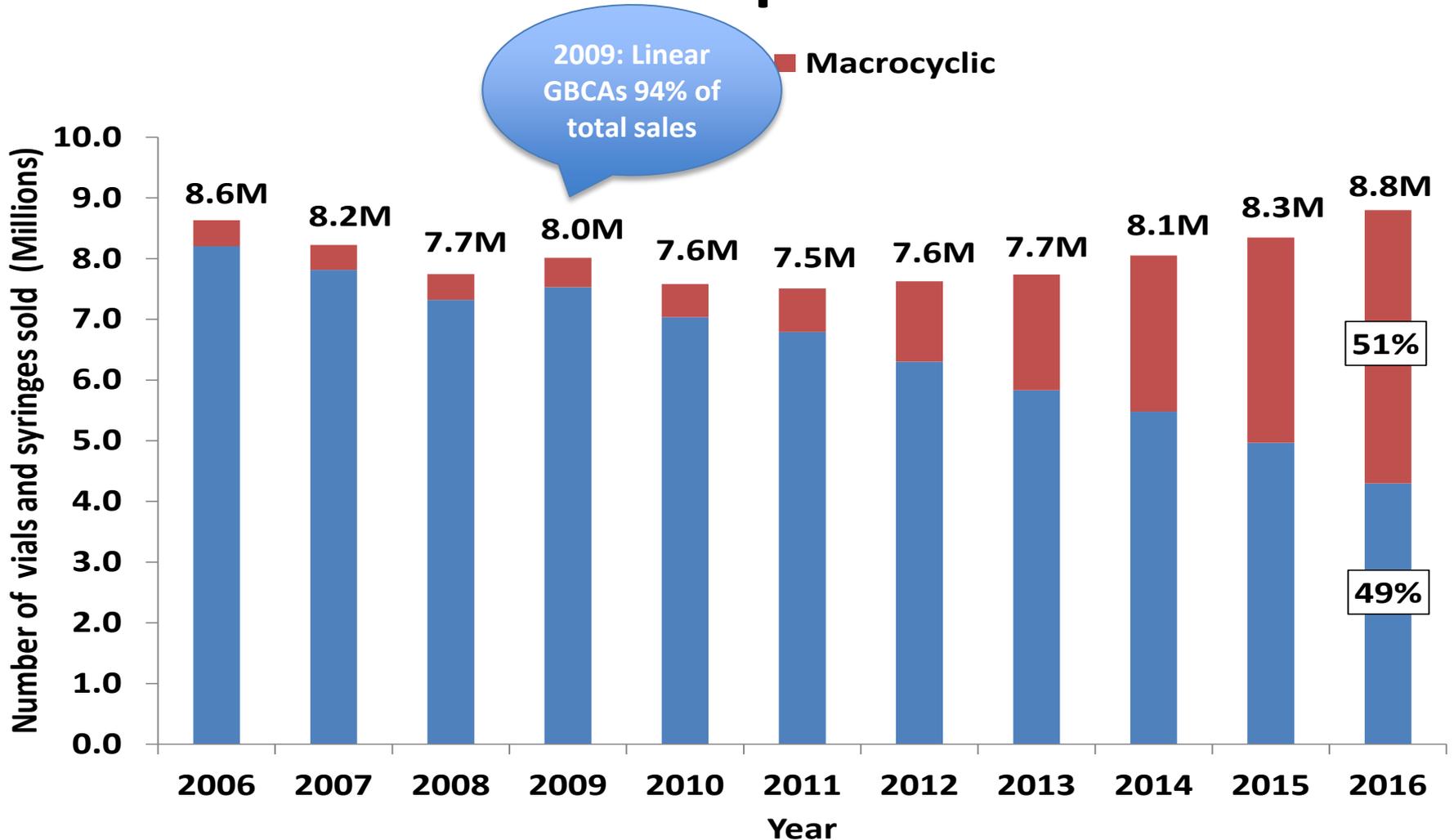
Medical Imaging Drugs Advisory Committee

U.S. Sales Database

- **QuintilesIMS Health, National Sales Perspectives™ Database**
 - Measures the number of packages* sold from manufacturers to hospitals and clinics
 - Data are nationally estimated from a nearly 90% capture of the market
 - Measure of sales volume, not direct patient utilization
 - No patient demographic information available

*Packages = vials/syringes sold

National Estimate of GBCA Sales from Manufacturers to Hospitals and Clinics



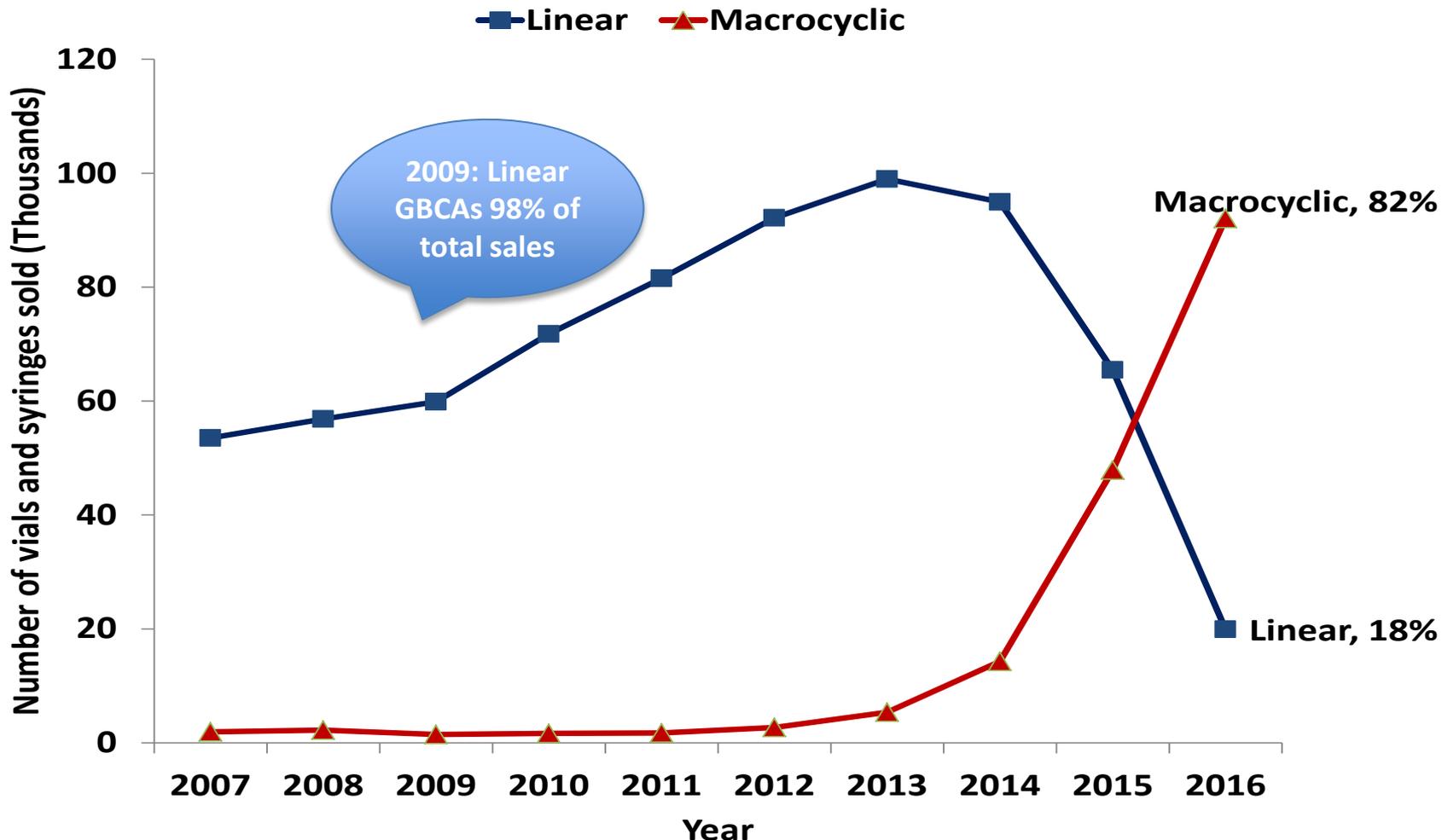
Source: QuintilesIMS Health, IMS National Sales Perspectives™. Data Extracted July 2017.

Pediatric Sales Database

- **Symphony Health Solutions' PHAST NonRetail Monthly Database**
 - Measures the volume of sales by number of packages* sold from manufacturers to 50 pediatric specialty hospitals and 5 pediatric clinics in the U.S.
 - National estimates are not available at this time
 - Measure of sales volume, not direct patient utilization
 - No demographic information available

*Packages = vials/syringes sold

GBCA Sales from Manufacturers to a Sample* of Pediatric Hospitals and Clinics



Source: Symphony Health Solutions' PHAST NonRetail Monthly . Data Extracted July 2017.

*Sample = 50 pediatric hospitals and 5 pediatric clinics

Summary

- **National trends show an increase in macrocyclic GBCAs and a decrease in linear GBCAs since 2009**
 - **Nearly evenly distributed market share in 2016**
- **In 2016, sales to a sample of pediatric specialty hospitals suggest a higher proportion of macrocyclic GBCAs use compared to trends nationwide**



Gadolinium Retention: A Summary

Karen Bleich, MD

Division of Medical Imaging Products

Medical Imaging Drugs Advisory Committee Meeting

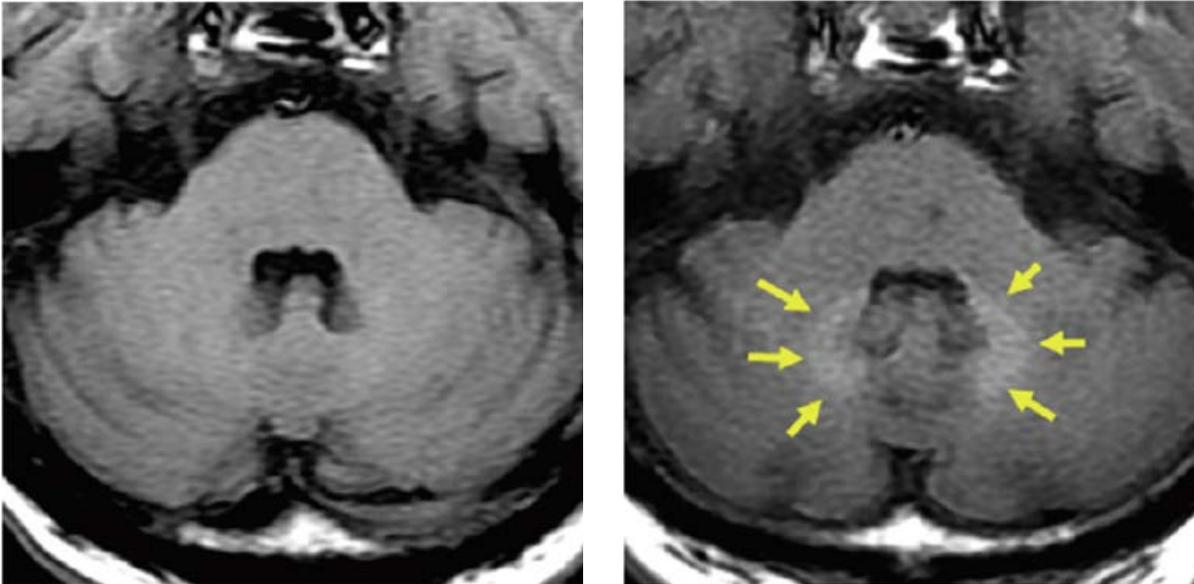
September 8th, 2017

Overview

- Highlights of the emerging science related to gadolinium retention
 - *Most of the studies presented here represent published and unpublished studies by the GBCA sponsors without review of primary data by FDA.*

