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TECHNICAL NOTE

Increased and More Heterogeneous Gadoxetic Acid Uptake of the Liver Parenchyma after Hepatitis C Virus Eradication by Direct Antiviral Agent

Nobuhiro Fujita[1], Akihiro Nishie[1*], Yoshiki Asayama[2], Kousei Ishigami[1], Tomohiro Nakayama[3], Yasuhiro Ushijima[1], Daisuke Kakihara[1], Yukihisa Takayama[1], Koichiro Morita[1], Keisuke Ishimatsu[1], Seiichiro Takao[1], Tomoharu Yoshizumi[4], Norihiro Furusyo[5], and Hiroshi Honda[1]

We evaluated the changes of gadoxetic acid uptake of the liver parenchyma after hepatitis C virus (HCV) eradication by direct-antiviral agent (DAA) therapy. The increase rate of the liver-to-muscle signal intensity ratio, the skewness and the kurtosis were calculated in the hepatobiliary phase. After sustained virological response, gadoxetic acid uptake of the liver parenchyma increased, but became heterogeneous. Our study proved that HCV eradication by DAA therapy could significantly affect gadoxetic acid uptake.

Keywords: *hepatitis C virus (HCV), direct-antiviral agent (DAA), sustained virological response (SVR), gadoxetic acid*

Introduction

With the current treatment of hepatitis C virus (HCV) including direct antiviral agents (DAAs), the rates of sustained virological response (SVR) exceed 90%.[1] Achievement of SVR has been associated with improvement of liver function as indicated by model for end-stage liver disease (MELD) or Child–Pugh score.[2] Regression of histological fibrosis following SVR also has been described.[3] That is to say, the liver parenchyma demonstrates damage-repairing and regenerative abilities after SVR. Gadoxetic acid is a hepatobiliary-specific contrast medium for magnetic resonance imaging (MRI) and is taken up to varying degrees by functioning hepatocytes. Previous studies have reported that the uptake of gadoxetic acid showed significant correlation with liver function[4] and liver fibrosis.[5] It can be considered that liver regeneration after SVR may affect the gadoxetic acid uptake of the liver parenchyma. One study reported that the gadoxetic acid uptake increased in 84% of the patients after HCV eradication,[6] but to the best of our knowledge, no reports have evaluated the changes of gadoxetic acid uptake before and after SVR including the degree and heterogeneity of uptake. The purpose of this study was to evaluate the changes of gadoxetic acid uptake of the liver parenchyma after SVR to DAA therapy in patients with HCV, with focus on the degree and heterogeneity of uptake.

Materials and Methods

Patients

Our Institutional Review Board approved this retrospective study, and the requirements for informed consent were waived.

For this retrospective study, we used electronic medical records including pharmacy records, imaging data and laboratory data. Between December 2015 and November 2017, referring to the medical data record, we enrolled 18 consecutive patients with HCV infection who achieved SVR by DAA therapy and underwent gadoxetic acid-enhanced MRI before and after therapy. In this study, we included the patients who underwent MRI using 3T MRI scanner (Achieva TX, 3T; Philips Healthcare, Best, The Netherlands) both before and after therapy. Seven patients were excluded because they underwent MRI examination using 1.5T MRI scanner (Intera Achieva Nova Dual, 1.5T, Philips Healthcare) scanner before and/or after therapy. A final total of 11 patients were enrolled in this study, and their characteristics are summarized in Table 1. Antiviral therapy and treatment

[1]Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
[2]Department of Advanced Imaging and Interventional Radiology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
[3]Department of Molecular Imaging & Diagnosis, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
[4]Department of Surgery and Sciences, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
[5]Department of General Internal Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuokas, Japan
[*]Corresponding author: Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka, Fukuoka 812-8582, Japan. Phone: +81-92-642-5695; Fax: +81-92-642-5708, E-mail: anishie@radiol.med.kyushu-u.ac.jp

