Diagn Interv Radiol 2019; 25:95–101

ABDOMINAL IMAGING

ORIGINAL ARTICLE

Focal nodular hyperplasia: a weight-based, intraindividual comparison of gadobenate dimeglumine and gadoxetate disodium-enhanced MRI

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PURPOSE
We aimed to qualitatively and quantitatively compare the enhancement pattern of focal nodular hyperplasia after gadobenate dimeglumine and gadoxetate disodium injection in the same patient.

METHODS
1.5 T magnetic resonance imaging (MRI) examinations of 16 patients with 21 focal nodular hyperplasias studied after the injection of both contrast media were evaluated. Both MRI studies were performed in all patients. A qualitative analysis was performed evaluating each lesion in all phases. For quantitative analysis we calculated signal intensity ratio, lesion-to-liver contrast ratio and liver parenchyma signal intensity gain on hepatobiliary phase. Statistical analysis was performed with the Wilcoxon sign-rank test for clustered paired data and the McNemar test for paired frequencies. A P value < 0.05 was considered statistically significant.

RESULTS
At qualitative analysis no statistically significant differences were evident during any of the contrast-enhanced phases. Signal intensity ratio ($P = 0.048$), lesion-to-liver contrast ratio ($P = 0.032$) and liver parenchyma signal intensity gain ($P = 0.012$) were significantly higher on hepatobiliary phase after gadoxetate disodium injection.

CONCLUSION
There were no significant differences in the MRI findings of focal nodular hyperplasia after the injection of a weight-based dose of either gadobenate dimeglumine or gadoxetate disodium.

Focal nodular hyperplasia (FNH) is a common benign hepatic tumor, usually discovered incidentally in young women (1, 2). While most FNH are confidently diagnosed on the basis of characteristic imaging appearance, they may sometimes mimic other liver masses, resulting in reduced diagnostic confidence by the radiologist (3, 4) and therefore in further test ordering and increased patient anxiety. An appropriate preoperative diagnosis is therefore essential in order to warrant conservative management.

Liver-specific MRI contrast agents are being increasingly used in clinical practice. Those currently available are gadobenate dimeglumine (MultiHance, Bracco) and gadoxetate disodium (Primovist, Bayer Schering Pharma; Eovist, Bayer Healthcare Pharmaceuticals). After injection, these agents circulate in the vascular system and diffuse into the interstitium, thus allowing the acquisition of multiple phases (i.e., arterial and portal venous phases). Moreover, after an interval time that varies between the two agents, these are uptaken by functioning (i.e., nondamaged) hepatocytes of both hepatic parenchyma and hepatocellular lesions on hepatobiliary phase, providing further insights for the noninvasive characterization of focal liver lesions (1, 5). Approximately 50% of gadoxetate disodium is uptaken by normally functioning liver hepatocytes, whereas gadobenate dimeglumine uptake by hepatocytes accounts for only 3%–5% of the injected dose (1, 5).

Hepatobiliary MRI contrast agents have been successfully used for the diagnosis of FNH lesions, which are typically isointense or hyperintense to the surrounding parenchyma on hepatobiliary phase (6, 7). Due to the different percentage of hepatocellular uptake of the

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Received 12 April 2018; revision requested 8 May 2018; last revision received 30 July 2018; accepted 8 August 2018.

Published online 12 February 2019.

DOI 10.5152/dir.2019.18165

You may cite this article as: Taibbi A, Brancatelli G, Matranga D, Midiri M, Lagalla R, Bartolotta TV. Focal nodular hyperplasia: a weight-based, intraindividual comparison of gadobenate dimeglumine and gadoxetate disodium-enhanced MRI. Diagn Interv Radiol 2019; 25:95–101.