- Regulatory evaluation of GBCAs: NSF and gadolinium retention - process and actions taken

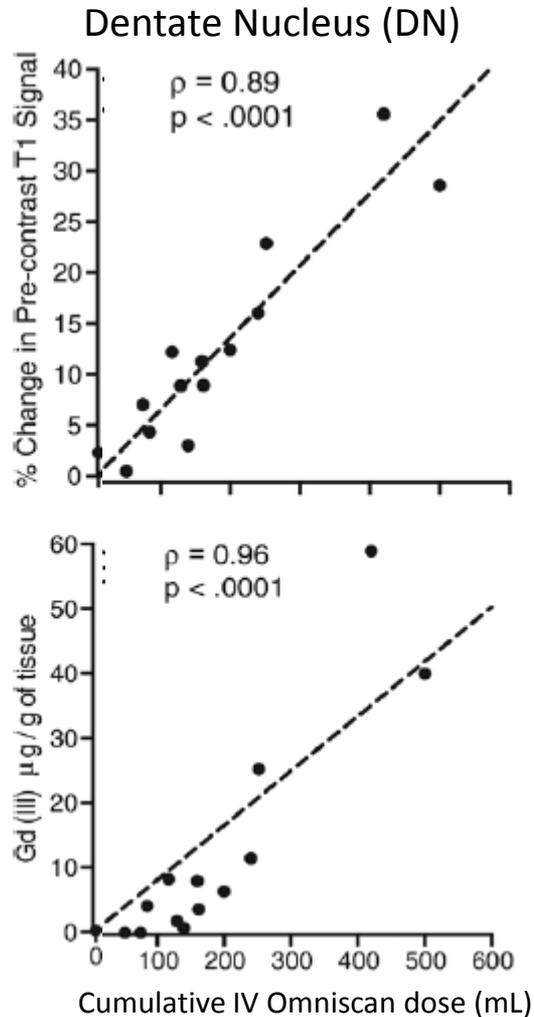
- Increased T1W signal in portions of brain related to prior GBCA administration



Increased signal intensity visualized after multiple administrations of linear GBCAs.

Kanda 2014, Errante 2014

➤ Imaging findings confirmed to be gadolinium



13 patients who underwent 4-29 MRIs with Omniscan.

The SI in the DN increases as the total Omniscan dose increases.

The concentration of Gd found in the DN increases as the total Omniscan dose increases

McDonald 2015

Human
autopsy study



Regulatory response 2015

➤ Gadolinium is retained in the brain



*7.27.2015 Drug Safety Communication:
FDA evaluating the risk of brain deposits with repeated
use of GBCAs*

NSF Regulatory Evaluation

- Intrinsic stability of GBCAs
- In vitro Gd dissociation kinetics
- Nonclinical evidence of toxicity
- Clinical evidence of toxicity
- Susceptible patient populations

In response to NSF, GBCAs were risk-stratified based on the totality of this evidence and risk mitigation steps were taken.

Gd Retention Regulatory Evaluation

- Intrinsic stability of GBCAs
- In vitro Gd dissociation kinetics
- Nonclinical evidence of toxicity
- Clinical evidence of toxicity
- Susceptible patient populations

} *How tightly the Gd ion is bound to the chelating molecule*

Gadolinium Toxicity

- Gd is a potent blocker of many types of Ca-dependent biological pathways
- Metal exchange between endogenous metals and Gd ion inhibits molecular processes
- Gd is a potent inhibitor of the mononuclear phagocyte system
- Gd has a proliferative effect on fibroblasts

GBCA Intrinsic Stability



Linear GBCAs

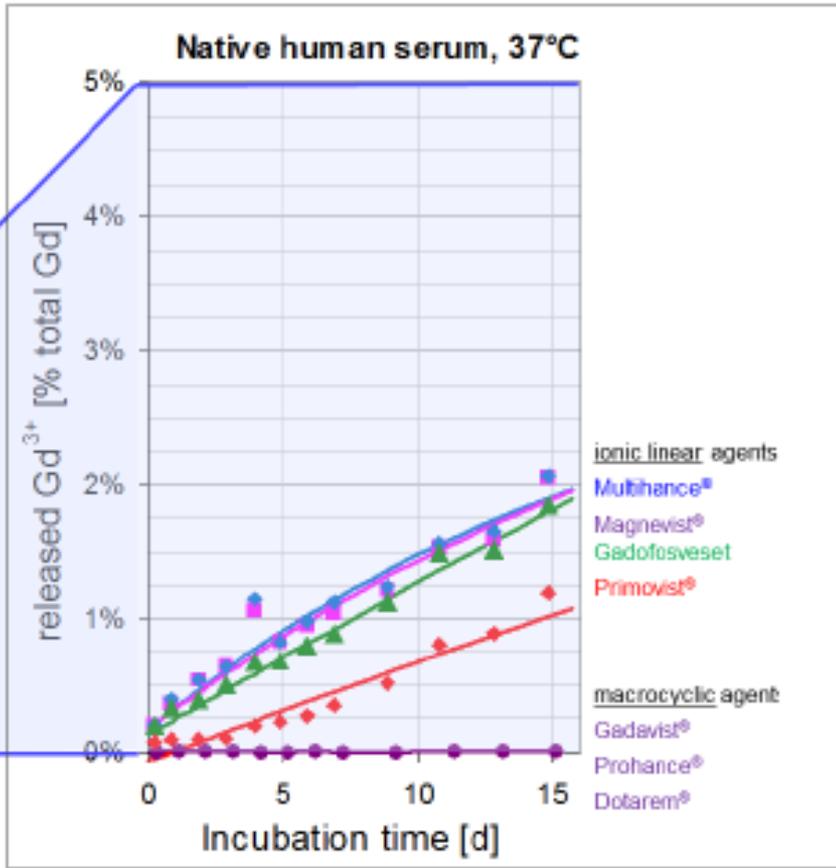
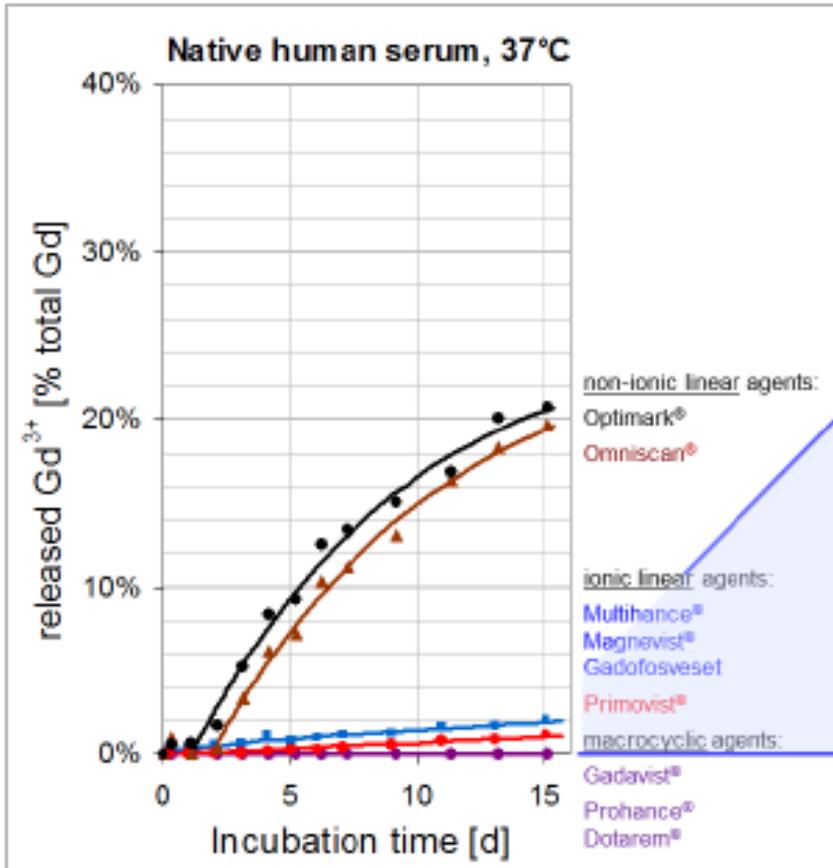
- » Omniscan
- » OptiMARK
- » Magnevist
- » Multihance
- » Eovist

Macrocyclic GBCAs

- » ProHance
- » Gadavist
- » Dotarem

The intrinsic stability of the GBCAs is not the whole story when evaluating NSF or gadolinium retention, and does not necessarily reflect comparative toxicity within the complex in vivo environment.

In vitro Gd Dissociation Kinetics



Frenzel 2008

Gd Retention Regulatory Evaluation

- Intrinsic stability of GBCAs
- In vitro Gd dissociation kinetics
- Nonclinical evidence of toxicity
- Clinical evidence of toxicity
- Susceptible patient populations



Does the intrinsic stability of GBCAs correlate with gadolinium dissociation in the setting of gadolinium retention?

Gd Retention Regulatory Evaluation

- Intrinsic stability of GBCAs
- In vitro kinetics of release of free Gd
- **Nonclinical evidence of toxicity**
- Clinical evidence of toxicity
- Susceptible patient populations

Nonclinical Evidence of Toxicity

- No histopathologic evidence of toxicity in animal brain after repeated high doses of GBCAs

Rats received 80x (surface adapted) human dose over 5 weeks. Histological analysis demonstrated no abnormality in the brain tissue.
Lohrke 2017 (Bayer)

- No behavioral or neurological abnormality detected in completed studies in rats

Juvenile rats received 36x (surface adapted) human pediatric dose over 3 weeks. Behavioral and neurologic testing was normal.
Bracco Study AB21194, unpublished

Nonclinical Evidence of Toxicity

- Gross and histopathologic toxicity HAS been demonstrated in the skin of animals after repeated high doses of the linear non-ionic agents Omniscan and OptiMark

Wible 2001 and Lohrke 2017 (Bayer)

Gd Retention Regulatory Evaluation

- Intrinsic stability of GBCAs
- In vitro Gd dissociation kinetics
- Nonclinical evidence of toxicity
- **Clinical evidence of toxicity**
- Susceptible patient populations

Clinical evidence of toxicity

- In the published human autopsy studies to date, there has been no histologic evidence of toxicity from gadolinium in the human brain.
- Pharmacovigilance and epidemiology reviews have not defined clinical signs or symptoms related to GBCAs
- Reports of patients with symptoms including pain, skin changes, and clouded mentation
- Gadolinium-associated plaques – 3 cases reported
- *Context of clinical use: over 450 million doses of GBCAs have been given since 1988, and can provide essential and life-saving information*

Gd Retention Regulatory Evaluation

- Intrinsic stability of GBCAs
- In vitro Gd dissociation kinetics
- Nonclinical evidence of toxicity
- Clinical evidence of toxicity
- Susceptible patient populations

Susceptible Patient Populations

- Higher lifetime doses
 - Pediatrics
 - Chronic conditions
- Longer GBCA exposure times
 - Renal impairment
 - Elderly
 - Pregnancy
- Immunologic interactions with GBCAs
 - Inflammatory conditions

In considering gadolinium retention, where we don't have a defined syndrome, susceptible patient populations include those with higher lifetime doses, longer exposure times, and an increased risk of immunologic reaction to the retained gadolinium.