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Table 1 Patient backgrounds

Sex (male/female)	6/5
Age (years)*	68.8 ± 8.5
Child–Pugh Class	
A	11
HCV genotype	
1b	9
2b	2
DAAs	
DCV/ASV	4
LDV/SOF	4
SOF/RBV	2
EBR/GZR	1

*At the time of SVR, data are means ± standard deviations.
HCV, hepatitis C virus; SVR, sustained virological response; DCV, daclatasvir; ASV, asunaprevir; LDV, ledipasvir; SOF, sofosbuvir; RBV, ribavirin; EBR, elbasvir; GZR, grazoprevir.

duration (12 or 24 weeks) was indicated in each patient according to the viral genotype/subtype and the severity of liver disease, in accordance with the current international guidelines.[7] SVR was defined as HCV ribonucleic acid results below the lower limit of quantification at a timepoint 24 weeks or more after the end of treatment.[7]

MR techniques

Gadoxetic acid-enhanced MR imaging was performed before therapy (12.2 ± 16.6 months) and after SVR (11.7 ± 7.3 months) using a superconducting magnet operating at 3T (Philips Healthcare) with a sensitivity encoding technique (SENSE) using a 32-channel phased-array coil.

For the gadoxetic acid-enhanced MR imaging, dynamic images using axial three-dimensional-enhanced T_1 high-resolution isotropic volume excitation were obtained. The detailed imaging parameters were as follows: 32-channel cardiac phased-array coil, TR/TE/FA = 3 ms/1.4 ms/10°, matrix 252 × 200, field of view 37.5 × 29.8 cm, SENSE factor 1.8, slice thickness = 3 mm, gap = −1.5 mm, linear *k*-space ordering, spectral attenuation with inversion recovery, acquired 133 sections, scan time 17.9 s, and breath-holding.

A multiphase dynamic study including arterial dominant, portal, late and hepatobiliary phases was performed after administration of gadoxetic acid (gadolinium–ethoxylbenzyl–diethylenetriaminepentaacetic acid, Primovist; Bayer, Osaka, Japan). The total amount of gadoxetic acid based on the patient's body weight (0.025 mmol/kg) was intravenously injected for 5 s followed by a 20-mL physiological saline flush via a power injector (Nemoto Kyourindo, Tokyo, Japan). Scanning of the hepatobiliary phase began 20 min after the injection of the contrast agent.

Liver-muscle signal intensity ratio

As indicators of liver function, we calculated the increase rate of the liver-to-muscle signal intensity ratio (ΔLMR).[5] Image analysis was performed in a consensus fashion by two radiologists who specialize in hepatic MR imaging (NF and AN with 15 and 24 years of experience in abdominal imaging, respectively) and who were blinded to the clinical results of each case.

We used images in the precontrast and hepatobiliary phase for the evaluation of LMR. First, three slices without significant artifacts were selected. By consensus, signal intensities were measured by placing the largest possible regions of interest (ROIs) on the liver parenchyma of each lobe (right and left) and on the erector spine muscle while avoiding vessels; for this, the commercially available PACS workstation (SYNAPSE, FujiFilm Medical, Tokyo, Japan) was used. Specifically, radiologists placed two round or oval ROIs for the liver parenchyma: one on the right lobe and the other on the left, and one round or oval ROI on the erector spine muscle (Fig. 1). Based on the average values of the six signal intensities of the liver parenchyma and the three signal intensities of the erector spine muscle, LMR was calculated using the following equation:

$$\text{LMR} = \frac{\text{Signal intensity of the liver}}{\text{Signal intensity of the erector spine muscle}}$$

Finally, the ΔLMR was calculated using the following equation:

$$\Delta\text{LMR} = \frac{\left(\begin{array}{l}\text{LMR in the hepatobiliary phase} - \\ \text{LMR in the precontrast image}\end{array}\right)}{\text{LMR in the precontrast image}}$$

Histogram analysis

For the evaluation of heterogeneity, the skewness and the kurtosis of the signal intensity in the hepatobiliary phase