Table 1. Precontrast MRI protocol

Sequence	TR/TE (ms)	Bandwidth (KhZ)	FOV	Thickness/gap (mm)	Matrix	NEX	Slices/time (s)
Breath-hold T2W SSFSE	946/182.7	62.5	40×40	6/1	384×224	0.57	22/20
Respiratory triggered T2W FSE		50	40×40	6/1	256×224	4	22/180
Respiratory triggered T2W FSE with FS	4286/83.7	50	40×40	6/1	320×224	4	22/210
Breath-hold T1W (FSPGR) (in and out of phase)	150/4.2/2.0	62.5	40×40	4.4/1	256×192	1	44/31 (2 acquisitions)
Breath-hold T1W 3D SPGR with FS	4.2/2.0	62.5	40×40	4.4/2.2 overlap	320×192	0.71	22/20

TR/TE, repetition time/echo time; FOV, field of view; NEX, number of excitations; T2W, T2-weighted imaging; SSFSE, single shot fast spin-echo; FSE, fast spin-echo; FS, fat suppression; T1W, T1-weighted imaging; FSPGR, fast spoiled gradient echo; 3D, three-dimensional.

two agents, we hypothesized that imaging features of FNH could be different when either contrast agent is used.

Therefore, the aim of our study was to qualitatively and quantitatively compare the enhancement pattern of FNH after the injection of a weight-based dose of gadobenate dimeglumine and gadoxetate disodium intravenous injection in the same patient studied at a single institution.

Methods

Patients and lesions

This study followed the Declaration of Helsinki principles. Institutional review board approval was not deemed necessary due to the retrospective nature of this study, and informed consent was waived.

We performed a search for the string terms "focal nodular hyperplasia" or "FNH" in the radiology databases at our institution in a five-year span and identified 140 consecutive patients. Sixteen of these patients had more than one MRI study performed with both gadobenate dimeglumine and gadoxetate disodium and formed our final study population.

Our study population consisted of 13 women and three men (age range, 30–63 years; mean age, 39.9±9.2 years) with a total of 21 FNHs (size range, 0.9–4.4 cm; mean size, 2.2±1 cm). Twelve patients had one lesion, three patients had two lesions, and one patient had three lesions.

None of these patients had history of chronic liver disease or malignancy. The mean interval time between MRI examinations in the same patient was 404.8±327.3 days (range, 130–1495 days).

No changes have been observed regarding the size of FNHs during imaging follow-up.

Main points

- At qualitative analysis, dynamic and hepatobiliary enhancement patterns of FNH do not significantly differ when a weight-based dose of either gadobenate dimeglumine or gadoxetate disodium is injected.
- At quantitative analysis, focal nodular hyperplasia signal intensity, liver parenchyma signal intensity and lesion-to-liver contrast ratio were stronger after gadoxetate disodium injection in comparison with gadobenate dimeglumine injection during the hepatobiliary phase.
- Gadobenate dimeglumine and gadoxetate disodium are equally valuable for the diagnosis of FNH, but gadobenate dimeglumine is more time consuming than gadoxetate disodium.

Standard of reference

Diagnosis of FNH on contrast-enhanced MRI was based on the presence of all of the following criteria: a) round or oval shape; b) signal intensity similar to that of the surrounding liver on T1-weighted and T2-weighted sequences; c) homogeneity; d) strong enhancement on arterial phase with no subsequent washout. Washout was defined as lower signal intensity in comparison to the surrounding liver on either portal venous or delayed phase on gadobenate dimeglumine-enhanced MRI and on portal venous phase only on gadoxetate disodium-enhanced MRI; e) absence of capsule. Capsule was defined as a continuous rim surrounding the FNH lesions, showing higher signal intensity in comparison to the surrounding liver on either portal venous or delayed phase on gadobenate dimeglumine-enhanced MRI or on portal venous phase only on gadoxetate disodium-enhanced MRI and lower signal intensity in comparison to the surrounding liver on hepatobiliary phase after gadobenate dimeglumine or gadoxetate disodium-enhanced imaging. A rim of peripheral, hyperintensity of the outer portion of FNH on hepatobiliary phase with either contrast agent was not considered as a capsule, but rather as one of the possible patterns of enhancement of FNH in the hepatobiliary phase (8). Presence of a central scar was not considered mandatory because of the low sensitivity and specificity for the diagnosis of FNH (9, 10). The MRI protocol used in both examinations is detailed as follows.

MRI technique

MRI was performed with a 1.5 T scanner (Signa Excite, General Electric Healthcare) by using a dedicated abdominal multichannel phased-array coil. The precontrast protocol is summarized in Table 1.