Gd Retention Regulatory Evaluation

- Intrinsic stability of GBCAs
- In vitro Gd dissociation kinetics
- Nonclinical histopathologic evidence of toxicity
- Clinical evidence of toxicity
- Susceptible patient populations

With NSF, the FDA was able to determine the comparative risks between the different GBCAs based on these critical data points.

Gd Retention Regulatory Evaluation

- Intrinsic stability of GBCAs
- In vitro Gd dissociation kinetics
- Nonclinical histopathologic evidence of toxicity
- Clinical evidence of toxicity
- Susceptible patient populations

With NSF, the FDA was able to determine the comparative risks between the different GBCAs based on these critical data points.

For gadolinium retention, there is no known safety margin. In making regulatory decisions, we have to consider the comparative exposure to gadolinium caused by each GBCA to evaluate the theoretical risk.

Gd Retention Regulatory Evaluation

- Intrinsic stability of GBCAs
- In vitro Gd dissociation kinetics
- Nonclinical evidence of toxicity
- Clinical evidence of toxicity
- Susceptible patient populations
- Comparative exposure to gadolinium from each GBCA

-Which agents are retained?
-Where does the retention occur?
-How much gadolinium is retained?
-For how long is the gadolinium retained?
-In what form is the gadolinium retained?

Comparative Exposure to Gadolinium

- Studies to date come largely from the sponsors of the GBCAs
- Highlights presented here do not represent definitive assessment of the comparative exposure from each GBCA and are not meant to support cross product comparisons
- Complete characterization of the GBCAs by standardized methods (amount, washout, dissociation, location) in relation to retention has not been done
- *While consideration of the comparative exposure to gadolinium from each GBCA is important, patient factors (in addition to renal function) are likely to play an important role in elucidating the clinical significance of gadolinium retention.*

Gadolinium retention – Which agents?

➤ All GBCAs are associated with Gd retention in brain

Linear

- Omniscan* ✓ *McDonald 2015*
- Optimark*
- Magnevist* ✓ *Kanda 2015*
- Multihance* ✓ *Murata 2016*
- Eovist* ✓ *Murata 2016*

Macrocyclic

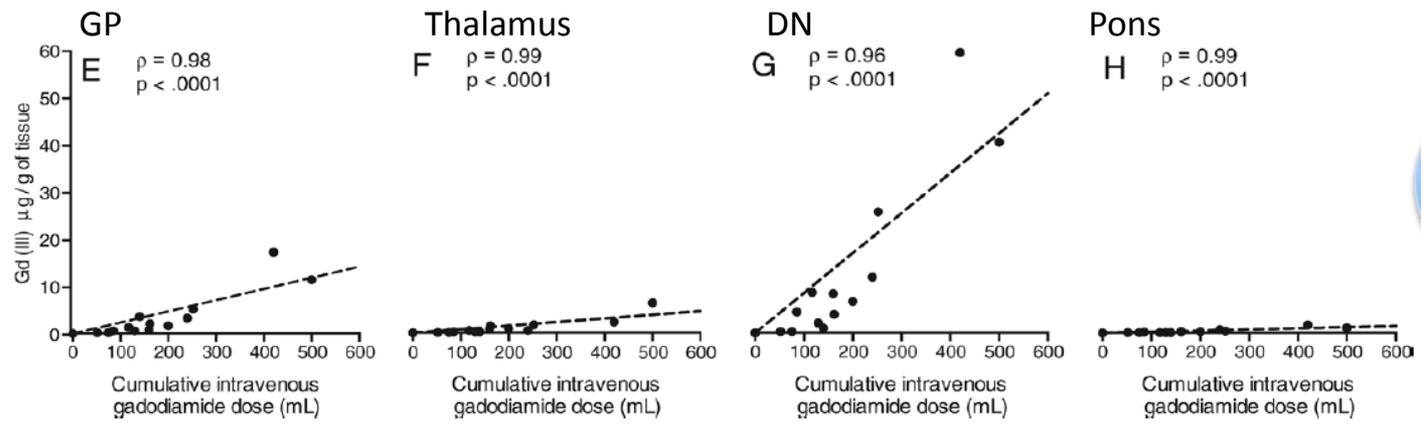
- Gadavist* ✓ *Murata 2016*
- ProHance* ✓ *Murata 2016*
- Dotarem* ✓ *Jost 2016*

✓ Human autopsy studies

✓ Animal studies

Gadolinium retention – Where?

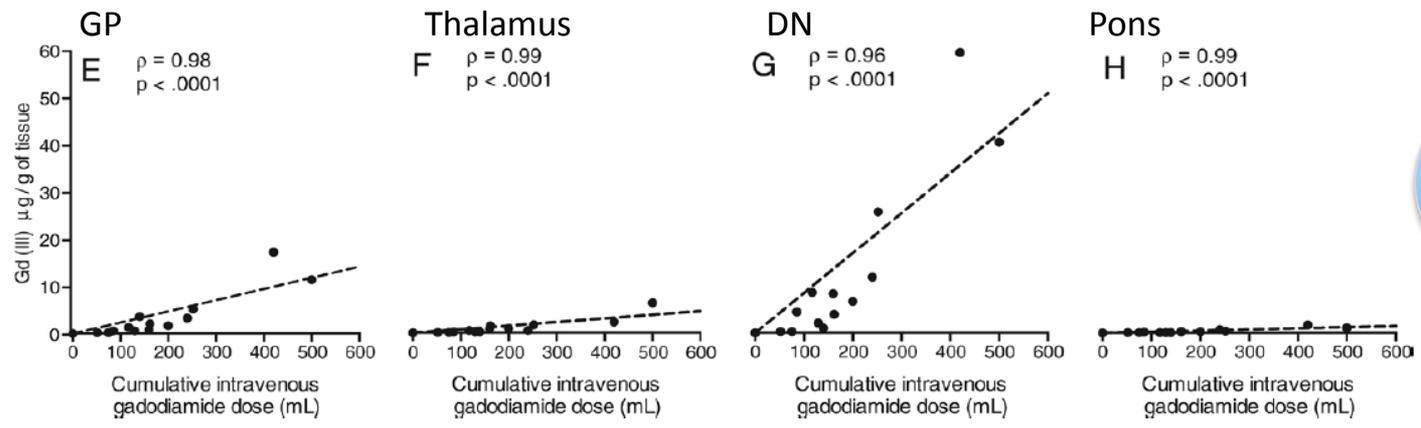
➤ All brain regions tested, not just DN and GP



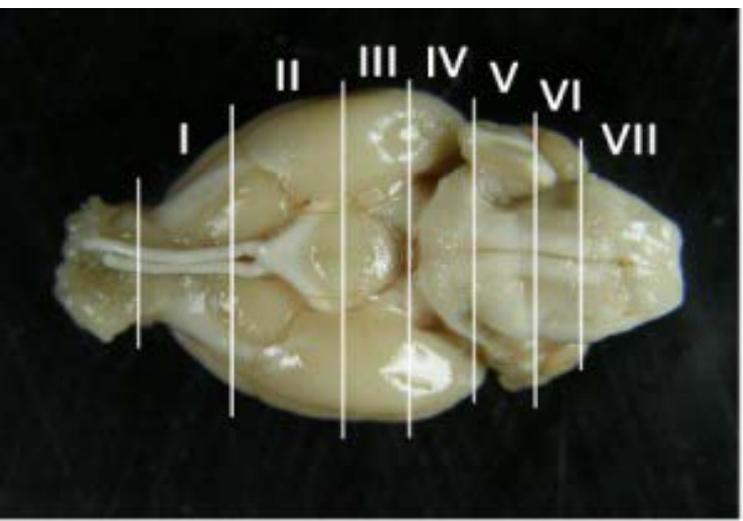
Human autopsy study, Omniscan, McDonald 2015

Gadolinium retention – Where?

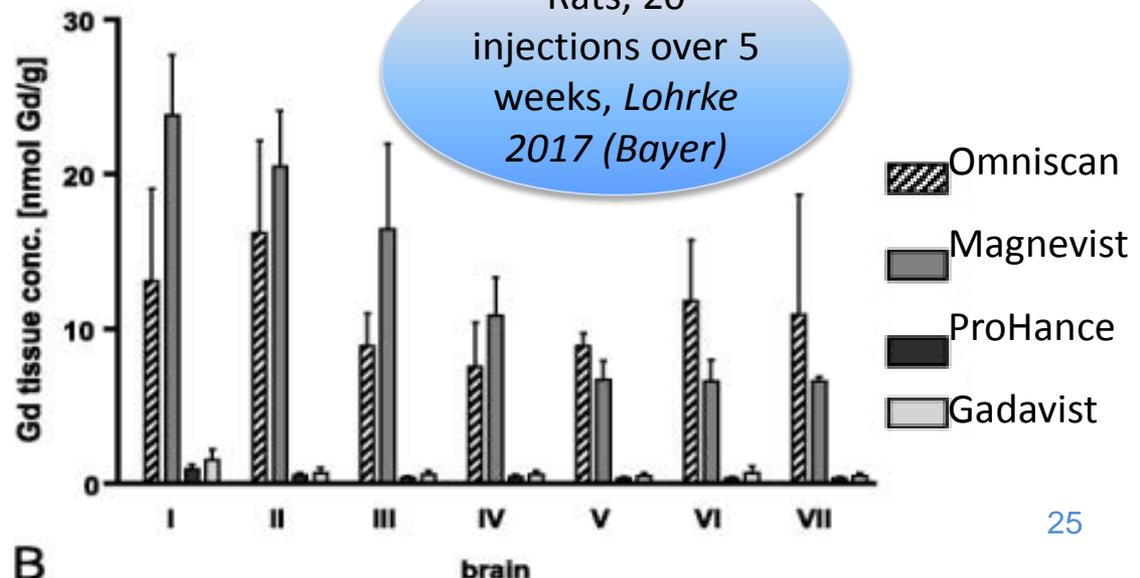
➤ All brain regions tested, not just DN and GP



Human autopsy study, *Omniscan, McDonald 2015*



Rats, 20 injections over 5 weeks, *Lohrke 2017 (Bayer)*



Gadolinium retention – Where?

