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Gadolinium-based contrast agents for imaging of the central nervous system

A multicenter European prospective study

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Abstract

Contrast-enhanced MR (CE-MR) imaging is required to improve lesion detection and characterization and to increase diagnostic confidence. This study aims to evaluate the safety, effectiveness, and usage patterns of recently introduced Clariscan™ (gadoterate meglumine) and other macrocyclic gadolinium-based contrast agents (GBCAs) used for magnetic resonance imaging (MRI) of the central nervous system (CNS). Data was obtained from a European multicenter, prospective, observational postmarketing study that included pediatric and adult patients undergoing contrast-enhanced MRI with a GBCA used in routine clinical practice. Safety data was collected by spontaneous patient adverse event (AE) reporting. Effectiveness was assessed via changes in radiological diagnosis, diagnostic confidence, and image quality. 766 patients with CNS-related indications were included from 8 centers across 5 European countries between December 2018 and November 2019. Clariscan (gadoterate meglumine) was used in 66% (503) of exams, Dotarem® (gadoterate meglumine) in 20% (160), Gadovist® (gadobutrol) in 13% (97), and ProHance® (gadoteridol) in 1%. GBCA use increased the diagnostic confidence in 95% (724/766) of patients and a change in radiological diagnosis in 65% (501/766) of patients. The Clariscan-specific data revealed an increase in diagnostic confidence in 94% (472/503) of patients and resulted in a change in radiological diagnosis in 58% (293/503) of patients. Image quality was considered excellent or good in 95% of patients across all GBCAs and in 94% of patients who received Clariscan. No AEs were reported in this cohort including Clariscan. This data demonstrates the excellent safety and efficacy profile of Clariscan and other GBCAs used in MRI examination of the CNS.

Abbreviations: AE = adverse event, BMI = body mass index, CE-MR = contrast enhanced magnetic resonance, CNS = central nervous system, GBCA = gadolinium-based contrast agent, MRA = magnetic resonance angiography, MRI = magnetic resonance imaging, NSF = nephrogenic systemic fibrosis, SAE = serious adverse event.

Keywords: adverse events, contrast media, gadoterate (Gd-DOTA) Clariscan, image quality, Magnetic resonance imaging

1. Introduction

Magnetic resonance imaging (MRI) contrast agents were introduced in the late 1980s. Gadolinium-based contrast agents (GBCAs) are now used routinely to enhance the sensitivity and specificity of MRI examinations, and over 450 million doses have been administered worldwide.[1–3]

Currently, 6 GBCA molecules are approved for use by the U.S. Food and Drug Administration (FDA). Based on the structure of the ligand, these can be classified into 2 groups: macrocyclic agents (including gadoterate meglumine [Clariscan/Dotarem], gadobutrol [Gadovist] and gadoteridol [ProHance]) and linear agents (gadodiamide [Omniscan], gadobenate dimeglumine [MultiHance] and gadoxetate [Eovist]). Clariscan, a recently introduced generic agent, contains the same active pharmacological ingredient (API) as Dotarem in the same concentration (0.1 mmol/kg) and equivalent formulation. The inactive ingredients (preservatives, buffers, etc) in both products are the same. Clariscan has been approved for use in 70 countries with over 7 million patient doses shipped globally.[1,3–7]

The recent concerns from gadolinium retention and the European Medicines Agency (EMA) decision to suspend the marketing authorization of linear GBCAs (with exceptions) has led to a steady decline in the use of linear agents in the USA.[8] Unlike the EMA, the USA FDA maintained the marketing authorization of the linear agents and asked the contrast media manufacturers of both linear and macrocyclic agents to conduct safety assessments of their product(s) through human and animal studies.[9]

The choice of GBCA for a patient in clinical practice is complex and often subject to local variability in availability of resources, local protocols, physician expertise, patient

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expectations, financial constraints, and physicochemical profiles, including molecule stability and adverse events.[1,3]

To our knowledge, there is no prospective study mapping the use of the 4 macrocyclic GBCAs since the EMA suspended the marketing authorization of linear agents in Europe in 2017 and the introduction of a first generic GBCA in the USA.[7,8] With this background, it is important to understand the usage patterns of GBCAs in clinical practice, including referral details, indications, dosing, diagnostic confidence, and their safety.