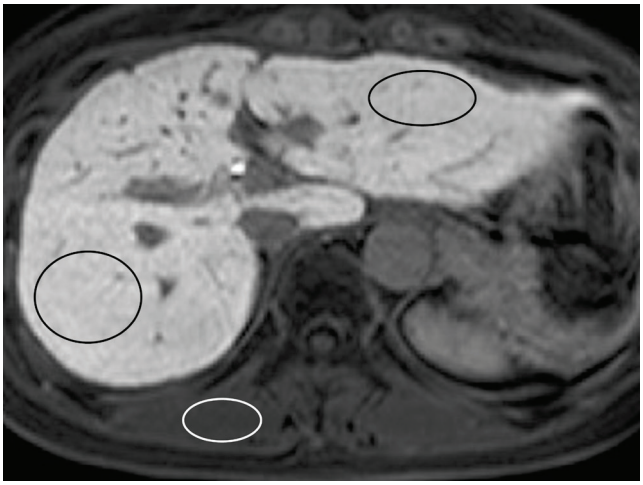

Fig. 1 The hepatobiliary phase of gadoxetic acid-enhanced magnetic resonance imaging. The signal intensities were measured by placing as large a region of interest as possible on the liver parenchyma of each lobe (black circles) and on the erector spine muscle (white circle), avoiding vessels and artifacts.

were calculated by histogram analysis using Image J 1.51 software (National Institutes of Health, Bethesda, MD, USA).[8] Image analysis was performed in a consensus fashion by two radiologists who specialize in hepatic MR imaging (NF and YA with 15 and 24 years of experience in abdominal imaging, respectively) without information regarding the clinical results.

By consensus, three slices without significant artifacts were selected. A largest possible round or oval ROI was carefully placed on the hepatic parenchyma of the right lobe so as to avoid large vessels (Fig. 2a). The signal intensity of all pixels within the selected ROI were measured, and values of kurtosis and skewness were automatically calculated by the software (Fig. 2b). Skewness is the degree of asymmetry of a histogram: a histogram with a long tail to the right has a positive skewness value, and a perfectly symmetric histogram has a skewness value of zero. Kurtosis is a measure of peakedness: a histogram with a higher peak than the normal distribution has a positive kurtosis value.[9] The average values of kurtosis and skewness of three ROIs in the hepatobiliary phase were used in this study.

Statistical analysis

Mean values of ΔLMR, kurtosis and skewness before and after SVR were compared using the paired *t*-test. JMP 13.2.1 Software (SAS Institute, Cary, NC, USA) was used for the analysis. *P*-values < 0.05 were considered significant.

Results

The post-therapy ΔLMR (1.02 ± 0.28) was significantly higher than the pre-therapy value (0.74 ± 0.29) ($P < 0.01$) (Fig. 3a). The post-therapy skewness (−0.82 ± 0.52) was significantly lower than the pre-therapy skewness (−0.34 ± 0.47) ($P < 0.01$) (Fig. 3b). The post-therapy kurtosis (2.53 ± 2.33) was significantly higher than that the pre-therapy kurtosis (1.10 ± 1.13) ($P = 0.02$) (Fig. 3c). One case (9.1%) showed a decrease in ΔLMR, an increase in skewness and a decrease in kurtosis after SVR. One case (9.1%) showed a decrease in ΔLMR, while showed a decrease in skewness and an increase in kurtosis after SVR. One case (9.1%) showed a decrease in kurtosis,