➤ All tissues tested – skin, bone, liver, spleen, etc

2004 – Gd present in bone 3-8 days (Gibby 2004)

2009 – Gd present in bone up to 8 years later (Darrah 2009)

2010 – EMA asked Sponsors to conduct a study of the potential for long-term retention of Gd in human bone and skin (in pts with normal renal function, and in pts with impaired renal function), study is ongoing



Human
studies

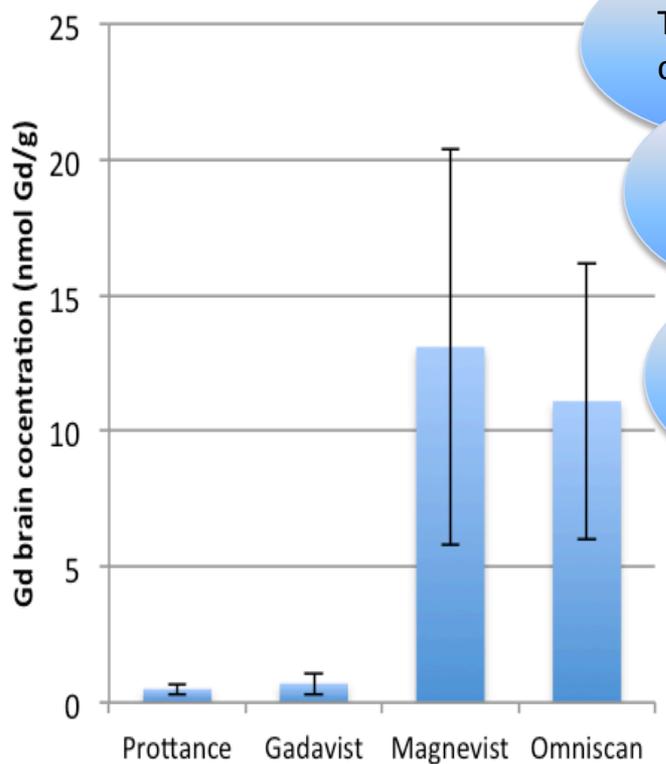
Gadolinium retention – How much?

➤ Linear GBCAs lead to greater Gd retention than macrocyclic GBCAs

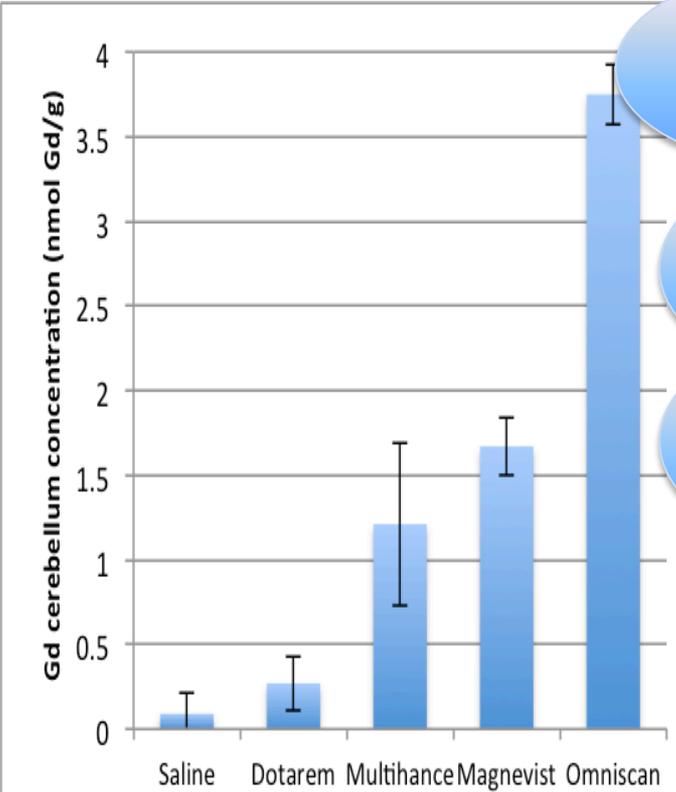
15 fold higher Gd concentration after linear agents compared to macrocyclic agents.
Lohrke 2017 (Bayer)

4-14 fold higher Gd concentration after linear agents compared to Dotarem
Robert 2016 (Guerbet)

Rats



Total brain Gd concentration
8 weeks after treatment
2.5 mmol Gd/kg x 20 doses



Cerebellum Gd concentration
4 weeks after treatment
0.6 mmol Gd/kg x 20 doses

Gadolinium retention – How much?

➤ Linear GBCAs lead to greater Gd retention than macrocyclic GBCAs

Rats

Gadolinium concentration in brain:

Omniscan	11.1 nmol Gd/g
Magnevist	13.1 nmol Gd/g
Gadavist	0.7 nmol Gd/g
ProHance	0.5 nmol Gd/g

Total dose:

80x surface adapted standard dose over 4 weeks

Lohrke 2017 (Bayer)

Gadolinium concentration in cerebellum:

Omniscan	3.75 nmol Gd/g
Magnevist	1.67 nmol Gd/g
Multihance	1.21 nmol Gd/g
Dotarem	0.27 nmol Gd/g
Saline	0.09 nmol Gd/g

Total dose:

20x surface adapted standard dose over 4 weeks

Robert 2016 (Guerbet)

Gadolinium retention – How much?

➤ Linear GBCAs lead to greater Gd retention than macrocyclic GBCAs

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Robert 2016 (Guerbet)

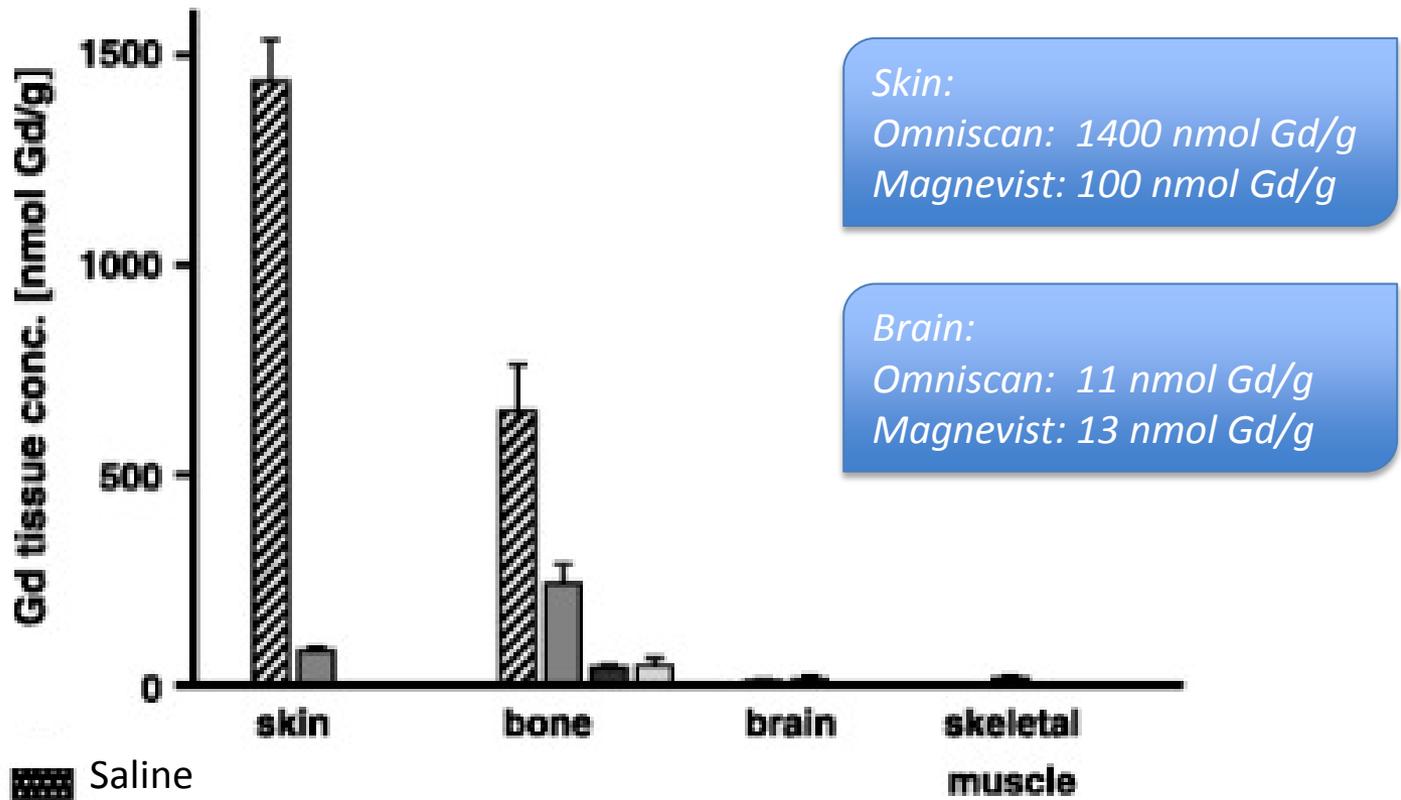
Human autopsy studies

	Kanda 2015	McDonald 2015	Murata 2016
Gd concentration In brain	0.43 - 13.4 nmol Gd/g (DN)	0.6 - 373.9 nmol Gd/g (DN)	BRL - 6.8 nmol Gd/g (DN)
Number of GBCA doses	2 - 4	4 - 29	1 - 11
Day since last dose	15-1170	13-623	5-392

Most of the comparative retention data has been done using animal models in order to provide controlled data that is not possible in humans

Gadolinium retention – How much?