The objective of this multi-national, prospective, observational study was to evaluate the safety, effectiveness, and usage patterns of recently introduced Clariscan™ (gadoterate meglumine) and other macrocyclic gadolinium-based contrast agents (GBCAs) used for magnetic resonance imaging (MRI) of the central nervous system (CNS).

2. Materials and Methods

2.1. Study design

The data for this study has been obtained from a larger scale European study, a cross-sectional multicenter observational study with prospective recruitment performed in patients scheduled for gadolinium contrast-enhanced magnetic resonance imaging (CE-MRI) as part of their routine clinical workup.[10] The study was registered on https://clinicaltrials.gov with identifier NCT01523873.

Eight centers across 5 European countries (France, Germany, Italy, Poland, and Spain) participated, and a total of 2118 consenting patients underwent CE-MRI examinations between December 2018 and November 2019. Centers participating in the current study required: (1) an independent decision to include Clariscan in the formulary for MR examinations and (2) the ability to maintain electronic patient data records to enable cumulative data reporting at end of the study. A minimum of 3 months recruitment period and 50 patients per site were targeted to warrant adequate representation.

The present study is a subanalysis of the data from the above European study, to assess the real-world safety and efficacy of GBCAs, including Clariscan for CNS (brain and spine) examinations at recommended/on label doses in the USA.[10]

2.2. Patient selection

Enrolled patients were adult and pediatric patients who were scheduled to undergo routine MRI with intravenous (IV) administration of contrast agents for CNS-related indications (brain, spine) at recommended/on label doses in US. Eligible patients received information about the study and a written consent and IRB approval was obtained.

2.3. Gadolinium-based contrast agents

Gadolinium-based contrast agents utilized by the participating centers for MRI exams of the CNS included gadoterate meglumine (Clariscan™; GE Healthcare), gadoteridol (ProHance®; Bracco Imaging), gadobutrol (Gadovist®; Bayer Healthcare) and gadoterate meglumine (Dotarem®; Guerbet). In each participating center, IV administration of GBCA was performed according to local standard protocols.

2.4. Clinical data retrieval

Patient demographics, working diagnoses, relevant medical histories, medications, referral details, indications for MRI examination, and details regarding administration of contrast agents were recorded on a standardized data collection form for each individual patient by trained study staff.

2.5. MRI effectiveness assessments

The assessment of effectiveness included changes in radiological diagnosis (yes/no), diagnostic confidence ratings, and MR image quality. The local radiologist assessed whether the contrast-enhanced MR (CEMR) images changed the radiological diagnosis in each patient. Diagnostic confidence was assessed by the local radiologist on a 0–100 percent scale both for the nonenhanced images (confidence before CEMR) and again after contrast-enhanced images (confidence after CEMR) were obtained. Image quality was reported on a 4-point scale (poor, fair, good, excellent) based on previously described scales for MRI.[11,12]

2.6. Safety monitoring

All included patients who received GBCAs were followed up in each center and AEs were recorded with details regarding diagnosis, onset date, severity (mild, moderate, or severe) and outcome. Spontaneously reported patient adverse events (AEs) were documented, and classified in terms of severity, course of treatment and latency (immediate: <1h postinjection, delayed: 1h–7d postinjection). The local radiologist assessed the likelihood that an AE was related to GBCA administration as follows: not related, related (doubtfully or possibly), or not assessable. AEs doubtfully or possibly related to GBCA administration were defined as adverse drug reactions (ADRs). AEs were summarized using the current MedDRA coding system. The data were recorded by the local investigators in all 8 eligible centers.