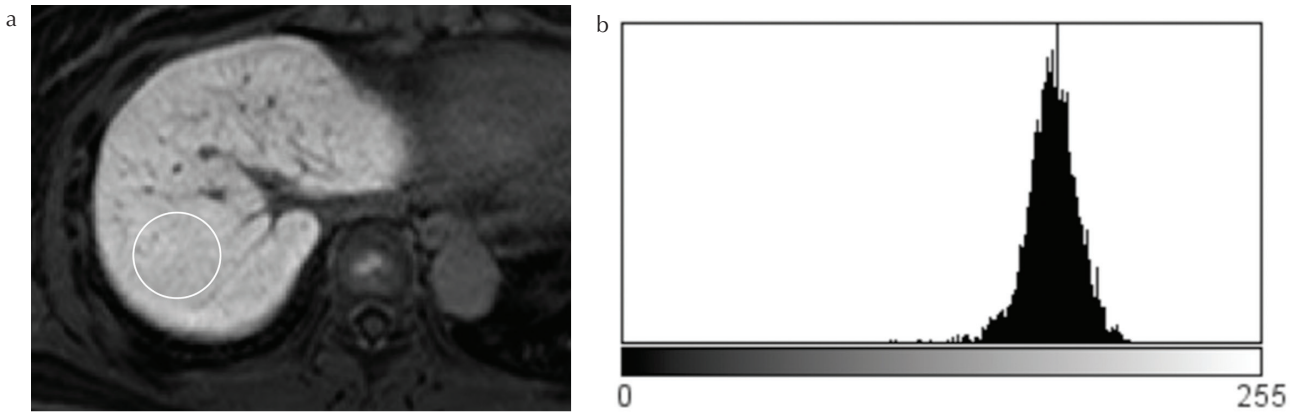

Fig. 2 (**a**) The hepatobiliary phase of gadoxetic acid-enhanced magnetic resonance imaging. The signal intensities were measured by placing as large a region of interest as possible on the liver parenchyma of the right lobe, avoiding vessels and artifacts (white circle). (**b**) The histogram shows a sharp peak with most values lying to the right side (skewness, –1.205; kurtosis, 6.077).

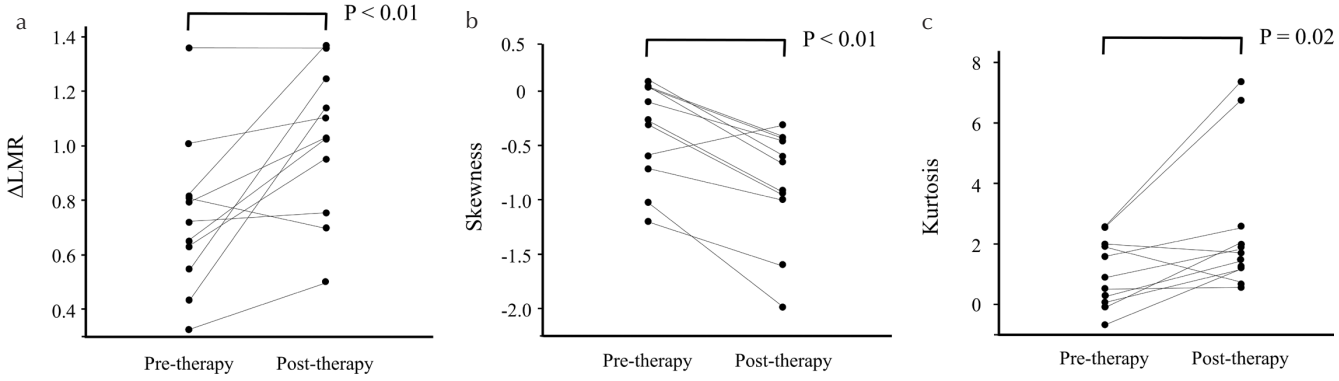

Fig. 3 (**a**) Pre- and post-therapy the increase rate of the liver-to-muscle signal intensity ratio (ΔLMR). The post-therapy ΔLMR (1.02 ± 0.28) was significantly higher than the pre-therapy value (0.74 ± 0.29) ($P < 0.01$). (**b** and **c**) Histogram analysis pre- and post-therapy. (**b**) The post-therapy skewness (–0.82 ± 0.52) was significantly lower than the pre-therapy skewness (–0.34 ± 0.47) ($P < 0.01$). (**c**) Post-therapy kurtosis (2.53 ± 2.33) was significantly higher than the pre-therapy kurtosis (1.10 ± 1.13) ($P = 0.02$).