Gadobenate dimeglumine-enhanced MRI

A multiphasic dynamic study was obtained after the administration of 0.2 mL/kg of gadobenate dimeglumine (MultiHance, Bracco Diagnostics) injected at a flow rate of 2 mL/s and flushed by 20 mL of saline solution using an automatic MRI-compatible injector (Medrad Spectris Solaris EP MR Injection System, Bayer Healthcare). Images were acquired using automated bolus detection technique (Smart-prep technique, GE Healthcare) during the arterial (16 s after bolus detection), portal venous and delayed phase (60 and 180 s after contrast injection, respectively). The dynamic study was followed by an acquisition during the hepatobiliary phase obtained 2 hours after the injection of contrast material.

Gadoxetate disodium-enhanced MRI

For the gadoxetate disodium-enhanced MRI, the two T2-weighted respiratory triggered sequences were acquired after the completion of the triphasic dynamic gadoxetate disodium-enhanced study. The triphasic dynamic contrast-enhanced study was obtained after the administration of an intravenous bolus of 0.1 mL/kg of gadoxetate disodium (Primovist or Eovist; Bayer Healthcare) injected at a flow rate of 1 mL/s and flushed by 20 mL of sterile saline solution using the same automatic MRI-compatible injector. The scanning delay for triphasic dynamic three dimensional (3D) gradient-echo imaging was 18 s after the automated bolus detection for the arterial phase, 60 s after the start of contrast injection for portal venous and 180 s for transitional phase, respectively. The dynamic study was followed by a hepatobiliary phase obtained 20 min after the injection of contrast material.

All examinations were digitally stored and evaluated using our institutional Picture Archiving and Communication System (PACS - Impax, Agfa-Gevaert) in order to perform both qualitative and quantitative analysis.

Image interpretation

Two experienced radiologists, both with more than 10 years of experience in liver MRI, randomly reviewed in consensus all images on PACS. None of the two readers were involved in the scanning, and they were blinded to any patient-related information and to the type of contrast agent, while they were aware of the diagnosis. Four consecutive randomized interpretation sessions with a seven-day interval to avoid recall bias were held to complete the review process of all scans.

Qualitative analysis

The two readers evaluated each lesion with respect to the surrounding liver parenchyma in all sequences before and after contrast medium administration as: 1) hypointense; 2) slightly hypointense; 3) isointense; 4) slightly hyperintense; 5) hyperintense. Readers defined each lesion as homogeneous or heterogeneous after contrast-media injection. Signal intensity was considered homogeneous when the lesion enhanced to the same degree in all its parts, with the exception of the central scar, when present. A ring-like enhancement pattern was defined as a lesion showing a peripheral iso-hyperintense rim surrounding a central hypointense portion during the hepatobiliary phase. Finally, readers described the signal intensity of the central scar on the different sequences.

Quantitative analysis

Quantitative analysis was performed in consensus by two different radiologists not involved in the qualitative analysis. Signal intensities (SI) of the liver parenchyma and FNH lesions were measured in each patient on all breath-hold 3D fat-saturated T1-weighted sequences before and after contrast medium administration. Regions of interest (ROIs) were positioned on the right and left liver lobes avoiding vessels, and a mean value was calculated. Then a ROI was drawn on the lesion, as large as possible, manually following its borders in all precontrast and postcontrast T1-weighted MRI sequences, including hepatobiliary specific phase for both contrast media. All ROIs were positioned at comparable slice levels and at identical positions for each sequence. SI ratio (SIR, %) was calculated for each FNH in all contrast-enhanced T1-weighted sequences using the following formula:

$$SIR_{FNH}\,(\%) = \frac{SI_{post} - SI_{pre}}{SI_{pre}} \times 100$$

where SI_{post} is SI measured on contrast-enhanced phases, and SI_{pre} is SI measured on precontrast images. Lesion-to-liver contrast ratio was also calculated using the following formula:

$$CR_{FNH\text{-}to\text{-}liver}\,(\%) = \frac{SI_{FNH} - SI_{liver}}{SI_{FNH} + SI_{liver}} \times 100$$

where SI_{FNH} is lesion SI and SI_{liver} is liver SI, both measured on the same contrast-enhanced phases.