2.7. Statistical analysis

Statistical analysis of the data was performed using SAS Software Version 9.4 (SASVR Institute Inc., Cary, NC). Quantitative (continuous) data was reported as means and standard deviations (SD) or medians and ranges. Qualitative (binary) data was reported as raw numbers, frequencies, and 95% confidence intervals. Descriptive analysis was complemented by explorative statistical tests (ANOVA for continuous endpoints, Chi-Square tests for categorical endpoints).

3. Results

3.1. Study cohort

A total of 2188 patients were enrolled in the original European study between December 2018 and November 2019. Of these 2188 patients, 902 patients met the CNS-related indications. Patients with doses over 0.10 mmol/kg were excluded (off label for USA) from this study. Thus, the subset contains 766 patients undergoing CNS imaging at the general/US recommended doses (up to 0.10 mmol/Kg) (Table 1). The majority of patients in this subset were adults; 19–59 years of age [446 patients (58%)] and 314 patients ≥ 60 years (41 %) and female (57%). The mean body mass index (BMI) was 26 kg/m^2 (range 15.6–58.6), with the following BMI categories, underweight and normal 322 (42%), overweight 330 (43%), obese and morbidly obese 114 (15 %) (Table 1). There were no significant differences in BMI among the different GBCAs used (P value = 0.3).

About half of the patients in this cohort (373 (49%)) had documented comorbidities. The most common was hypertension (22%), followed by history of malignancy and allergic conditions (8.4% each), and neurologic symptoms (6.9%). Concomitant medications were reported in 35% of patients, mostly antihypertensive (20%), chemotherapy (6.4%) and antidiabetic medications (5.4%) (Table 1).

There were 6 patients with a reported prior allergic-like reaction to contrast agents (5 patients to iodinated contrast agents and 1 patient to GBCA). As premedication, steroids were administered in 0.6%[5] and antihistamines in 0.4%[3] of the

Table 1

Demographic data and baseline characteristics of study population.

Subjects recruited, n (%)	766	(100)
Country, n (%)		
Poland	338	(44)
Italy	83	(11)
Germany	167	(22)
Spain	58	(7.6)
France	120	(16)
Sex, n (%)		
Female	434	(57)
Male	332	(43)
Age (y, mean (SD))	53.1	(16)
Age category, n (%)		
0–18	6	(0.8)
19–59	446	(58)
≥60	314	(41)
Height (m, mean (SD))	1.7	(0.1)
Weight (kg, mean (SD))	75.7	(16)
BMI (kg/m^2, mean (SD))	26.4	
Underweight (BMI < 18.5)	4	(0.5)
Normal (BMI ≥ 18.5 to < 25)	318	(42)
Overweight (BMI ≥ 25 to < 30)	330	(43)
Obese (BMI ≥ 30 to < 40)	105	(14)
Morbidly obese (BMI ≥ 40)	9	(1.2)
Comorbidity, n (%)		
Hypertension	166	(22)
Malignancy/cancer	64	(8.4)
Allergy	64	(8.4)
Diabetes mellitus	47	(6.1)
Neurologic symptom	53	(6.9)
Autoimmune disease	25	(1.2)
Renal impairment	11	(1.4)
Hepatic impairment	2	(0.3)
Other	33	(4.3)
Premedication, n (%)		
Steroids	5	(0.6)
Antihistamines	3	(0.4)
Concomitant medications, n (%)		
Antihypertensives	150	(20)
Chemotherapy	49	(6.4)
Antidiabetic drugs	41	(5.4)
Other reported	101	(13)
No co-medication	443	(58)

cases. Renal impairment was reported in 11 cases (1.4%), while hepatic impairment was seen in 2 patients (0.3%).