➤ Gd retention in the skin and bone is greater than in the brain



Skin:
 Omniscan: 1400 nmol Gd/g
 Magnevist: 100 nmol Gd/g

Brain:
 Omniscan: 11 nmol Gd/g
 Magnevist: 13 nmol Gd/g

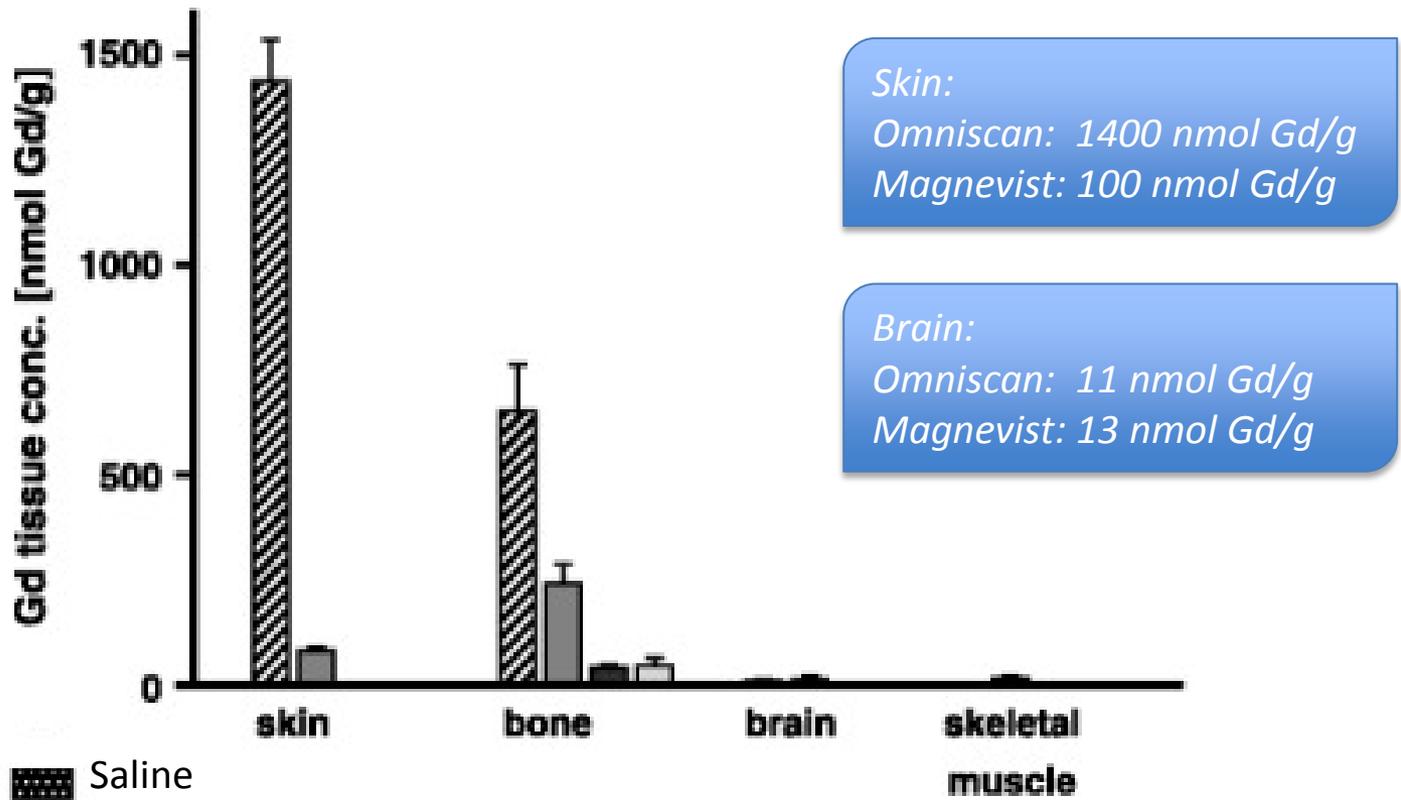
Rats

*Gd concentration in the skin were 10-100x more than brain.
 Lohrke 2017 (Bayer)*

- Saline
- Omniscan
- Magnevist
- ProHance
- Gadavist

Gadolinium retention – How much?

➤ Gd concentrations vary among the linear GBCAs outside of the brain



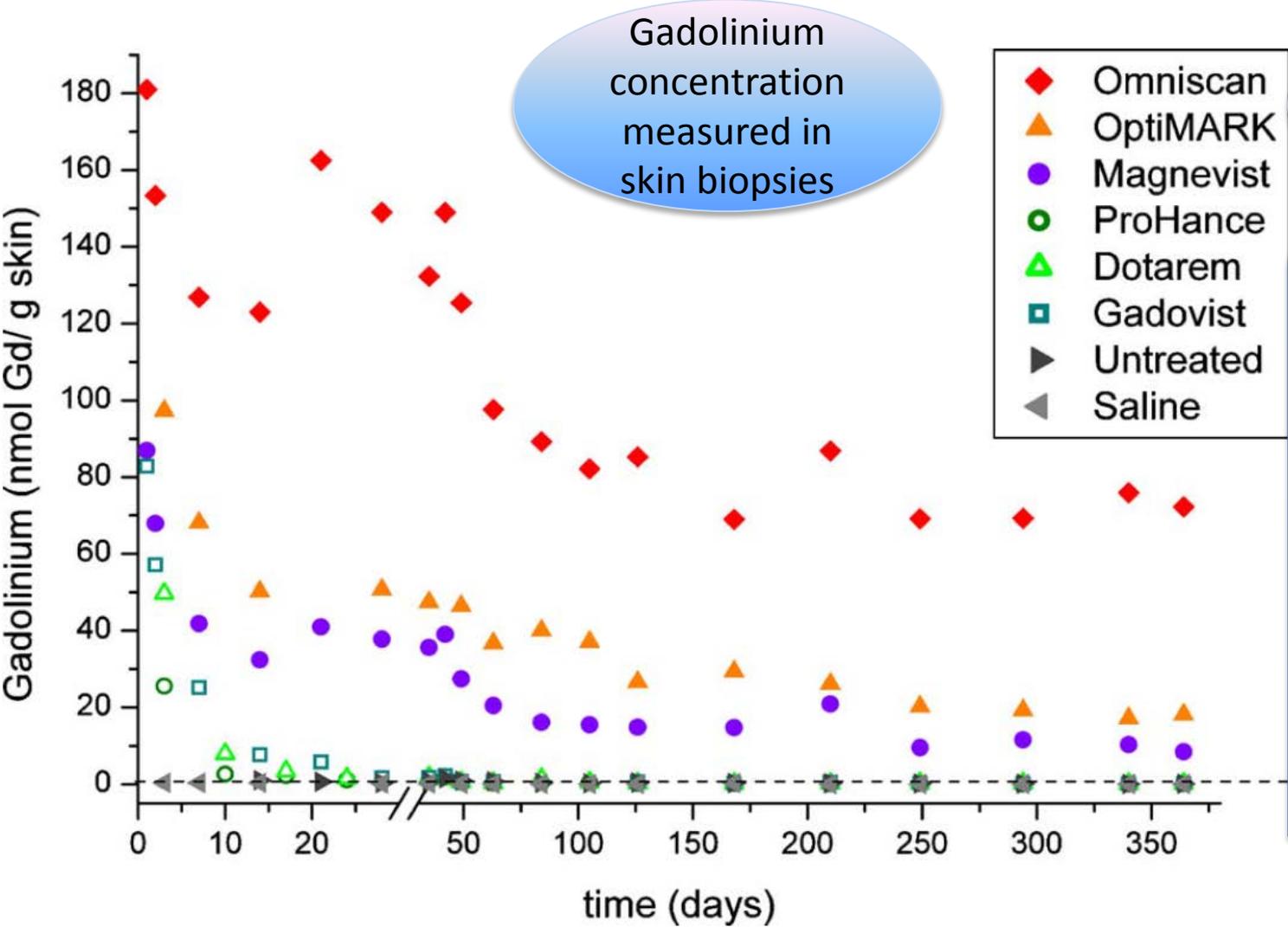
Rats

Differences in Gd concentration not only between linear and macro, but also between individual linear GCBAs.
 Lohrke 2017 (Bayer)

- Saline
- Omniscan
- Magnevist
- ProHance
- Gadavist

Gadolinium retention – For how long?

➤ Gd clearance from skin after macrocyclic agents occurred at a much faster rate than for linear agents

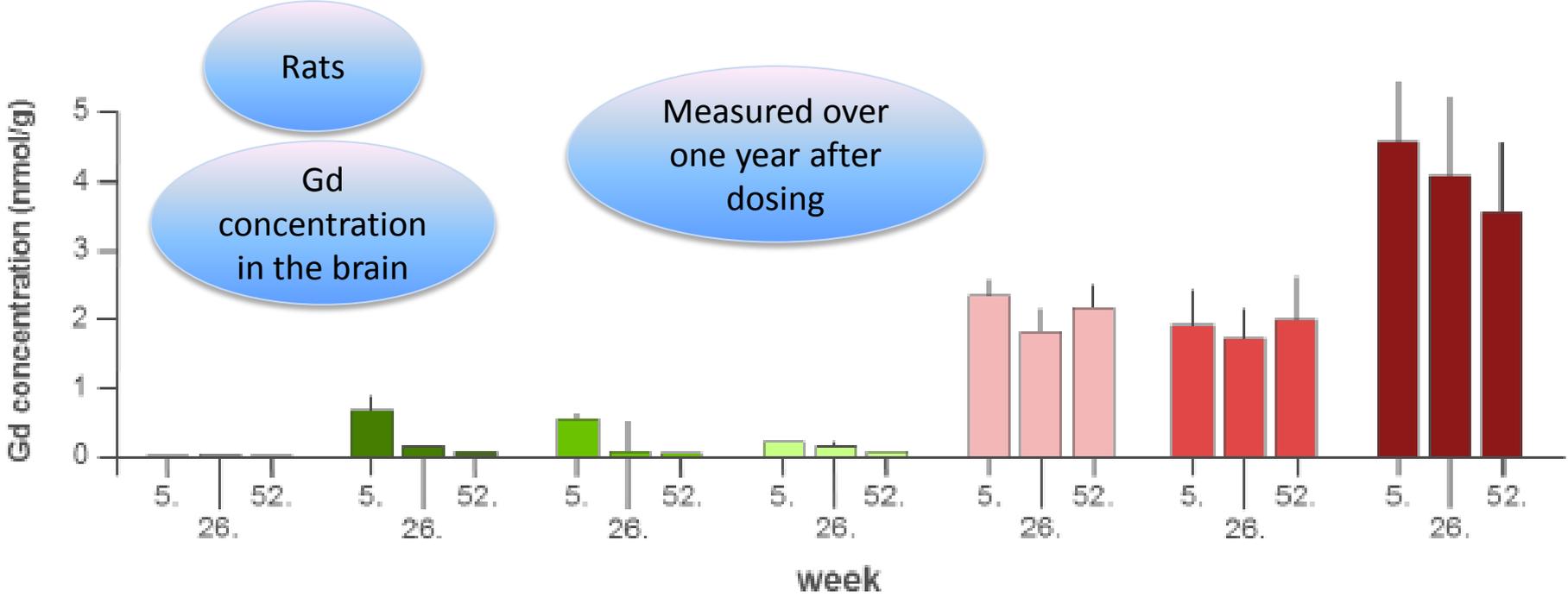


Rats
2.5 mmol/kg x 5 doses

After macrocyclic GBCAs, Gd concentration in the skin was in the same range as controls from day 24 post-injection.
(Gadavist NDA Study A42495, 2011)

Gadolinium retention – For how long?

➤ Gd clearance from brain tissue after macrocyclic agents occurred at a much faster rate than for linear agents



- Prohance®
- Dotarem®
- Gadovist®
- Saline
- Omniscan®
- MultiHance®
- Magnevist®

Continuous decrease in Gd concentration over one year after macrocyclic GBCAs.