In addition, liver parenchyma SI gain was evaluated for hepatobiliary phase as follows:

$$SI\ gain = \frac{SI_{hepatocyte\ phase} - SI_{precontrast}}{SI_{precontrast}} \times 100$$

Finally, a relationship between central scar detection and lesion size was also evaluated.

Statistical analysis

Data were expressed as counts and percentage for qualitative variables and as medians and interquartile range for quantitative variables. The dependencies among multiple lesions within the same patient were considered explicitly in the statistical analysis. With respect to qualitative evaluation, the McNemar test for paired frequencies was used in order to evaluate statistically significant differences between gadobenate dimeglumine and gadoxetate disodium for each postcontrast phase after both contrast media administration. With respect to quantitative evaluation, the Wilcoxon sign-rank test for clustered paired data was used in order to assess statistically significant differences between gadobenate dimeglumine and gadoxetate disodium patterns (11, 12). Statistical analysis was performed using the R software (https://cran.r-project.org). The Wilcoxon sign-rank test for clustered data was performed using the *clusrank* package running in the R environment. A P value < 0.05 was considered statistically significant.

Results

All lesions were round or oval in shape. On precontrast T1-weighted images, 15 out of 21 FNHs (71%) were slightly hypointense, whereas the remaining six (29%) were respectively isointense (n=3) and slightly hyperintense due to surrounding hypointense fatty liver (n=3). On T2-weighted images, 18 of 21 (86%) were slightly hyperintense and the remaining three (14%) were isointense.

After injection of either gadobenate dimeglumine or gadoxetate disodium, all lesions (100%) were homogeneously hypervascular in the arterial phase.

All (n=21, 100%) FNHs were iso-hyperintense 180 s after both gadobenate dimeglumine and gadoxetate disodium injection. On hepatobiliary phase, lesions showed uptake of contrast medium and were homogeneously iso-hyperintense in 17 of 21 cases (81%) after gadobenate dimeglumine and in 16 of 21 cases (76%) after gadoxetate disodium (Fig. 1).

A ring of peripheral enhancement surrounding a central hypointense portion was noted in 4 (19%) and 5 (24%) cases after gadobenate dimeglumine and gadoxetate disodium administration, respectively (Fig. 2; Table 2). No statistically significant differences were evident in contrast enhancement patterns between the two contrast media during the arterial (P = 1.0),