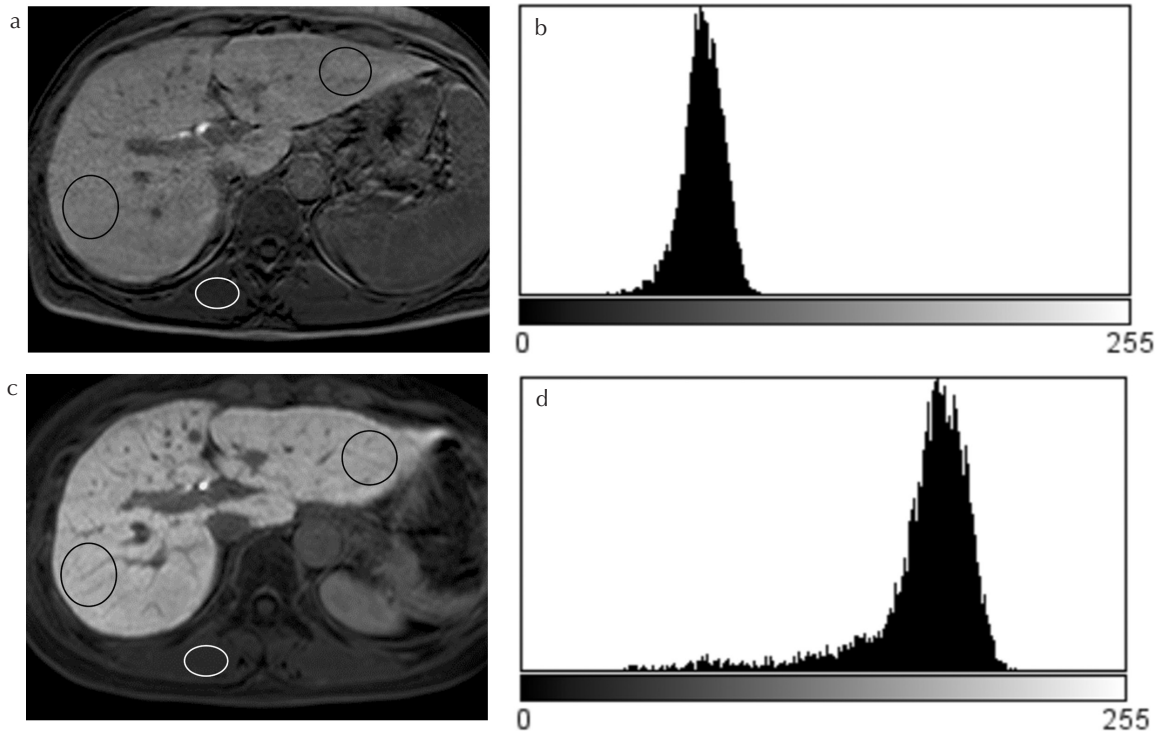

Fig. 4 A woman in her 60s with hepatitis C, achieved sustained virological response by direct-antiviral agent therapy (Daclatasvir/Asunaprevir). (**a**) The hepatobiliary phase of gadoxetic acid-enhanced magnetic resonance imaging (MRI) of pre-therapy. The regions of interest were placed on the right and left lobe of the liver (black circles), and on the erector spine muscle (white circle). The increase rate of the liver-to-muscle signal intensity ratio (ΔLMR) was 0.44. (**b**) Histogram of the signal intensity at pre-therapy. The skewness was −0.08 and the kurtosis was 0.94. (**c**) The hepatobiliary phase of gadoxetic acid-enhanced MRI at post-therapy. The ΔLMR was 1.14, which was higher than the ΔLMR before therapy. (**d**) Histogram of the signal intensity at post-therapy. The skewness was −0.45 and the kurtosis was 1.94, which meant the histogram showed a longer tail to the left and a higher peak than the histogram before therapy.

while showed an increase in ΔLMR and a decrease in skewness.

Figure 4 presents a representative case.