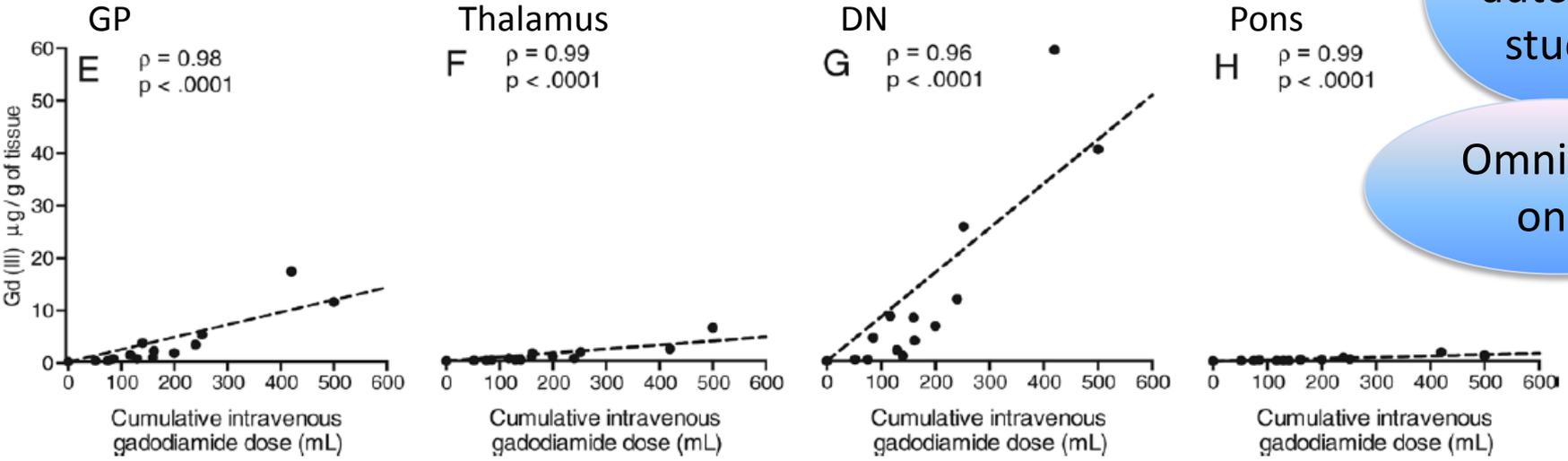
Bayer Briefing Document

Gadolinium retention – For how long?

➤ Brain gadolinium concentration in humans is cumulative after Omniscan

Human autopsy study

Omniscan only

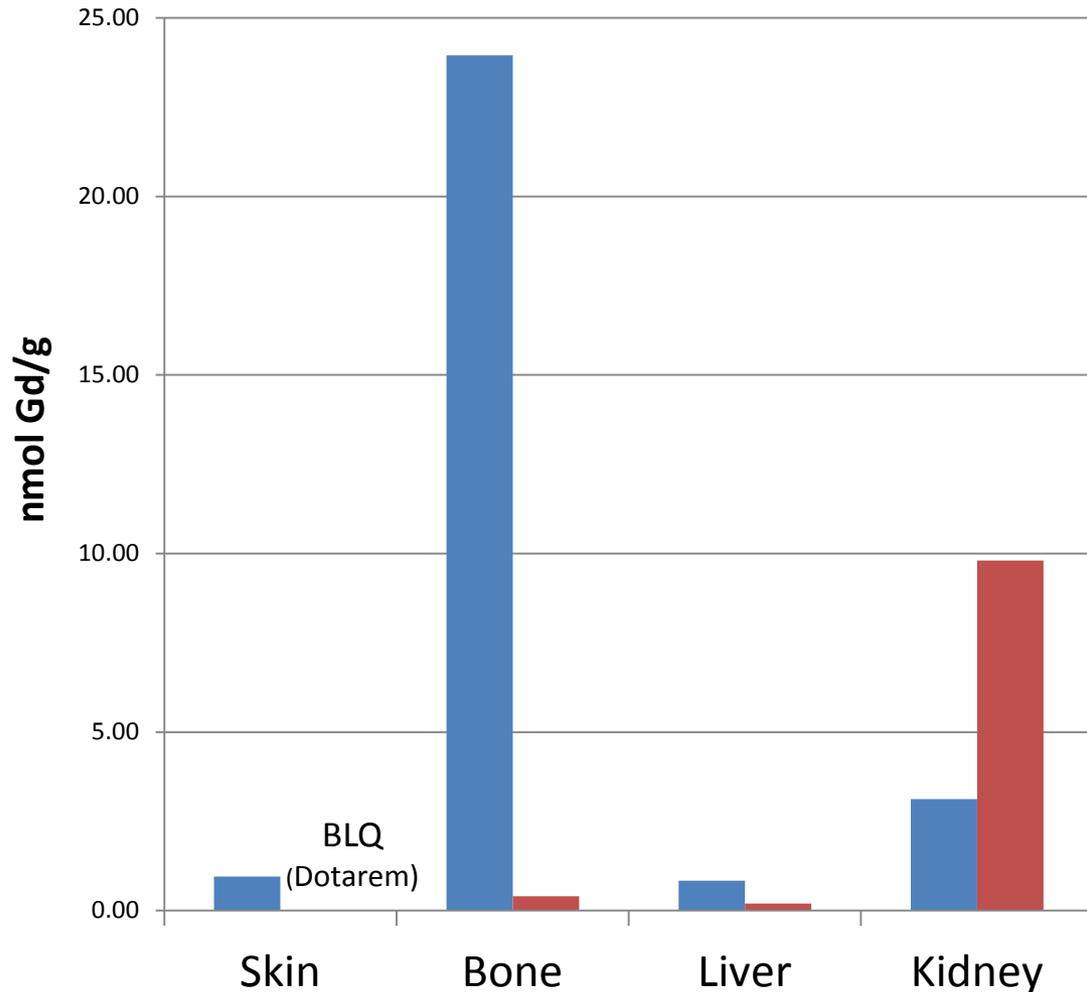


Neuronal tissue deposition of gadolinium appears to be cumulative over a patient's lifetime, in the absence of renal dysfunction.

McDonald 2015

Gadolinium retention – How much and how long in juvenile models?

➤ Limited data available, studies are on-going



Juvenile rats

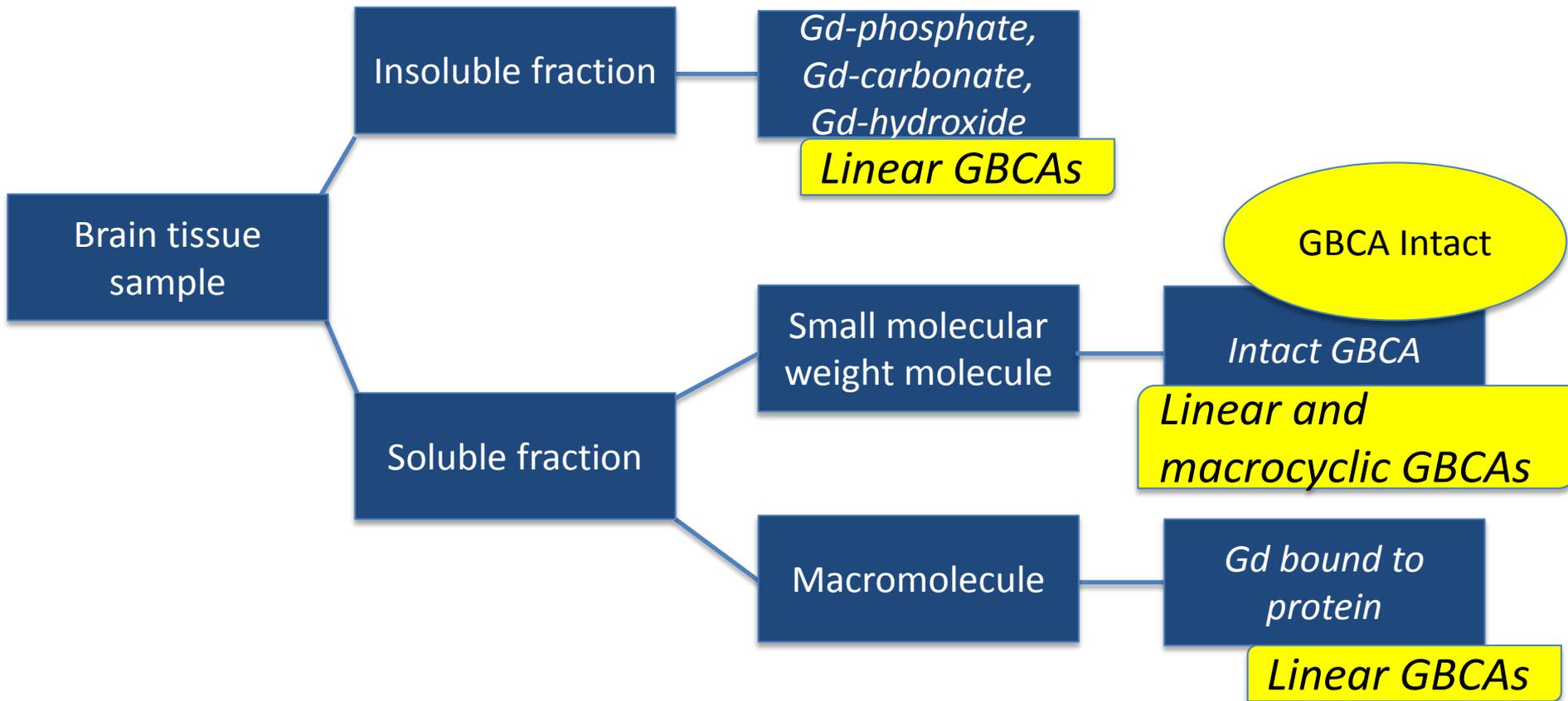
Dose: 15 mmol Gd/kg

Gd concentration measured at Day 60

■ Multihance
■ Dotarem

Bracco Study AB21194, unpublished, and Giorgi 2015 (Guerbet)

Gadolinium retention – In what form?



These two studies suggest that there is more dissociation of the linear GBCAs than the macrocyclic GBCAs in the brain

Frenzel 2017 (Bayer) and Guerbet ER-16-0005 unpublished

Regulatory Response 2017



- No clinical consequences of Gd brain retention have been identified
- No histopathological changes have been seen in rat brain tissues after repeated administration of GBCAs



*5.22.2017 Drug Safety Communication:
No harmful effects identified to date with brain retention of GBCAs
Review to continue
Advisory Committee meeting planned*

- There is a theoretical risk associated with Gd retention in the brain.
- Clinical consequences could take many years to identify.
- The concentration of Gd in the brain is higher after linear GBCAs.
- Gd clearance from brain tissue occurs at a much faster rate after macrocyclic GBCAs, compared to linear GBCAs.
- There is greater dissociation of Gd from the linear GBCAs compared to the macrocyclic GBCAs.
- Clinically, the multipurpose GBCAs are interchangeable.