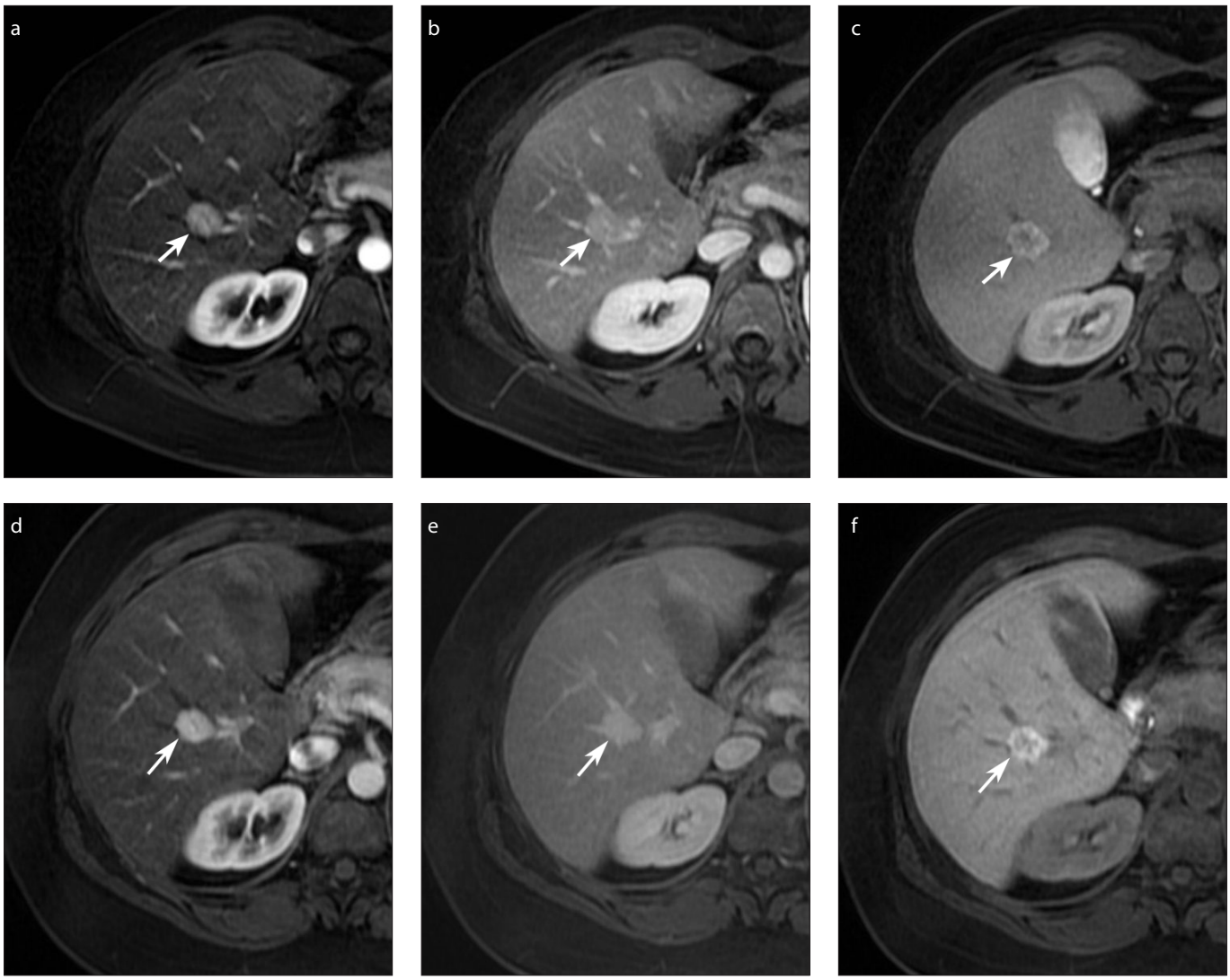

Figure 1. a–f. Focal nodular hyperplasia (FNH) in a 30-year-old woman. After injection of gadobenate dimeglumine **(a–c)**, T1-weighted 3D gradient echo fat-saturated magnetic resonance image obtained in the arterial phase **(a)** shows a strongly and homogeneously hypervascular 1.8 cm lesion *(arrow)* remaining moderately hyperintense at 180 seconds **(b,** *arrow)*. Two hours after the injection of gadobenate dimeglumine **(c)**, lesion shows contrast uptake appearing hyperintense in comparison to the surrounding liver parenchyma, confirming its hepatocellular nature *(arrow)*. After the administration of gadoxetate disodium **(d–f)**, lesion shows the same enhancement pattern on arterial **(d)**, 180 seconds **(e)**, and hepatobiliary phases **(f)** *(arrows)*.

Table 2. Qualitative analysis of 21 FNHs at contrast-enhanced MRI

	Arterial	Portal–venous	180 seconds	Hepatobiliary
Gadobenate dimeglumine (n=21)	Hyperintense (n=21, 100%)	Hyperintense (n=14, 66%) Isointense (n=7, 33%)	Hyperintense (n=14, 67%) Isointense (n=7, 33%)	Hyperintense (n=12, 57%) Isointense (n=5, 24%) Ring-like (n=4, 19%)
Gadoxetate disodium (n=21)	Hyperintense (n=21, 100%)	Hyperintense (n=15, 71%) Isointense (n=6, 29%)	Hyperintense (n=12, 57%) Isointense (n=8, 38%) Slightly hypointense (n=1, 5%)	Hyperintense (n=8, 38%) Isointense (n=8, 38%) Ring-like (n=5, 24%)

portal-venous ($P = 0.416$), 180 s ($P = 0.416$), and hepatobiliary ($P = 0.199$) phases.

No central scar was detected in 7 of 21 FNHs (33%) after injection of either gadobenate dimeglumine or gadoxetate disodium.

A central scar was noted after both gadobenate dimeglumine and gadoxetate disodium in 9 FNHs (43%), only after gadobenate dimeglumine in 4 cases (19%) and only after gadoxetate disodium in one case (5%).