Discussion

In the present study, the ΔLMR at post-therapy was significantly higher than that at pre-therapy. That is to say, the gadoxetic acid uptake of the liver parenchyma increased after SVR. Previous studies have demonstrated that the gadoxetic acid uptake of the liver parenchyma reflects liver function[4] and fibrosis.[5] Based on these results, we conclude that the uptake of gadoxetic acid, in addition to liver function and fibrosis, improves reversibly as a result of the damage-repair and regeneration after SVR. However, a subsequent risk of hepatocellular carcinoma (HCC) may persist in some patients even after achieving SVR. The diagnostic accuracy and sensitivity to HCC of gadoxetic acid MR imaging worsens with the severity of liver dysfunction because of the tendency toward decreased gadoxetic acid uptake for the liver parenchyma.[10] Therefore, the increased uptake of gadoxetic acid of the liver parenchyma after SVR might improve the diagnostic ability of HCC. On the contrary, in the present study, two (18.2%) patients showed decreased uptake of gadoxetic acid in the liver parenchyma after SVR. Haider et al.[6] reported similar result that 16% of the patients showed decreased uptake of gadoxetic acid after SVR. Additionally, they reported that such patients were associated with a substantially increased risk of further hepatic decompensation.[6] Considering these results, the prognosis of the patients after SVR might be predicted by gadoxetic acid-enhanced MRI, although the significance of this finding is limited by the low number of patients.

In the histogram analysis of our study, the skewness at post-therapy (−0.82 ± 0.52) was significantly lower than that at pre-therapy (−0.34 ± 0.47). The skewness value of a normal distribution is zero, usually implying symmetric distribution. A negative skewness value indicates that the tail on the left side of the distribution is longer than that on the right side.[9] Therefore, it can be said that the uptake of gadoxetic acid of the liver parenchyma becomes more heterogeneous with a longer and thicker left tail after SVR. With respect to kurtosis, the post-therapy kurtosis (2.53 ± 2.33) was significantly higher than the pre-therapy kurtosis (1.10 ± 1.13) in our study. Kurtosis is a measure of the peak height of a distribution. The kurtosis should be zero for a perfectly normal distribution. Distributions with excess positive kurtosis are said to be leptokurtic, indicating the presence of a high

kurtosis peak.[9] Hence, the gadoxetic acid uptake of the liver parenchyma is considered to become heterogeneous with a higher peak after SVR. Although the risk of HCC after SVR is still a controversial subject, some studies have reported an unexpectedly high incidence of HCC following SVR by DAA therapy.[11] Pathologically, it is well known that irregular regeneration of hepatocytes is an important predictive factor of hepatocarcinogenesis.[12] Our result of histogram pattern can account for irregular regeneration of hepatocytes, and the conditions may reflect a high risk of HCC after SVR. We speculate that histogram analysis of gadoxetic acid uptake of liver parenchyma might predict the occurrence of HCC after SVR. The correlation among MRI findings, histological findings and perspective HCC occurrence should be investigated in the future.

There are some limitations to this study. First, our population of 11 was small. According to power analysis of our paired *t*-test ($n = 11$), the power was 0.668 for a large effect size (0.8) and 0.323 for a medium effect size (0.5). A larger number of cases would make our findings more reliable. Second, the interval between gadoxetic acid-enhanced MRI and DAA therapy was rather long in some cases. Inclusion/exclusion criteria of the interval time would make our results more reliable. Third, the histogram analysis data could be affected by small vessels and small bile ducts. Although we avoided large portal veins and large ducts, the ROIs used in the histogram analysis may contain such small-size structures. Thus, vessels or bile ducts containing excreted contrast medium may have affected the signal intensity. Fourth, we analyzed the imaging data in a consensus fashion. The independent evaluation would be more reliable, however, we believe the consensus of two well-experienced radiologists was justified. Finally, the results of our study and histological findings were not compared directly. Therefore, we cannot directly explain the reason for the changes of gadoxetic acid uptake after SVR.

Conclusion

After SVR, gadoxetic acid uptake of the liver parenchyma increased, but became more heterogeneous. Our study with gadoxetic acid-enhanced MRI directly proved that HCV eradication by DAA therapy could significantly affect liver function.

Acknowledgment

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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