3.2. Pattern and quality of referral

The cohort consisted of 4.4% (34 cases) emergency procedures, 62% (476 cases) referred for routine diagnosis, and 33% (256 cases) follow-up procedures for a known disease. Referral information was considered well detailed with a clear medical question in 104 cases (14%), satisfactory in 641 cases (84%) and insufficient in 21 cases (2.7%). In terms of satisfactory level of medical information, there was no statistically significant difference among these examined cohorts. (P value = 0.5).

3.3. GBCA and MRI exam details

The GBCAs dose was ≤ 0.10 mmol/kg with median GBCA volume of 14 ml, (range 3–25 ml). Gadoterate meglumine was used in most of the patients, with Clariscan being used in 503 patients (66%) and Dotarem in 160 patients (21%), followed by gadobutrol (Gadovist) in 97 patients (12%) and gadoteridol (Prohance) in 6 patients (1%) (Table 2).

Table 2

Injections details by GBCA*

	N (%)
N	766
Type of exam	
Routine	476 (62%)
Follow-up	256 (33%)
Emergency	34 (4.4%)
1.5T (vs 3T)	634 (83%)
MR angiography	53 (6.9%)
GBCA volume (ml median) (min-max)	14 ml (3–25)
GBCA dose (mmol/kg)	0.10≤
GBCA administered	
Clariscan	503 (66%)
Dotarem	160 (21%)
Gadovist	97 (13%)
ProHance	6 (0.8%)

1.5 Tesla MRI was used in 83 % (n = 634) of the studies included in our analysis and 17% (n = 132) were performed using 3 Tesla MRI. Majority of Clariscan (n = 415 (83%)), Dotarem (n = 132 (83%)), Gadovist (n = 87 (90%)) studies were performed using 1.5 Tesla MRI. There was no statistically significant difference among GBCAs group (P = .2) (Table 2).

3.4. GBCA effectiveness

The use of GBCAs increased the confidence in diagnosis in 95% of the examinations. Mean confidence in diagnosis increased from 51 to 90% and median confidence from 50 to 93% (0–100 scale) and resulted in a change in the radiological diagnosis in 65% of the patients (Table 3), (Fig. 1).

Overall, image quality was considered excellent or good in 95% of the cases (excellent (n = 424) 55%, good (n = 303) 40%, fair (n = 38) 5%, and poor (n = 1) 0.1 %. Quality of the images with Clariscan was considered excellent or good or in (471) 94% of the cases, excellent 58% (n = 293), good 35% (n = 178), fair 6.2% (n = 31), poor 0.2%.[1] There was no statistically significant difference in the quality of Clariscan images compared to other CE-MR images (P = .70).

3.5. GBCA safety

There were 6 patients with a reported history of prior allergic-like reaction to contrast material. In our subset of MRI examinations, there were no reported AEs post administration of Clariscan or any other GBCAs.

4. Discussion

This multi-center, prospective real-world study involving adult and pediatric patients demonstrated an excellent safety and efficacy profile of the recently introduced gadolinium-based contrast agent (GBCA) gadoterate meglumine Clariscan™ and other GBCAs used for CNS imaging.

In this cohort, the consistent with prior studies (90–99.7%).[6,13–17] Image quality was good to excellent in 95% of the cases in our cohort, which is comparable amongst all GBCAs despite the difference in relaxivity. This real-world study complements the data obtained from a randomized control trial by Maravilla et al (REMIND study) that demonstrated current administration of GBCAs had a significant effect on patient care by improving the diagnostic confidence in more than 95% of cases when comparing nonenhanced to contrast-enhanced MRI. Additionally, GBCA administration in this cohort affected/changed the radiological diagnosis in more than 65% of examinations. Overall, these findings reinforce the

Table 3

Changes in radiological diagnosis and confidence after CE-MRI/MRA* and image quality.