In particular:

In the arterial phase: not evident (n=1) or hypointense (n=13) after injection of either gadobenate dimeglumine or gadoxetate disodium;

In the portal-venous and/or at 180 s: a) hypointense (n=9) and hyperintense

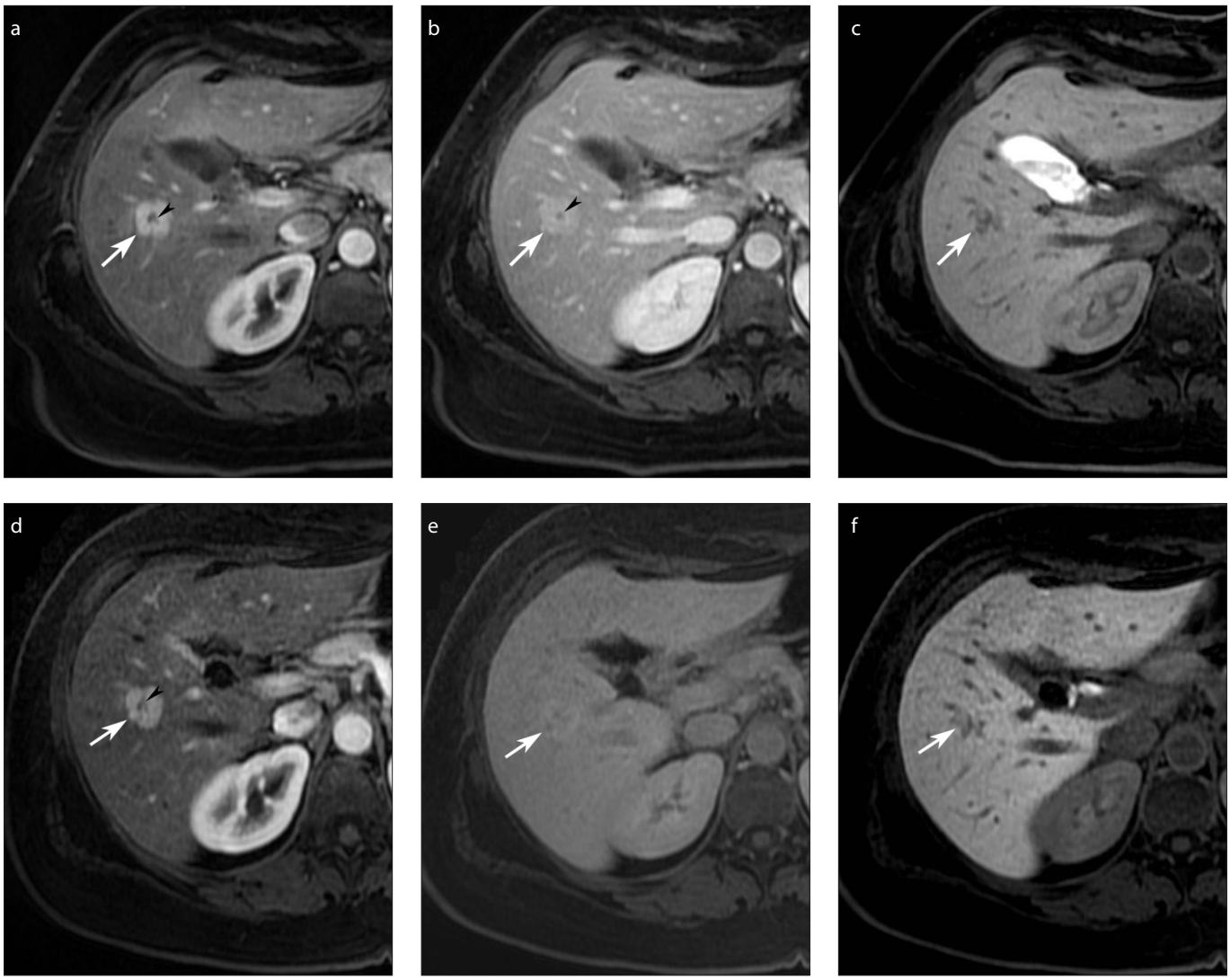

Figure 2. a–f. FNH in a 43-year-old woman. After gadobenate dimeglumine injection in the arterial phase **(a),** a 2.1 cm sized lesion shows a bright and homogeneous contrast enhancement *(arrow)* except for a central hypointense area corresponding to the central scar *(arrowhead)*. FNH appears hyperintense at 180 seconds **(b**, *arrow)*, whereas the central scar is hypointense *(arrowhead)*. Two hours after the injection of gadobenate dimeglumine **(c)**, the lesion shows a ring-like pattern. After the administration of gadoxetate disodium **(d–f)**, similar findings are observed in the arterial **(d)**, 180 seconds **(e),** and hepatobiliary phases **(f)**.