Gadolinium Retention – Summary (1)

➤ Intrinsic stability of GBCAs/In vitro dissociation

Linear agents are more likely than macrocyclic agents to release free gadolinium

➤ Nonclinical evidence of toxicity

Skin toxicity is demonstrated in animal model ; no toxicity demonstrated in brain

➤ Clinical evidence of toxicity

No definitive signs, symptoms, or syndrome; further evaluation is necessary

➤ Susceptible patient populations

Related to higher doses, longer exposures, and potential immunologic predisposing factors

Gadolinium Retention – Summary (2)

➤ Comparative exposure to retained gadolinium from each GBCA

Locations of gadolinium retention

Gadolinium retention occurs everywhere, greatest in skin and bone

Amount of gadolinium retention

Higher concentrations of gadolinium after linear GBCAs than macrocyclic GBCAs

Length of time of gadolinium retention

Faster washout of macrocyclic GBCAs than for linear GBCAs

Form of retained gadolinium

Greater dissociation with linear GBCAs than macrocyclic GBCAs (brain)

Without a defined safety margin, the clinical relevance of the comparative retention data is unknown

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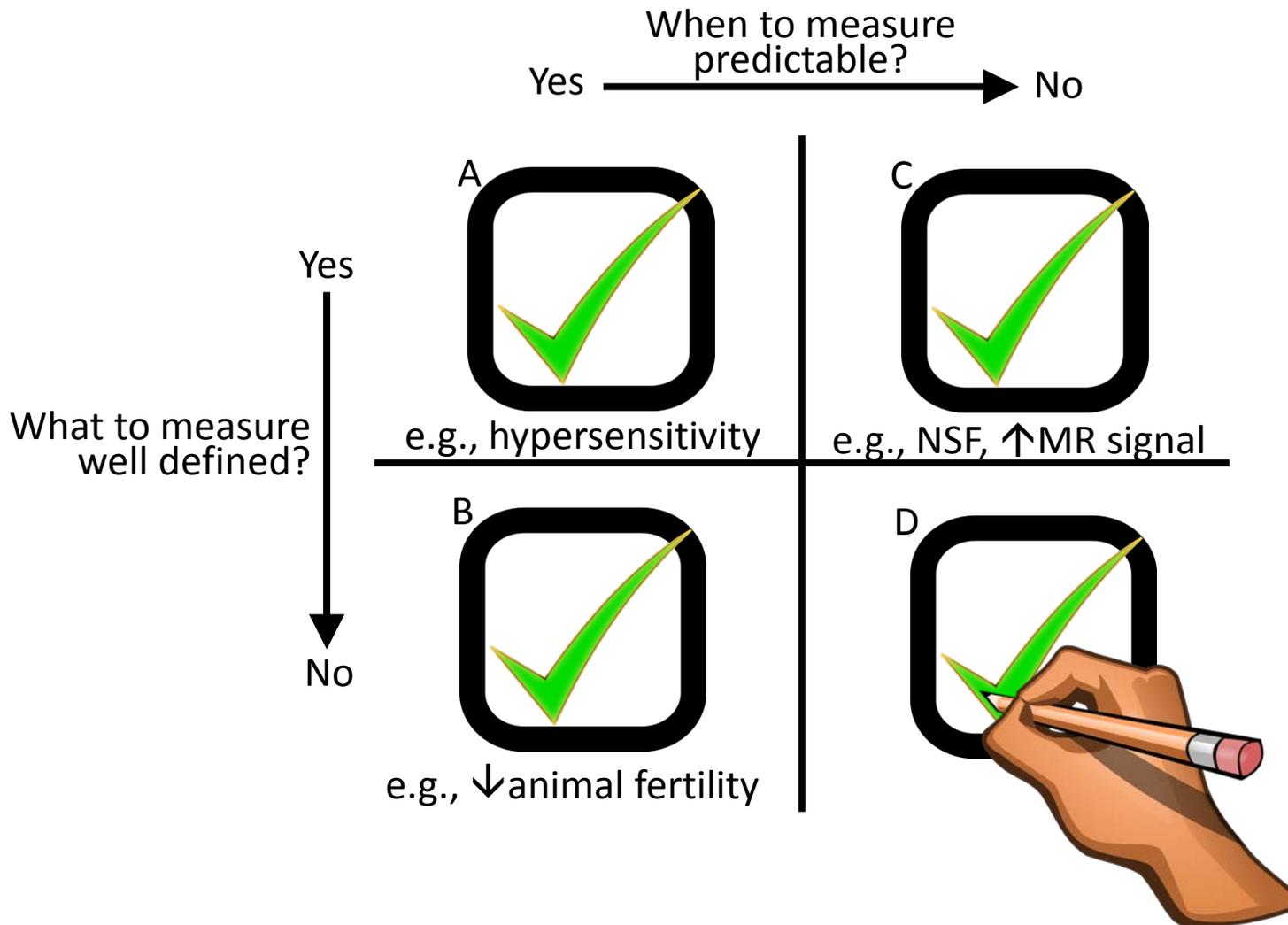
Toward More Sensitive Endpoints in Evaluating the Safety of Post-GBCA Gadolinium Retention

Anthony Fotenos, MD, PhD
Lead Medical Officer, Division of Medical Imaging Products (DMIP)
Office of Drug Evaluation IV (ODE IV)
Office of New Drugs (OND)
Center for Drug Evaluation and Research (CDER)

Medical Imaging Drug Advisory Committee (MIDAC) on Gadolinium Retention
September 8, 2017

Objective

Matrix of potential adverse GBCA reactions



Outline

1. Current state
2. Study design lead generation
3. Future approaches
4. Conclusion

Current State: Knowledge Gap



How are the risks of gadolinium retention best characterized?

Current State: What We Know

Surveillance and epidemiology

- Some clustering of adverse events
- Causal association to retention not established
- Usage patterns changing

Medical imaging

- Retention GBCA class-wide issue
- Retention in other tissues more than brain
- Retention of linears more than macrocyclics
- Considerable variability in retention among the linears
- Omniscan and to a lesser extent certain other linear agents have caused fibroplastic pathology in high-repeat-dose experiments in animals with normal renal function

Current State: What We Know (2)

FDA's imaging drug review

- Assumes single or infrequent rather than chronic use
- Placebo-controlled, parallel-arm clinical trials not required
- Pre-market, hundreds of animal and dozens of human studies involving thousands of subjects reviewed per GBCA
- Post-market, millions of patients have benefited from GBCAs without reported adverse reactions

Completed GBCA animal toxicology

- Brain safety studies for initial GBCA approval typically limited to acute neurological observations
- Recent non-comparative repeat-dose studies in juvenile rats for certain GBCAs have evaluated cognitive, motor, and sensory functions and identified no safety signals

Current State: Ongoing Investigations

- Heightened pharmacovigilance
- GBCA-wide toxicokinetic studies in animals that include functional neurological assessment
- Human epidemiological and database mining studies
- Phase IV prospective uncontrolled study to explore long-term retention of gadolinium in adult patients scheduled for orthopedic surgery with bone and skin sampling (NCT01853163, EudraCT Number 2012-001439-30, filed 2013)

Current State: Knowledge Limitations

System	Question	Yes/No
Brain	<ul style="list-style-type: none"> • Have the most sensitive cognitive, psychomotor, and pathological methods been adapted for studies of brain gadolinium retention? 	No
Body	<ul style="list-style-type: none"> • Have symptomatic patients received systematic clinical evaluation, including centralized pathological analysis? • Has recent progress in understanding gadolinium pathophysiology been translated into more sensitive endpoints compared to originally established criteria for NSF? 	No

Study Design Lead Generation: Sources

Any safety signal identified through studies of retention caused by administration of...

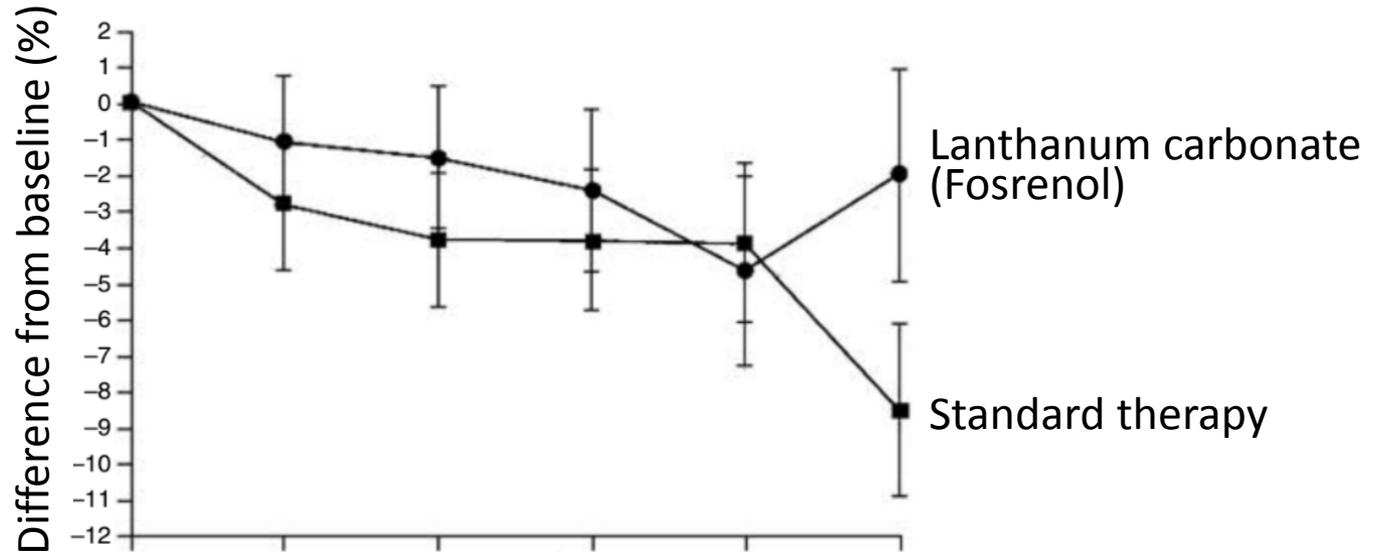
	Gadolinium or related metal in animals?	Gadolinium or related metal in humans?	GBCA in animals?	GBCA in humans?
Brain	Yes ¹	Yes ²	Yes ³	Yes ⁴
Body	Yes ⁵	Yes ⁶	Yes ⁷	Yes ⁸

Caveat: These are some examples of endpoints and designs which might or might not be applicable and are provided not as part of any regulatory recommendation but rather as something to consider.