	Clariscan	Dotarem	Gadavist	ProHance
N	503	160	97	6
Changes in radiological diagnosis, n (%)	293 (58%)	126 (79%)	79 (81%)	3 (50%)
Increased confidence in diagnosis, n (%)	472 (94%)	153 (96%)	94 (97%)	5 (83%)
Confidence before CEMR (median)	52	41	39	51
Confidence after CEMR (median)	95	91	91	100
Image quality				
Poor	1 (0.2%)	0	0	0
Fair	31 (6.2%)	2 (1.3%)	5 (5.2%)	0
Good	178 (35%)	70 (44%)	51 (53%)	4 (67%)
Excellent	293 (58%)	88 (55%)	41 (42%)	2 (33%)

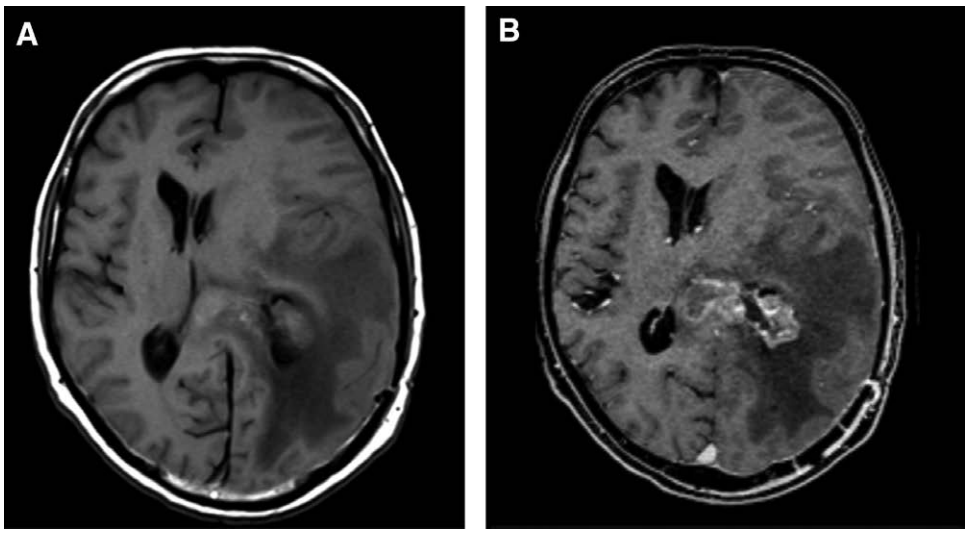

Figure 1. High grade brain glioma pre (a) and post administration of contrast (b), in a 32-year-old male patient. A poorly defined Heterogeneous left parietal mass in T1 without contrast, associated with marked vasogenic edema and midline shift to the contralateral side. After administration of contrast (Clariscan, 0.10 mmol/kg), it shows heterogeneous enhancement and allows to distinctly define the border of the left periventricular parietal mass with ependymal extension with marked vasogenic edema and midline shift. Image quality was reported as good by site investigator.

clinical benefits of GBCA use with US recommended doses (up to 0.10 mmol/Kg) for patients undergoing MR examinations for CNS indications.

We found an overall image quality (fair, good, and excellent) rate of 99.8% for MR examinations using gadoterate meglumine (Clariscan), the noninferiority of gadoterate meglumine (Dotarem) vs gadobutrol (Gadovist) for overall visualization and characterization of primary brain tumors despite the higher relaxivity and molarity of gadobutrol.[13]

A common strategy for increasing MRI sensitivity in the detection of brain lesions is increasing the dose of the contrast agents.[16,18] However, present data suggest that using a standard dose (<0.1 mmol/kg) is sufficient to accomplish high quality diagnostic imaging in majority of the patients. This result is important, because GBCAs are sometimes administered at more than this standard dose, which could result in safety concerns related to the use of GBCAs, including gadolinium retention and NSF.

Our study found that Clariscan is a well-tolerated GBCA, with no AEs reported in this cohort of patients undergoing CNS examination (brain and spine). However, in the complete European cohort that included higher doses of GBCAs and different indications, the adverse event rate was 0.19% (0.05% serious AEs). These findings corroborate with prior studies of gadoterate meglumine safety.