(n=4) after gadobenate dimeglumine and hypointense (n=10) after gadoxetate disodium;

In the hepatobiliary phase: a) hypointense (n=14) after gadobenate dimeglumine and hypointense (n=10) after gadoxetate disodium.

No statistically significant differences were observed in the detection and the imaging features of the central scar after the injection of the two contrast media during the arterial (P = 0.564), portal-venous (P = 0.607) phases, at 180 s (P = 0.172), and during the hepatobiliary phase (P = 0.572).

No statistically significant differences were found in SIR after either gadobenate dimeglumine and gadoxetate disodium administration during all enhanced phases except for hepatobiliary phase in which SIR was higher after gadoxetate disodium (P = 0.048) (Table 3).

No statistically significant differences were found in $CR_{FNH\text{-}to\text{-}liver}$ after either gadobenate dimeglumine and gadoxetate disodium administration during the arterial (P = 0.485) and portal-venous (P = 0.360) phases and at 180 s (P = 0.936), respectively. $CR_{FNH\text{-}to\text{-}liver}$ resulted significantly higher after gadoxetate disodium than after gadobenate dimeglumine during hepatobiliary phase (P = 0.032) (Table 4).

Liver parenchyma SI gain on hepatobiliary phase resulted significantly higher for gadoxetate disodium (P = 0.012) (Table 5).

Discussion

In this study we performed an intraindividual comparison of 21 FNH lesions after the injection of gadobenate dimeglumine and gadoxetate disodium, the two hepatobiliary contrast agents that are currently available in the market. We found that the dynamic and hepatobiliary enhancement patterns of FNH do not significantly differ when either contrast agent is injected. Homogeneous iso-hyperintensity on hepatobiliary phase was noted in similar percentages after injection of either contrast agents (gadobenate dimeglumine, 81% vs. gadoxetate disodium, 76%).

We did not find any statistically significant difference between gadobenate

Table 3. Signal intensity ratios of 21 FNHs

SIR	Arterial	Portal-venous	180 seconds	Hepatobiliary
Gadobenate dimeglumine	127.5 (108.6–150.7)	148.4 (120.6–160.5)	123.8 (105.4–150.7)	117.5 (84.4–140.5)
Gadoxetate disodium	112.2 (0.7–144.6)	115.3 (93.6–169.1)	117.6 (106.5–152.7)	140.2 (124.9–157.1)
P	0.405	0.336	0.996	0.048

Data are presented as median and interquartile range (Q_1–Q_3).
SIR, signal intensity ratio.

Table 4. Lesion-to-liver contrast ratio of 21 FNHs

Lesion-to-liver contrast ratio	Arterial	Portal-venous	180 seconds	Hepatobiliary
Gadobenate dimeglumine	19.9 (14.5–25.8)	8.0 (3.7–11.6)	8.1 (0.9–10.7)	0.1 (-3.8 to 4.1)
Gadoxetate disodium	20.8 (11.1–27.0)	7.2 (5.5–9.8)	4.8 (0.2–8.2)	0.7 (-1.8 to 5)
P	0.485	0.360	0.936	0.032

Data are presented as median and interquartile range (Q_1–Q_3).

Table 5. Liver parenchyma SI gain on hepatobiliary phase

SI gain	Hepatobiliary
Gadobenate dimeglumine	104.7 (61.7–119.0)
Gadoxetate disodium	119.2 (99.0–133.1)
P	0.012

Data are presented as median and interquartile range (Q_1–Q_3).
SI, signal intensity.

dimeglumine and gadoxetate disodium in central scar detection in any of the phases. However, at 180 s the central scar showed enhancement in 5 cases after gadobenate dimeglumine administration, while it was hypointense after gadoxetate disodium administration. This could be explained with the prolonged extravascular interstitial phase and a delayed hepatocyte uptake of gadobenate dimeglumine in comparison to gadoxetate disodium. These data are similar to those reported by Karam et al. (13).