Brain Study Design Lead (1)

Cognitive function in Stage 5 chronic kidney disease patients on hemodialysis: No adverse effects of lanthanum carbonate compared with standard phosphate-binder therapy P Altmann¹, ME Barnett^{2,3} and WF Finn⁴,

Randomized safety trial of cognitive risk from lanthanide brain retention (shown is one of five subdomains in Cognitive Drug Research [CDR] battery)

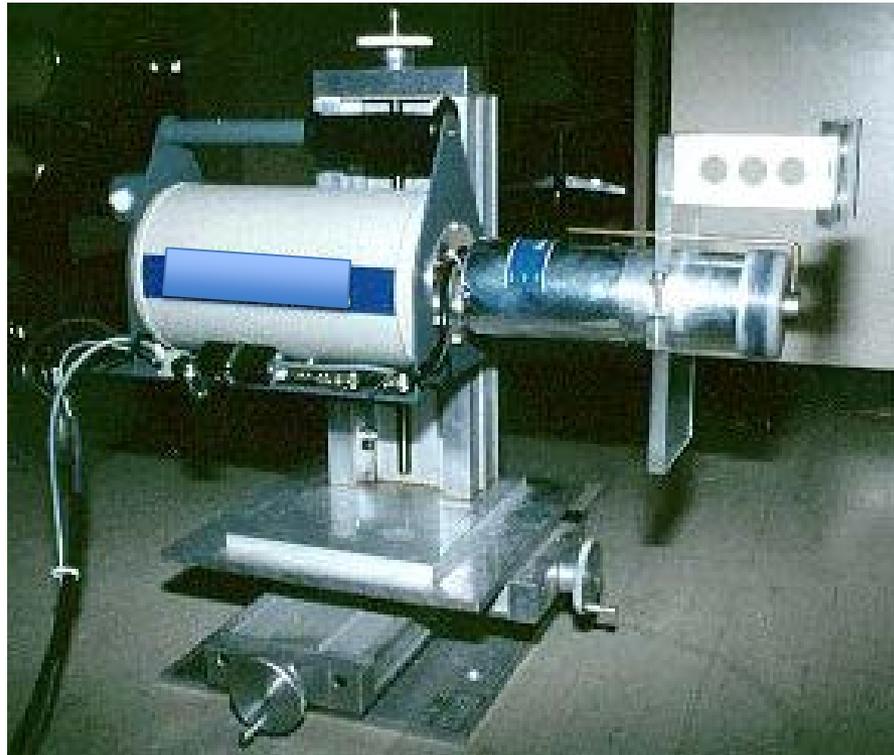


	Baseline	Visit 9	Visit 12	Visit 15	Visit 18	Final
Month	0	3.5	6	12	18	24
Lanthanum carbonate (n)	174	153	121	89	63	47
Standard therapy (n)	178	153	143	121	93	77

Brain Study Design Lead (2)

Confirming improved detection of gadolinium in bone using *in vivo* XRF¹

M.L. Lord^{a,*}, F.E. McNeill^b, J.L. Gräfe^c, A.L. Galusha^{d,e}, P.J. Parsons^{d,e}, M.D. Noseworthy^{f,g,h,i},
L. Howard^j, D.R. Chettle^b



¹See also Shih 2007, Kim 2011

Body Study Design Lead (3)

Gadolinium-Induced Fibrosis

Derrick J. Todd^{1,2} and Jonathan Kay³

Cutaneous Fibrosis and Normal Wound Healing

Emily Hamburg-Shields, Peggy Myung, and Shawn E. Cowper

Pathophysiology of gadolinium-associated systemic fibrosis

Brent Wagner,^{1,2} Viktor Drel,² and Yves Gorin²

Phagocyte

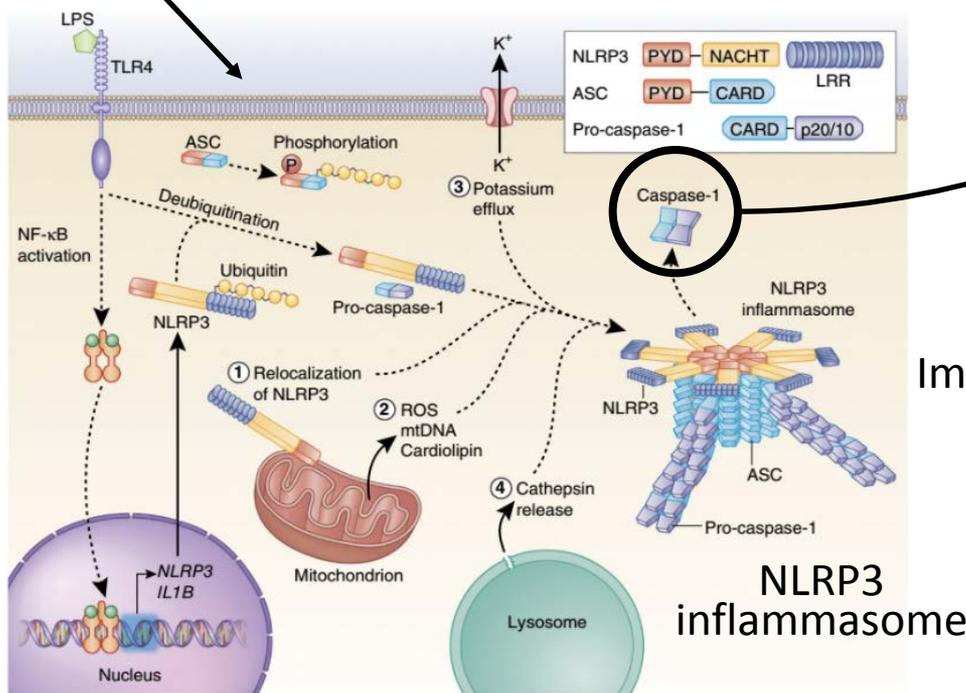
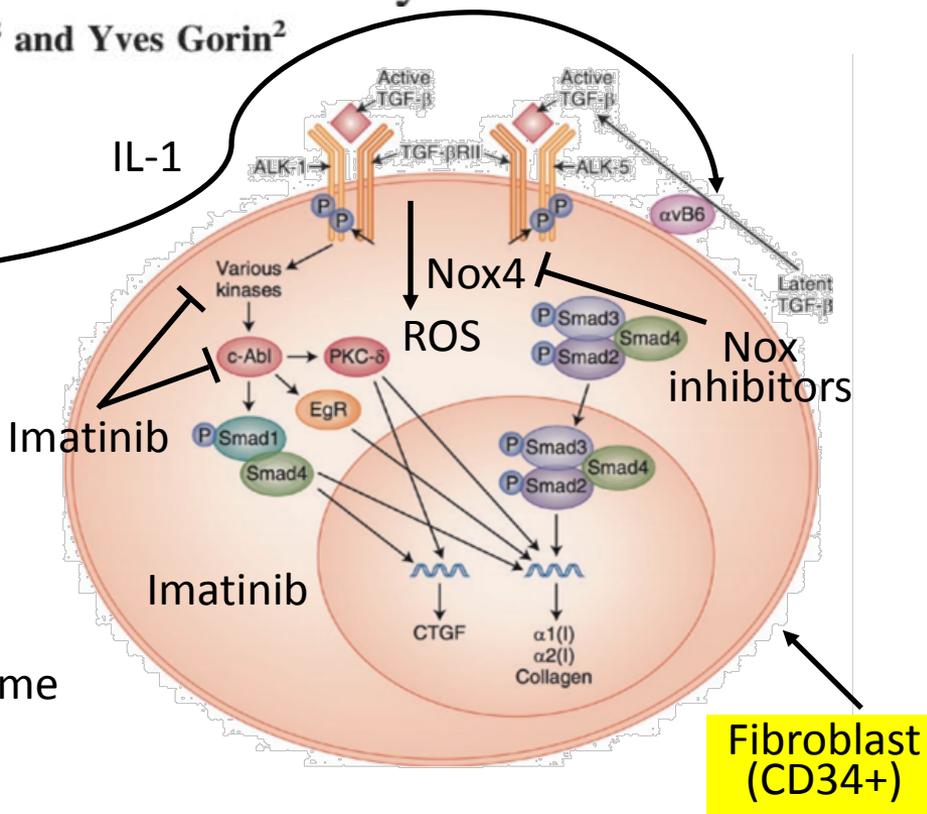


Figure from Guo 2015



Body Study Design Lead (4)

Can abnormalities established for immunological measurements in animal studies be translated into more sensitive probes for evaluation of potential body reactions in patients with normal renal function?

Quantitative pathology

- Skin thickness¹
- Skin cell count²

Cytokines

- Interleukin-1 family (IL-1)^{3,4}
- Interleukin-4 (IL-4)^{3,5}
- Monocyte chemoattractant protein-1 (MCP-1/CCL2)^{3,5}
- Osteopontin³
- Tumor necrosis factor- α (TNF- α)³

Extracellular matrix proteins

- α -smooth muscle actin (α -SMA)^{2,4}
- Tissue inhibitor of metalloproteinase type-1 (TIMP-1)^{3,5}



How are the risks of gadolinium retention best characterized?

Approaches to Gadolinium Retention Evidence Generation



Classification	Type of data source	Example	Status
Descriptive	Spontaneous adverse event reporting	FAERS, manufacturer databases	Ongoing
	Publications	Scientific literature: case reports, cases series	Ongoing
		Non-peer-reviewed sources	Ongoing
	Enhanced pharmacovigilance	Standardized data collection, development of case definition	Ongoing, registries to be considered
Analytical	Administrative databases	Mother-baby linkages	Ongoing
	Epidemiologic observational	Cohort prospective and retrospective	Ongoing
	Prospective uncontrolled	Longitudinal	Ongoing
	Prospective controlled	Parallel-arm	Feasibility
		Randomized	To be considered

Prospective Controlled Approach Considerations

- As part of further discussion at this meeting and of our questions to the committee, we will discuss registries and pharmacovigilance; is there an additional role for prospectively controlled clinical studies?
- How might symptomatic patients be systematically evaluated and compared to patients studied prospectively?
- How should prospective studies be powered?
- How might prospective study protocols proposed by different GBCA manufacturers be integrated?

Good Gadolinium Retention Study Design: Points to Consider



In vitro studies

- Compare multiple GBCAs, concentrations bracketing in vivo exposure, and exposure durations
- Account for potential osmolarity effects in design of positive and negative controls

Animals studies

- Prioritize questions least amenable to human study (e.g., effects of retention on early neurodevelopment)
- Administer GBCA doses that span full range of dose-toxicity curve from no to maximally tolerated effect
- Include positive and negative comparator controls
- Select maximally sensitive endpoints
- Extend dosing over a period of months for repeat-dose studies and compare endpoints both before and after drug-free washout periods
- Do not exclude sensitive species

Human studies

- Include neurological endpoints sufficiently sensitive for detection of subclinical adverse reactions caused by retention of metals with known toxicology
- Include endpoints more sensitive than NSF for potential body reactions
- Maximize control over sources of confounding and bias
- FDA encourages meetings to discuss protocol questions during planning phase

Conclusions

- Gadolinium retention safety is a priority for the MRI community
- Focus of this presentation on gaps that remain between
 - What we'd like to know and do
 - What experimental designs we might adapt and have
- Regulators and manufacturers aligned on understanding of available data but consensus lacking on implications for risk
- FDA awaiting results from ongoing studies by manufacturers and academic community
- Ongoing and additional sensitive safety studies have potential to build on mostly reassuring evidence reviewed to date in order to shed more light on this important public health issue

Preview of Upcoming Questions for the Advisory Committee

- **Question 1:** how do you characterize the risks of gadolinium retention?
- **Question 2:** is there a causal relationship to symptoms in patients ?
- **Question 3:** what investigations do you recommend to address gaps?
- **Question 4:** are planned labeling revisions premature, just right, or not enough?

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