A study of 3444 patients following gadoterate meglumine (Dotarem) administration by Ishiguchi and Takahashi yielded an overall 1.16% incidence of AEs including 0.12% serious AEs.[1] Other studies of Dotarem by Soyer et al (overall AE incidence 0.12%; serious AEs 0.03% in 35,499 patients) and Maurer et al (overall AE rate of 0.34%; serious AEs < 0.01% in 84,621 patients) yielded similar results.[14,15]

Additional studies have examined AEs following administration of other GBCAs. Power et al reported an incidence of 0.32% allergic-like reactions in 32,991 patients after gadobutrol injection.[19] Morgan et al found an overall adverse reaction rate of 0.67% (0.01% severe) in 28,078 patients following gadoteridol injection.[20] A major European prospective registry with 72,839 GBCA enhanced cardiac MRs reported a total incidence of AEs of 0.36% and severe AEs of 0.03%,[19] based on their data gadoterate had the lowest incidence of AEs (OR 0.89), that was not statistically different from gadobutrol (reference OR 1), while gadoteridol was found to have a statistically significant higher incidence of AEs (OR 3.58).[21] In reflection of these AE incidences, the introduction of Clariscan as a new brand of gadoterate does not seem to be associated with a higher rate of adverse events or a potential Weber effect.[22]

Other known safety issues with GBCAs include gadolinium retention in tissues and nephrogenic systemic fibrosis (NSF). In vitro studies have shown that macrocyclic GBCAs including gadoterate meglumine, gadobutrol, and gadoteridol have higher stability constants and have a lower risk of gadolinium dissociation compared to linear GBCAs including gadodiamide and gadobenate.[23] To our knowledge, very few single-agent nephrogenic systemic fibrosis (NSF) cases have been associated with the macrocyclic agent gadobutrol, while no unconfounded cases of NSF have been reported for gadoterate, gadobenate,

or gadoteridol.[24] The RESCUE Study by Deray et al, which assessed the safety of gadoterate-enhanced MRI compared to unenhanced MRI on 514 patients with impaired renal function, including end-stage or dialysis patients, found that gadoterate did not affect renal function and was a safe contrast agent in patients with chronic kidney disease.[5]

Our study included a broad range of patients, with heterogenous patient demographics and medical histories. Notes from referring physicians were found to vary in detail and accuracy, with only 12% of cases with well-detailed information with a clear medical question, demonstrating that there seems to be room for improvement in clinical practice, sufficient information in 84% of cases, and insufficient information in 4.8% of the cases. As previously reported, accurate referral notes are key to ensure that radiologists perform the appropriate exam including GBCA use and parameters.[25] Additionally, paucity of details regarding patient history and medications can negatively impact patient safety when alternative sources of data to the referral notes are not available.[26]

This study had several limitations. First, the cohort represented a limited number of cases, thus the study was underpowered to fully examine the rate of adverse events (AEs) and to compare different macrocyclic agents. AEs may have been underestimated if they developed after the patient left the radiology department. Nevertheless, this is unlikely to impact the reported rate of serious adverse events, which most likely occur as immediate reactions. Second, this study was observational and therefore was not designed to compare GBCAs for differences in efficacy or assess the reliability of changed diagnosis with each disease for different types of contrast agents. Additional prospective larger multicenter studies are needed for direct GBCA comparisons and generalizability of our findings to determine the rate of AEs more accurately.

5. Conclusions

In conclusion, this study of usage patterns of GBCA in a real-world clinical setting indicates that Clariscan and other GBCAs are safe and effective when intravenously administered in adults and children for MR examination of the CNS (brain and spine). These findings corroborate and complement previously published clinical trials evaluating safety and efficacy of GBCAs.

Author contributions

AHB and JM: Data interpretation, first manuscript drafting and manuscript review. Authors read and approved the final manuscript.

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