We noted some statistically significant differences in the quantitative analysis regarding: 1) SIR of FNHs (P = 0.048), 2) $CR_{FNH\text{-}to\text{-}liver}$ (P = 0.032), and 3) parenchymal SI gain (P = 0.012) on hepatobiliary phase in favor of gadoxetate disodium. These data could be explained with the different percentage of contrast media uptake by hepatocytes and excretion into the biliary system (50% for gadoxetate disodium vs. 3%–5% for gadobenate dimeglumine) (14). Gupta et al. (15) reported results similar to ours on 30 patients with FNHs who underwent both gadobenate dimeglumine and gadoxetate disodium enhanced MRI, in particular regarding SI ratio and $CR_{FNH\text{-}to\text{-}liver}$. However, they noted that SIR values were higher in the portal phase after gadobenate dimeglumine than after gadoxetate disodium, whereas we did not observe any statistically significant difference. This different result could be due to the lack of standardization of the dose of gadoxetate disodium and to the multicentric nature of their study that implied some protocol variability, whereas we correlated the dose of contrast with patient's weight and conducted a single institution study (15).

Despite our findings indicate some statistically significant difference on hepatobiliary phase between the two contrast media at quantitative evaluation, FNHs did not show any difference at qualitative analysis. Consequently, on the basis of widely known diagnostic imaging criteria for FNH, these differences do not compromise the final diagnosis. The only difference between these two contrast agents is the length of the examination: approximately 30 minutes with gadoxetate disodium, longer with gadobenate dimeglumine because the hepatobiliary phase is acquired 1–3 hours after contrast injection. This difference should be considered to appropriately manage MRI unit daily routine.

Finally, FNHs showed a ring-like appearance on the hepatobiliary phase after administration of gadobenate dimeglumine in four cases and after gadoxetate disodium in five cases. On this regard, it has been demonstrated that, after the injection of gadoxetate disodium, a minority of FNH lesions can show this peculiar ring pattern of enhancement on the hepatobiliary phase, and the explanation is the higher expression of uptake transporter OATP1B3 (organic anion transporter polypeptide) on the membrane of the sinusoidal side of those hepatocytes located in the periphery of the lesion in comparison to the relative scarcity of OATP1B3 receptors on those hepatocytes located in the center of FNH lesions (8). Although we do not have pathologic proof to confirm our hypothesis, we speculate that this could be the explanation for our findings as well (7, 9, 16–19).

Our study presents some limitations. First, we had a selection bias. Our patients were selected on the basis of their pre-

sumed diagnosis in an imaging database. Consequently, those with FNH lesions lacking all typical imaging findings were not included. We acknowledge that this selection bias reduces the value of our study, as atypical FNH would be the lesions for which optimising imaging would be most important. Nevertheless, this bias would not have affected both gadobenate dimeglumine or gadoxetate disodium MRI scan. Second, a final diagnosis was not established by histological evaluation. However, since our patients did not have history of chronic liver disease or known malignancy, the diagnosis of FNH was obtained when clinical, biochemical, and imaging criteria were met. The differential diagnosis between arterioportal shunting and FNH can be challenging, because these observations are both hypervascular in the hepatic arterial phase and tend to fade to isointensity on portal venous phase. However, FNH is typically round or oval in shape, while arterovenous shunting is usually triangular and in a subcapsular location. Whatever the nature, when hypervascular observations are smaller than 1 cm, differential diagnosis can be very tough, although clinically irrelevant in patients with no chronic liver disease or other risk factors (i.e., extrahepatic tumor). Third, imaging analysis was performed by consensus and interobserver agreement was not assessable. Finally, our study population is limited due to the intraindividual comparison in a single department between two different contrast media.

In conclusion, there were no significant differences in the MRI findings of FNH after the injection of a weight-based dose of either gadobenate dimeglumine or gadoxetate disodium.

Conflict of interest disclosure

Giuseppe Brancatelli: speaker for Bayer and Guerbet; Guerbet advisory board; funding for an educational meeting from Bracco. The remaining authors declared no conflicts of interest.

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